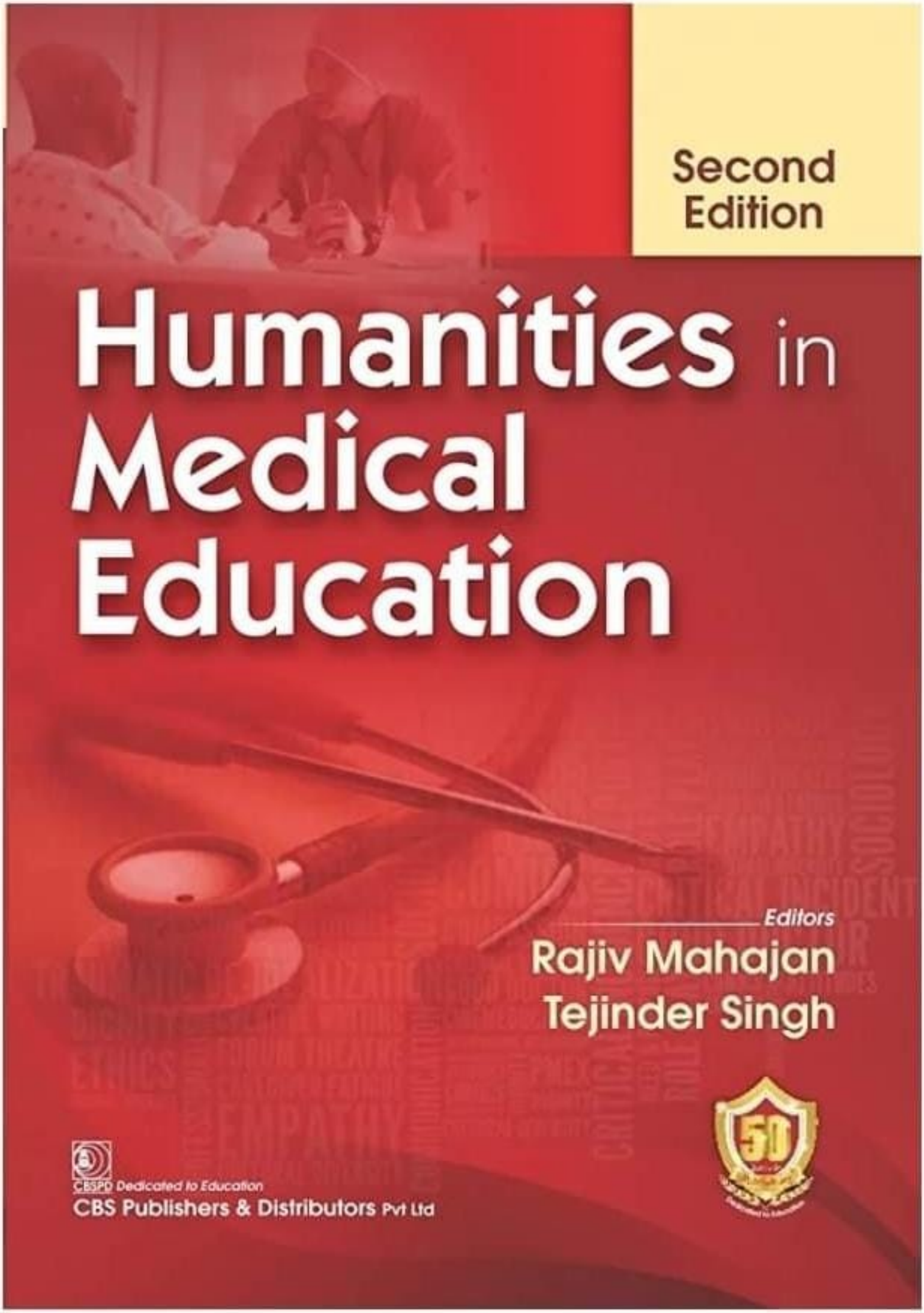
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Humanities in Medical Education
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CBSPD Dedicated to Education
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CHAPTER

9

Confidentiality and Privacy

Sunita Y Patil

Key Points

- Confidentiality is the right of every patient and reflects the respect and dignity.
- Confidentiality is based on the four grounds of patient autonomy, implied promise, virtue ethics and consequentialism.
- Clinical practice requires the doctors to share the confidential information of the patients to specific authorities and third parties under special circumstances.
- It is important to develop a system to protect patients' personal digital data and medical records.
- Taking steps to address privacy concerns by developing social media policies and implementing strategic safeguards help protect patients and reduce liability exposure.
- Though there are no specific laws related to confidentiality in medical practice in India, National Medical Commission has regulations concerned with confidentiality and patient privacy.

INTRODUCTION

Confidentiality in the medical setting refers to *'the principle of keeping secure and secret from others, information given by or about an individual in the course of a professional relationship' and 'it is taken to the right of every patient, even after death'* (Bourke J et al, 2008).

'I shall respect and maintain my patients' secrets. Where required, with the patient's permission, I shall also take into confidence the family, so that my patient gets the best treatment possible. There will be occasions when, in the greater interests of society, I am required by law to divulge confidential information. I will do all I can to ensure that my patient's interests are protected and that the need for making confidential information public is known to my patient'.

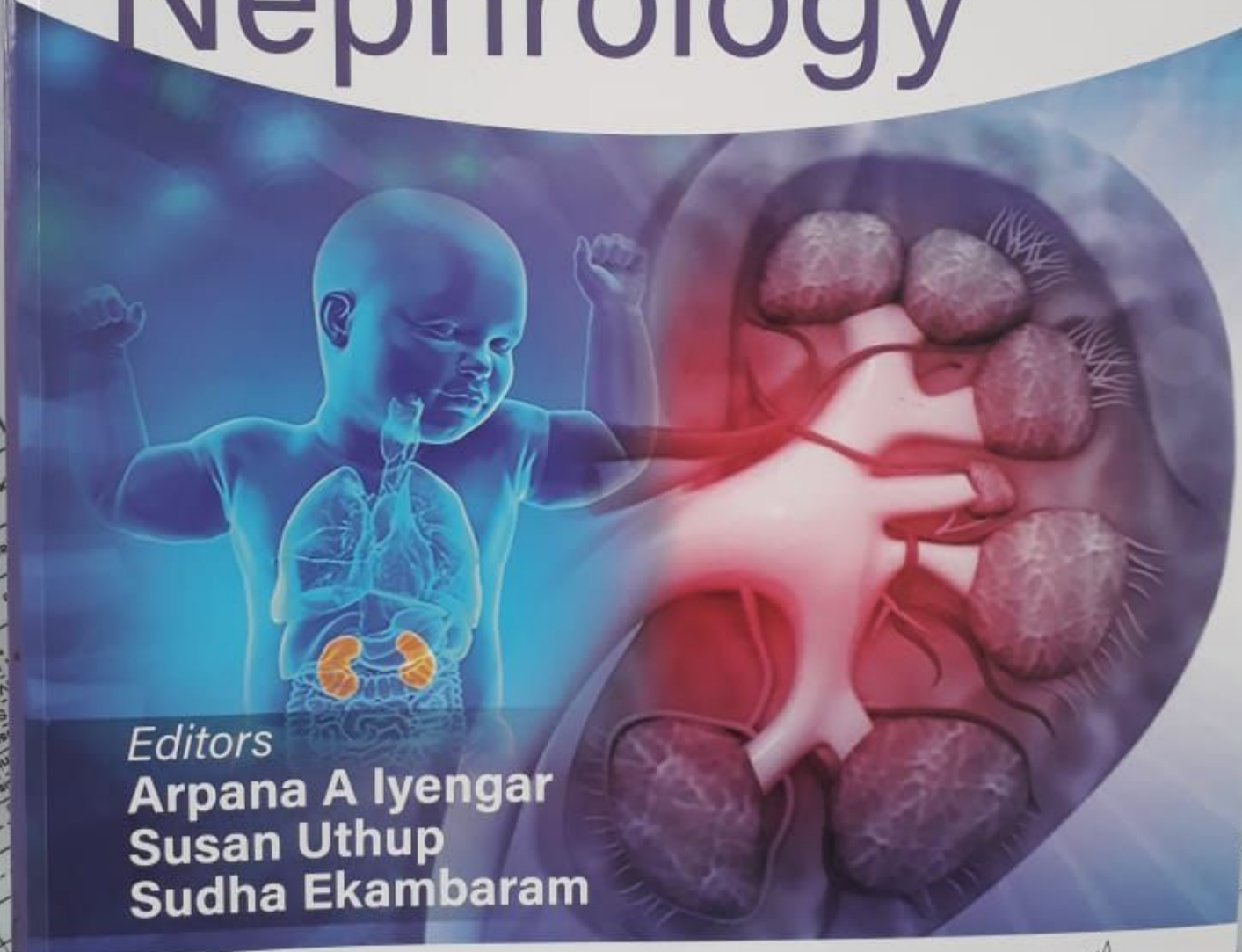
— Hippocratic Oath

'I will respect the secrets which are confided in me even after the patient has died'.

— Geneva Declaration

Every individual values privacy and hence every patient has the right to determine how, when, why and to what extent the information about the self can be revealed

Nammalwar's Principles and Practice of Pediatric Nephrology



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CHAPTER

8.3

Bartter Syndrome and Gitelman Syndrome

Mahantesh V Patil, Jyoti Sharma

INTRODUCTION

Bartter and Gitelman syndromes (BS and GS, respectively) are hereditary salt-losing tubulopathies (SLT) characterized by variable extents of volume depletion, hypokalemic, and hypochloremic metabolic alkalosis. Since the first description of BS by Frederic Bartter in 1962, there have been great advancements in understanding of the pathophysiology and in molecular diagnosis. The initial classification of different subtypes of BS was mainly focused on the age at presentation, distinguishing *antenatal variants of BS* (including BS1, BS2, BS4, and BS5), all typically associated with severe polyhydramnios causing premature birth from *classical BS* (BS3) that has a later milder presentation.[1] At present, mutations in at least seven genes involved in the reabsorption of sodium and chloride in the thick ascending limb of the loop of Henle (TAL) and/or the distal convoluted tubule (DCT) have been implicated in these disorders.[2] Bartter syndrome 1–4, GS, and EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) are inherited as autosomal-recessive disorders, while BS type 5 is inherited as an X-linked recessive disorder.

A pathophysiological classification proposes separating the various types into disorders of the TAL, of DCT, or of both segments. *Disorders of the TAL*, present in the antenatal period, are characterized by hypercalciuria and nephrocalcinosis and are equivalent to the use of loop diuretics. They occur due to mutations in *SLC12A1* (NKCC2) or *ROMK* (KCNJ1). In contrast, *disorders of the DCT* are characterized by hypo- or normocalciuria and hypomagnesemia and typically manifest later in childhood or adolescence. They mimic the use of thiazide diuretics and may occur due to mutations in *CLCNKB* or *SLC12A3* (NCCT). The *compound disorders* affecting both segments are usually caused by BSND (Barttin) mutations or combined CLCNK-B/A mutations and typically have a severe antenatal presentation.[3,4] However, there is significant clinical heterogeneity in presentation and a precise genotype–phenotype correlation is not possible.[2] Hence, when a precise diagnosis is required, genetic analysis should be done **(Table 1)**.

PATHOPHYSIOLOGY OF SALT-LOSING TUBULOPATHIES

Physiology of Sodium Chloride and Magnesium Reabsorption

Healthy kidneys reabsorb almost 99% of the filtered load of water and electrolytes, with about 60% of the reabsorption of *sodium* occurring in the proximal tubule, 30% in the TAL, 5–10% in the early DCT, and the remainder in the aldosterone-sensitive distal tubule (ASDT). Approximately 2,500 mg of *magnesium* is filtered per day, of which 96% is reabsorbed along the nephron. Only a small portion (5–15%) is reabsorbed in the proximal tubule and 50–72% is reabsorbed passively through the paracellular pathway in the TAL. Active reabsorption of Mg^{2+} takes place at the apical Mg^{2+} channel, TRPM6, at the DCT and accounts for 10% of the total filtered load and determines the final urinary secretion of Mg^{2+}.[3]

Sodium transport in the TAL and early DCT is accomplished by the active reabsorption of Na^+ with Cl^- from the tubular fluid[5] **(Fig. 1)**. In the TAL, luminal sodium (Na^+) is reabsorbed electroneutrally—half by the sodium–potassium–chloride co-transporter (NKCC2) and half by taking a paracellular route by cation-selective intercellular pathways. The NKCC2 also transports one K^+ and two Cl^- ions for each sodium ion. Potassium that enters the TAL cell via NKCC2 is recycled back to the tubular urine through the luminal renal outer medulla potassium channels (ROMK). This replenishes the urinary K^+ that would otherwise decrease along the TAL and ensures NKCC2 activity along this tubular segment. In addition, it establishes a lumen-positive transepithelial voltage gradient that drives paracellular transport of cations such as Na^+ (50% of the total absorbed in this portion of the tubule), Ca^{2+}, and Mg^{2+} via claudins. Sodium is actively pumped out of the TAL cell by the basolateral sodium–potassium-ATPase pump (Na–K-ATPase) in exchange for K^+. Chloride leaves the cell basolaterally through specific chloride channels (ClC-Ka *and* ClC-Kb). The operation of both chloride channels requires the B-subunit Barttin.[5-7]

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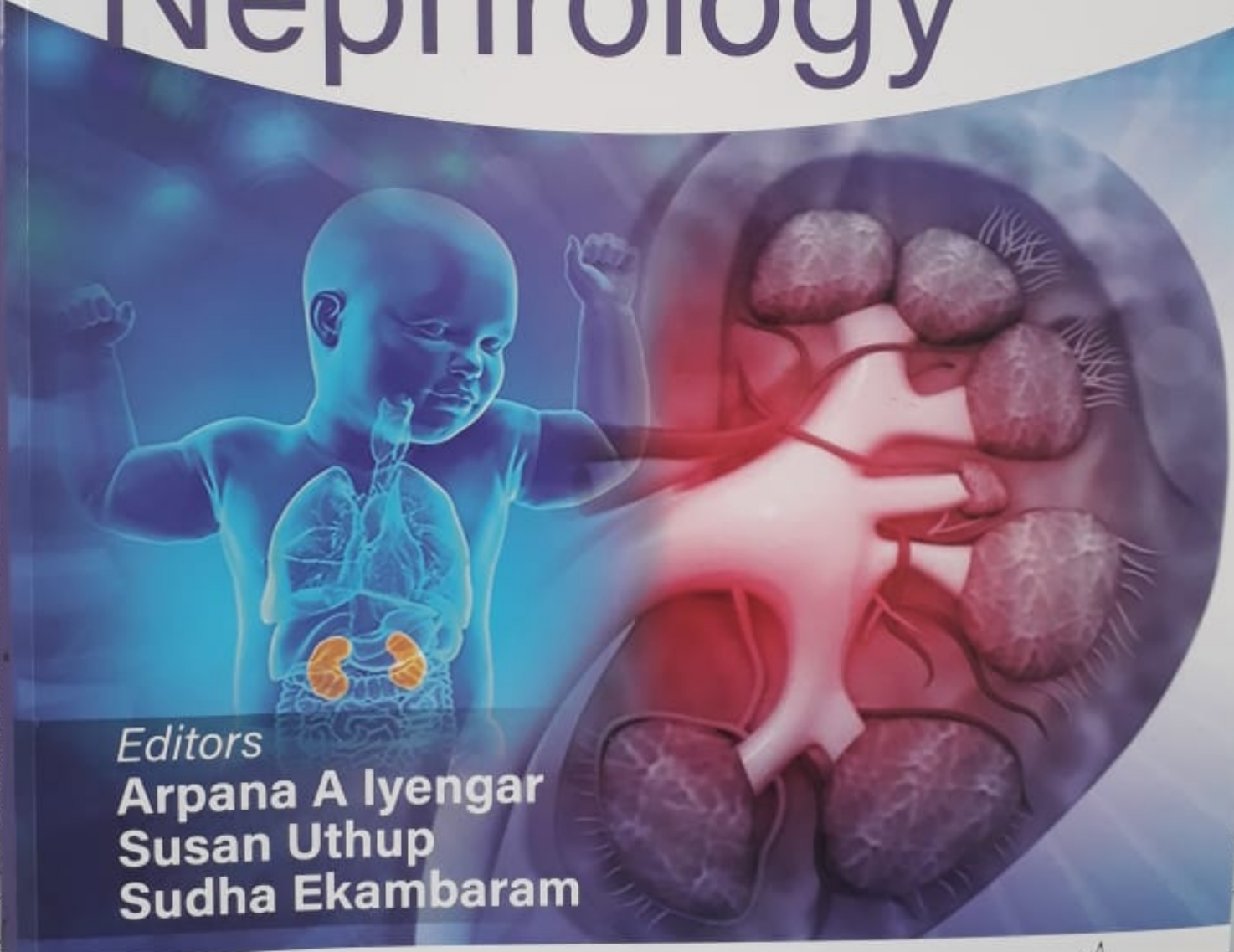

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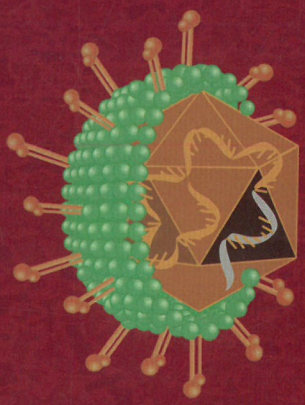

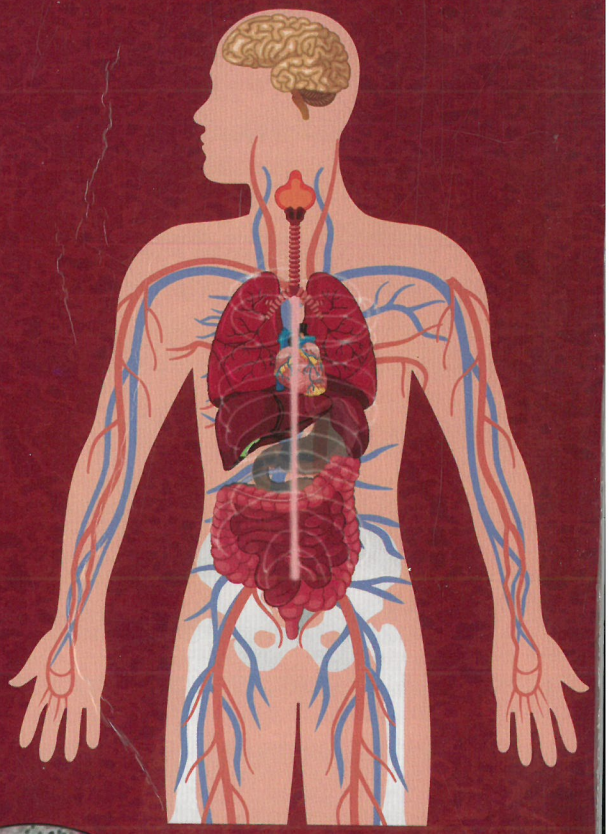

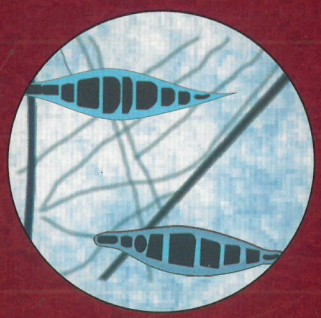

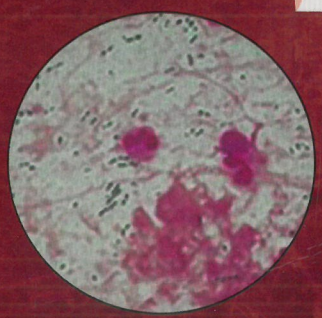

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chapter 41 PARASITIC INFECTIONS OF RESPIRATORY SYSTEM

Dr. M.B. Nagamoti

Specific Learning Objectives

- Parasites Infecting the Respiratory System, Clinical Features, Life Cycle, Laboratory Diagnosis, Treatment, and Prevention

Introduction

Parasitic infections were earlier predominant in tropical and subtropical areas however, urbanization, climate changes, wide international travel, increased use of immunosuppressive drugs, and a rise in the number of people living with compromised immune systems have enabled the parasites to prevail even in the non-endemic regions. The respiratory system can be affected by a wide range of protozoal and helminthic parasites as part of their developmental phases (life cycle) habitat (Table.1). Parasitic lung infections can remain silent, or present with protean and nonspecific manifestations making the disease diagnosis a challenging task. Thus the physician needs to obtain a detailed patient's history, dietary habits, occupation, and travel that aid in the accurate diagnosis of parasitic lung diseases. In addition, being aware of the epidemiology, life cycles, and clinical presentation, of such diseases, is essential for prompt and accurate diagnosis, and treatment of patients.

PROTOZOAN INFECTIONS OF LUNG

Pulmonary amebiasis occurs rarely as a complication of intestinal amebiasis caused by *Entamoeba histolytica.* The active trophozoites can infiltrate the intestinal mucosa and enter into circulation or local expansion of the amoebic liver abscess into surrounding tissues can result in pleuropulmonary amebiasis. Immunocompromised individuals especially those infected with HIV are more prone to develop invasive amebiasis.

Diagnosis is made by wet mount microscopic examination of sputum which may exhibit trophozoites. These are pathognomonic of invasive amebiasis of the lung. Antibody detection by indirect hemagglutination, ELISA and immunofluorescence tests are helpful in the majority of cases. The latex agglutination test is rapid and simple and can be used for screening.

Pulmonary Leishmaniasis

Visceral leishmaniasis is caused by Leishmania donovani which is transmitted by the sand fly. Pulmonary leishmaniasis can manifest as pneumonitis, pleural effusion, and lymphadenopathy. Amastigote forms of the parasite can be found in the alveoli and lymph node biopsies. Leishmaniasis can be diagnosed by examining the bone marrow aspirates for the parasites or by detecting amplified leishmania antigen by PCR.

Pulmonary Manifestations of Malaria

Pulmonary involvement in malaria is a highly fatal condition, which can occur as a complication of malaria. It is caused by Plasmodium falciparum and spread by Anopheles mosquitoes. The condition can rapidly progress into Acute Respiratory Distress Syndrome (ARDS). Laboratory diagnosis is carried out by examining Giemsa stained thick and thin blood smears for parasitic forms. Other tests such as fluorescent microscopy, Quantitative buffy coat (QBC), histidine-rich protein (HRP) antigen detection, indirect immunofluorescence test, indirect hemagglutination, and ELISA for antibody detection can be used.

Pulmonary Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite, Toxoplasma gondii. Cats are the definitive hosts of T. gondii. Man acquires infection after eating contaminated or undercooked food. The disease is common in HIV-infected patients. Pulmonary manifestations include,

Disease/Agent	Mode of Infection	Clinical Features	Diagnostic Features
Protozoa Infections			
Pulmonary amebiasis *E.hystolytica*	Ingestion	Fever, abdominal pain, lung abscess	Lung biopsy shows trophozoites of E.hystolytica
Pulmonary leishmaniasis *L.donovani*	Sand fly borne	Pneumonitis, pleural effusion, mediastinal lymphadenopathy	Lymph node biopsy shows L.donovani
Pulmonary malaria *Plasmodium falciparum*	Mosquito borne	Cough, fever, Acute Respiratory Distress Syndrome (ARDS)	Non specific
Pulmonary babesiosis *B.microti, B.divergens*	Tick-borne	Fever, ARDS	Non specific
Pulmonary toxoplasmosis *T.gondii*	Ingestion	Lymphadenopathy, interstitial pneumonia,	Lung biopsy shows tachyzoites of T.gondii
Cestode Infections			
Pulmonary hydatidosis *E.granulosus*	Ingestion	Cough, chest pain, hemptysis	Hydatid cyst with scolices
Trematode Infections			
Schistosomiasis *S.haematobium, S.mansoni,S. japonicum*	Skin penetration	Katayama fever, pulmonary hypertension	Raised eosinophils in BAL fluid, no parasites
Paragonimiasis *P.westermani*	Ingestion of infested crustaceans	Fever, cough, hemoptysis, chest pain	Sputum shows eggs of P.westermani
Nematode Infections			
Ascariasis *A.lumbricoides*	Ingestion	Cough, dyspnea, wheeze, eosinophilic pneumonia	Microfilaria in sputum/BAL, Raised eosinophils in BAL fluid
Hook worm infection *A.duodenale, N.americans*	Skin penetration		
Strongyloidiasis *S.stercoralis*	Skin penetration		
Tropical pulmonary eosinophilia *W.bancrofti, B.malayi*	Mosquito borne		Marked eosinophilia Microfilaria in peripheral smear
Visceral larva migrans *T.canis, T.catis*	Ingestion		Non specific
Trichinellosis *T.spiralis*	Ingestion		

Table1. Details of common parasitic infections of respiratory system

diffuse interstitial or necrotizing pneumonia The patients can present with severe myalgia and generalized lymphadenopathy.

Diagnosis of toxoplasmosis is based on the detection of the bradyzoites of *T. gondii* in body tissue. The trophozoites have been found in BAL and lung biopsy. Active infection is detected based on demonstrating trophozoites in body fluids A real-time PCR-based assay in BAL fluid. Serological tests can support the diagnosis.

PULMONARY INFECTIONS BY CESTODES

Echinococcosis/Hydatidosus

Human hydatid illness is caused by *Echinococcus granulosus* and *E. multilocularis*.

Man can get infected by being in close contact with definitive hosts, such as dogs, or by consuming food contaminated with parasite eggs.

Normally the parasites reside in the liver; from here they migrate to various places of the body through the bloodstream and lymphatic circulation. Pulmonary symptoms include cough, fever, dyspnea, and chest pain. In endemic locations, early identification is possible using ELISA and indirect hemagglutination assays.

Demonstration of scolices and hooklets of the parasite in vomitus, urine, and sputum is pathognomonic. Needle aspiration is dangerous as leakage may induce anaphylactic shock

An increased specific serum IgE and eosinophilia may be observed. Serological tests have been used with varying results. The Casoni's test involves the injection of hydatid fluid in the dermis which produces an erythematous papule in 50-80% of patients in less than 60 minutes. This test is useful when it is strongly positive; at times a false negative test is due to an infected cyst. Casoni's test

remains positive for life.

Other serological techniques, like Elisa, immunofluorescence antibodies, and indirect hemagglutination, have been used in the diagnosis.

Pulmonary Infections by Trematodes

Schistosomiasis

It is one the commonest helminthic infections caused by, S.haematobium, S. mansoni, and S. japonicurn. People acquire the infection when they come in contact with fresh water that contains cercaria/larva, which penetrates the skin to enter the liver, lungs, and various other organs. Patients present with shortness of breath, wheezing, dry cough, and myalgia (Katayama fever), and with signs of hepatosplenomegaly and eosinophilia.

Rectal biopsy or microscopic analysis of feces and urine is used to confirm the diagnosis. ELISA tests may be utilized for screening purposes.

Paragonimiasis

Paragonimiasis is caused by *P.westermani*, the disease is acquired by consuming larvae (metacercaria) that present in the undercooked crab/crustaceans. On entry, larvae penetrate the intestinal wall, and migrate through the diaphragm and the pleura, into the bronchioles.

Life Cycle

1. The eggs are produced by mature adult worms which are excreted in the sputum or stool.
2. The eggs grow in the environment and hatch into miracidia, which are consumed by snails.

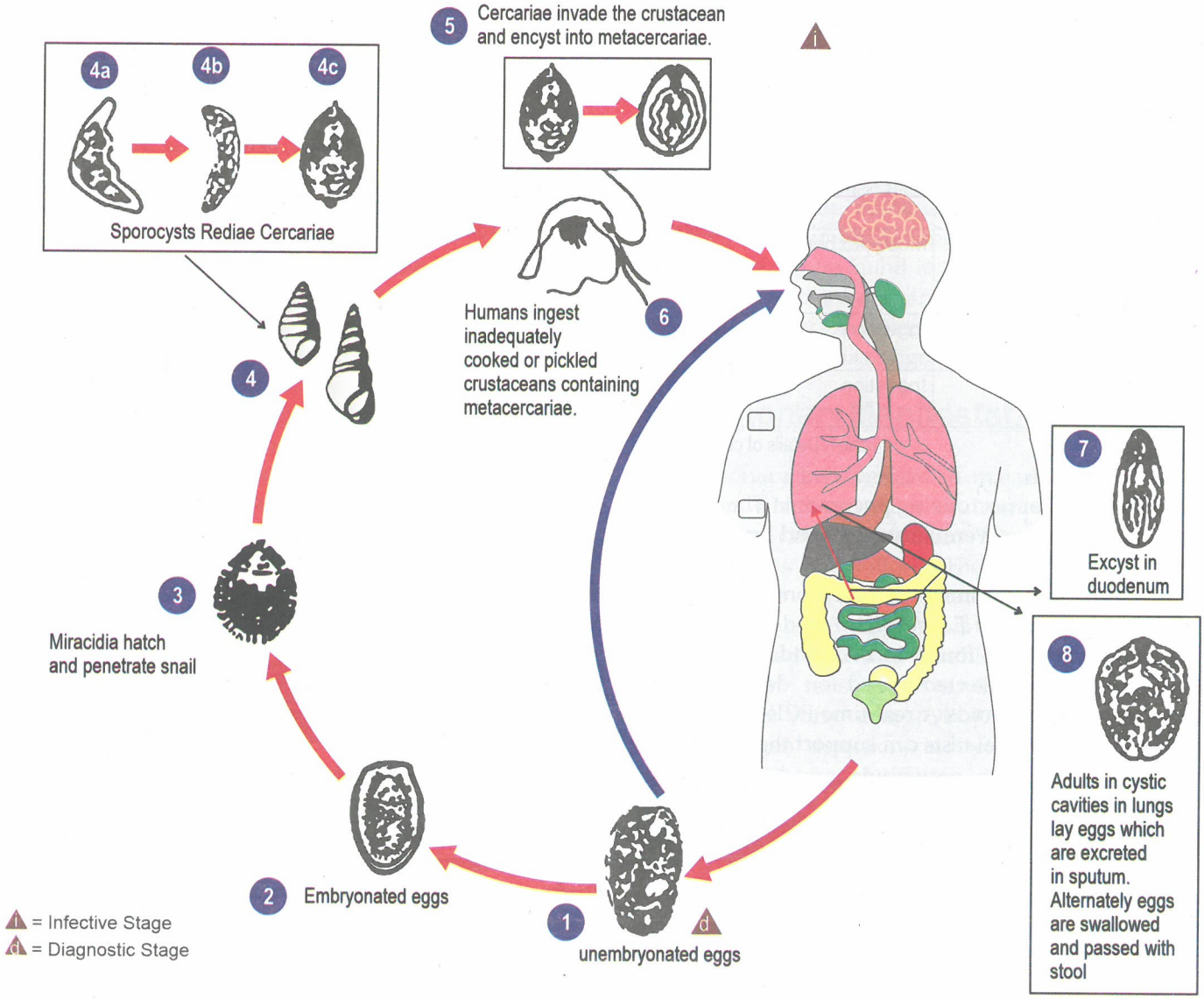


Figure. 1 Life cycle of Paragonimiasis

Source; https://www.cdc.gov/parasites/paragonimus/biology.html

3. Miracidia passes through sporocysts, radiae, and cercarial stages.

4. Cercariae infect crabs and crayfish, causing cysts (called metacercariae).

5. Cysts in raw, undercooked, or pickled freshwater crabs or crayfish cause infection in humans.

6. The larvae move through the diaphragm and into the lungs after penetrating the intestinal wall. Adults mature there and lay eggs, which are passed in sputum, which is coughed up and spat out or ingested. The eggs are approximately 80X45 µm in dimension, ovoid, and have a thick shell with a characteristic operculum.

Clinical Presentations

Patients can present with sudden onset fever, chest pain, and cough with hemoptysis.

Sputum is typically rusty and may contain eggs and Charcot-Leyden crystals. The disease may progress to bronchiectasis, pleural effusion, and fibrosis. The disease sometimes mimics pulmonary tuberculosis.

Laboratory Diagnosis

Diagnosis is made by the detection of eggs in sputum or stools. The diagnosis is confirmed by the presence of eggs or larvae in the sputum sample. Serological tests with ELISA and a direct fluorescent antibody (DFA) are highly sensitive and specific for establishing the diagnosis.

Microscopy

Sputum samples collected in the morning are appropriate for a direct wet smear investigation of parasite eggs. Numerous Paragonimus ova and Charcot-Leyden crystals are commonly seen in the rusty brown or blood-stained sputum.

Stool examination for Paragonimus ova is recommended in children who usually swallow sputum and in patients whose sputum samples are negative for ova. (Figure.3)

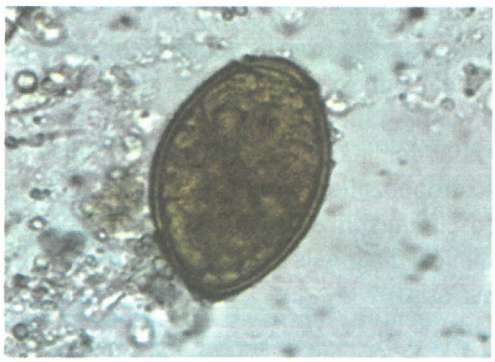


Figure.3 Egg of Paragonimus species in unstained sputum preperation.
Source; https://www.cdc.gov/dpdx/paragonimiasis/index.html

Immunodiagnosis

Intradermal (ID) test, complement fixation test (CFT), immunodiffusion, indirect haemagglutination test (IHA), ELISA, and Western blot are among the immunological tests that have been explored.

PULMONARY INFECTIONS BY NEMATODES

Ascariasis

Ascaris Lumbricoides is the most common parasitic infestations transmitted through the feco-oral route. Ascaris larvae migrate to the lungs through the portal venules or lymphatics and result in Loffler's syndrome, consisting of wheezing, pulmonary infiltrations

The diagnosis of pulmonary ascariasis is challenging. Ascaris larvae may be occasionally found in the sputum, stool examination is generally negative for eggs since, the adult worms are absent in the intestine. A high index of suspicion and serological tests can support the diagnosis.

Ancylostomiasis (Hookworm Disease)

Ancylostoma Duodenale and ***Necator Americanus*** can involve the lungs as part of the migratory phase of their life cycle resulting in a hypersensitivity reaction and pneumonitis and alveolar hemorrhage. This is typically described as Loffler's syndrome. Sputum examination may reveal occult blood, eosinophils, and rarely, the motile larvae.

Strongyloidiasis

Strongyloides Stercoralis is endemic in the tropical area,

The mode of infection is through skin penetration by the filariform larvae. The larvae then migrate into soft tissues and enter the lungs via the bloodstream. There is a possibility of autoinfection and hyperinfection in strongyloidiasis.

The hyperinfection syndrome is mostly seen in immunocompromised patients with acute and severe pulmonary symptoms, a large number of larvae may be found in stool and sputum. ELISA is used to measure IgG responses to the Strongyloides antigen.

Tropical Pulmonary Eosinophilia

Tropical pulmonary eosinophilia (TPE) is typically a hypersensitivity reaction to microfilaria of *Brugia malayi* and *Wuchereria bancrofti*. It is a mosquito-borne infestation.

Occasionally, microfilaria can be identified on bronchial brushings or lung biopsies

Diagnosis is done based on the history of persons living in the endemic area chronic and severe eosinophilia. Haemagglutination and Elisa tests are done to detect anti-filarial antibodies in the serum. Predominant eosinophilia is characteristic of this condition. Detection of micro-filaria in the lymph nodes, and lung tissues is the gold standard.

Visceral Larva Migrans

Toxocariasis

A clinical syndrome comprising eosinophilia, hepatomegaly, and pneumonitis due to prolonged migration of the nematode larvae into human visceral tissues. The most common causes are *Toxocara. canis* and *Toxocara. Cati.* They are the roundworms that primarily affect the dog and cat respectively. They can accidentally cause eosinophilic lung disease in humans. It is transmitted through the ingestion of food contaminated with parasite eggs.

Patients present with fever, cough, wheezing, and seizures. The diagnosis is done by the typical history of exposure to dogs, clinical findings of eosinophilia, hepatomegaly, and hypergammaglobulinemia, and laboratory confirmation of detecting larval antigens by ELISA and demonstration of larvae in the eosinophilic granuloma.

Trichinella Infection

Trichinellosis is caused by *Trichinella spiralis,* it is acquired by consuming undercooked pork containing larval forms of the parasite. Patients can present with dyspnea due to the production of pulmonary infiltrates and involvement of respiratory muscles. The diagnosis is done by, demonstration of *T. spiralis* larvae in muscle biopsy and *Trichinella* IgG antibodies by ELISA.

Multiple Choice Questions

1. A 45 year old man, from north eastern India presented with symptoms of cough with hemoptysis, fever with loss of weight for six months. He was treated with antitubercular drugs but failed to respond. He gave the history of dietary consumption of crabs. Sputum wet mount examination showed operculated oval structures. Which of the following is the likely pathogen involved in this case?

a. Atypical Mycobacteria
b. T. gondi
c. P. westermani
d. Y.pseudotuberculosis

2. A, 63 year old women presented with fever, cough with hemoptysis for more than six months. She was treated by the local practitioner but failed to respond. She gave the history of consuming improperly cooked crabs. Her sputum was negative for acid fast bacilli but, showed parasitic ova. What is the likely pathogen associated with this condition?

a. L.loa
b. W.bancrofti
c. H.nana
d. P.westermani

3. A two year old girl was brought to the hospital with history of fever and cough and dyspnea. On chest examination showed pneumonitis like picture. Her mother gave the past history of child passing whitish long worms in the stool and having the habit of mud eating (geophagia). Which of the following agent is likely to be associated with this condition?

a. S. stercoralis
b. W.bancrofti
c. E. granulosis
d. A.lumbricoides.

4. A 48 year old man was admitted with fever and cough. He was found to have swollen left leg and microfilaria detected in the bronchial brushings. What is the likely diagnosis in this case?

a. Babesiosis
b. Malaria
c. Pulmonary amoebiasis
d. Pulmonary tropical eosinophilia

5. A known HIV seropositive patient developed fever, cough, severe myalgia and generalized lymphadenopathy. On examination, trophozoites were found in BAL fluids and the tachyzoites were demeonstrated in lymph node biopsy. Patient is likely to be suffering from which of the flollowing condition?

a. Hydatidosis
b. Schistosomiasis
c. Toxoplasmosis
d. Pulmonary tropical eosinophilia

6. A 45 year old male from endemic area, was admitted to the hospital with low grade fever, cough and wheezing for the past 3-4 months. Past history of chronic dysentery and abdominal pain was present. Her lung biopsy showed trophozoites of of a parasite. Her chest X-ray showed circumscribed collections of pus. What is the likely clinical diagnosis?

a. Babesiosis
b. Malaria
c. Amoebiasis
d. Toxoplasmosis

FUNGAL INFECTIONS OF RESPIRATORY SYSTEM

chapter 42

Dr. M B Nagamoti

Specific Learning Objectives

- Fungus Infecting the Respiratory System, Clinical Features, Laboratory Diagnosis, and Treatment.

Introduction

Fungal respiratory infections are on the rise; with invasive aspergillosis being on the top of the list. They form the important causes of morbidity and mortality in immunocompromised persons. Pulmonary fungal infections are caused by endemic or opportunistic fungi. The endemic mycoses are known for their ability to cause disease in otherwise healthy individuals. Fungi can affect the lungs through direct invasion, or by initiating a hypersensitivity reaction when the fungal forms are inhaled. Recent years have witnessed an increasing number of people living with immunocompromised states due to various causes.

Some endemic fungi can cause primary fungal pneumonia, while others that commonly exist in the environment can cause opportunistic infections in the immunosuppressed hosts (Table. 1). Pulmonary infections occur either by the reactivation of latent infection or through dissemination from the primary site, the latter most commonly occurs in the immunocompromised patients. In such cases, severe disseminated infections can be observed in the nervous system, liver, kidneys, heart, and eyes. The diagnosis of pulmonary fungal infection can be challenging due to nonspecific clinical presentation and the need for invasive tests. Although such infections are uncommon, early diagnosis and prompt and specific treatment is important to reduce the associated life-threatening complication.

Table.1 Types of fungal respiratory infections and causative agents

Type	Fungi	Disease
Endemic fungal pneumonia	*Histoplasma capsulatum*	Histoplasmosis
	Coccidioides immitis	Coccidioidomycosis
	Blastomyces dermatitidis	Blastomycosis.
	Paracoccidioides brasiliensis	Paracoccidioidomycosis.
Opportunistic fungal pneumonia	*Aspergillus* spp.	Aspergillosis
	Candida spp.	Candidiasis
	Pnuemocystis carini	Pneumocystis pneumonia
	Mucor spp.	Mucormycosis.
	Cryptococcus neoformans.	Cryptococcosis
	Sporothrix schenkii	Sporotrichosis

ENDEMIC FUNGAL PNEUMONIA

Histoplasmosis

Histoplasmosis is the commonest fungal pulmonary infection worldwide. It is also called the Cave disease, Darling's disease, or Ohio valley disease. Histoplasmosis is caused by Histoplasma capsulatum which is endemic in the Ohio River valley. Although the disease primarily affects the lungs, other organs may be involved in disseminated histoplasmosis which can be fatal if left unattended. The disease is common among HIV/AIDS patients. Infection occurs by inhalation of spores that germinate and transform into budding yeast cells in the lungs. Acute histoplasmosis presents with flu-like illness,

while chronic cases can present with tuberculosis-like symptoms. The disseminated histoplasmosis presents with varied clinical manifestations and can pose diagnostic challenges.

The fungus is thermally dimorphic, existing in the mycelial form in the environment and yeast at body temperature.

Laboratory Diagnosis

Specimens that are collected in invasive histoplasmosis are blood, bone marrow, and biopsy specimens. Rapid diagnosis of disseminated histoplasmosis can be established by, microscopic examination of the clinical specimen after staining with Wright, Giemsa, PAS, or methenamine silver stains. *H. capsulatum* is seen as small, oval yeast cells (2-5 um in diameter), with narrow-based unequal budding and typically packed inside the cytoplasm of macrophages or monocytes. Yeast forms typically occur in clusters (Figure. 1)

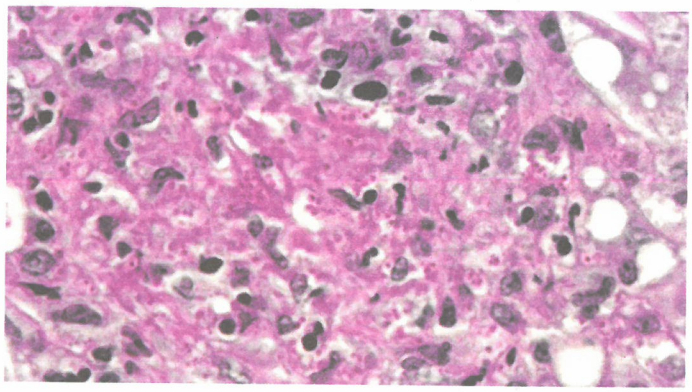


Fig.1 Micrograph showing histoplasmosis (clumps of small bright red circles) by PAS stain. (Source; https://wikipedia.org)

Culture

Specimens are cultured in enriched blood agar at 37°C and Sabouraud's dextrose agar (SDA) or inhibitory mold agar at 25-30°C. On SDA, white to tan fluffy colonies are formed with septate branching hyphae.

Serological tests like, radio-immunoassay or ELISA are used for the detection of specific antibodies or antigens in serum. Histoplasmin skin test becomes positive soon after infection and remains so for many years. The test does not differentiate active from past infections. It has limited value in invasive infections. The test can be positive in 90% of the people living in endemic areas.

COCCIDIODOMYCOSIS

Coccidioidomycosis is also known as Valley fever, California fever, or Desert rheumatism, caused by *Coccidioides immitis* or *C. posadasii*. It is one of the endemic fungal diseases, which mainly affects the lungs. *C. immitis* is a dimorphic fungus that exists as a mycelium in the soil and as a spherule in the host at 370C. The infection is caused by inhalation of spores (arthroconidia) that are present in the soil. The acute pulmonary stage is characterized by lung consolidation, adenopathy, and pleural effusion, and the chronic phase by nodulations, cavities, fibrosis, and bronchiectasis.

The disease can present in three different clinical types, primary pulmonary, primary cutaneous, and disseminated coccidioidomycosis. Few patients present with flu-like illness with fever, cough, headaches, rash, and myalgia, while others present with chronic pulmonary symptoms such as malignancies. In HIV/AIDS patients, it can manifest with widespread invasive infections.

Laboratory Diagnosis

The specimens include Sputum, pus, and biopsy material. Demonstration of fungal spores in sputum and biopsy tissue is confirmatory. Morphological identification of coccidiodes can also be done from fungi grown on SDA medium. The arthroconidia are highly infectious and thus the culture should be attempted only in category-3 laboratories with high containment facilities. Serological tests such as the precipitin test, latex agglutination test, and complement fixation test can be employed. Skin tests with coccidioidin when performed may turn positive in three days to three weeks. Molecular methods like PCR can aid in direct detection of fungal antigens from a clinical specimen.

BLASTOMYCOSIS

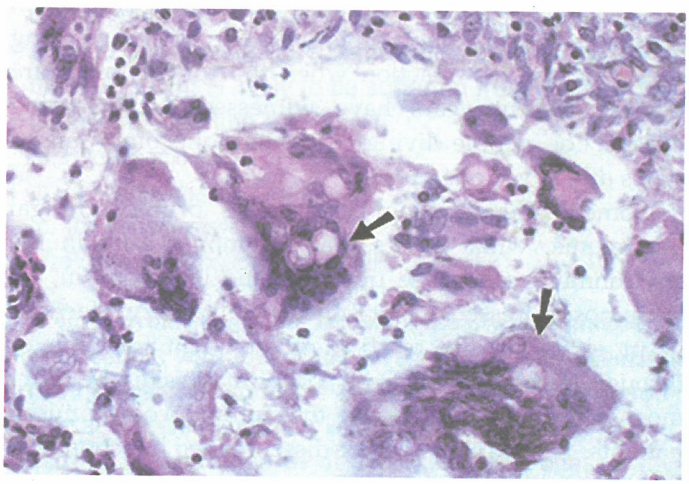


Figure.2. Large yeast-like fungi seen within giant cells (Source; https://wikipedia.org)

Blastomycosis also known as Gilchrist's disease, is caused by *Blastomyces dermatitidis*. Infection occurs by inhalation of the fungal mycelia from the soil. The mycelia will transform into yeast form in the lungs which may

disseminate through the blood and lymphatics to other organs, including the skin, bone, genitourinary tract, and brain (Figure.2). The incubation period is from one-three months. The disease can remain asymptomatic, or may present similar to histoplasmosis.

Laboratory Diagnosis

The diagnosis of blastomycosis is done by demonstration of the characteristic, broad-based budding organisms in sputum or tissues by KOH preparation or histopathological studies.

Fungal-specific antigens can be tested from urine, which is reliable in cases where the organism is not readily detected. Fungal culture is the gold standard diagnostic method however; the fungi require longer incubation periods to yield growth.

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis is an infection caused by the dimorphic fungus *Paracoccidioides brasiliensis*. The disease is endemic in central and South America, and usually involves the skin and lungs of the people who work in the fields. A severe and progressive form of the disease is seen in the immunocompromised hosts. Infection occurs by inhalation of airborne fungal spores. In the lungs, the spores are converted to yeasts that may spread to other sites. Patients with pulmonary paracoccidioidomycosis present with fever, cough, breathlessness, lymphadenopathy, hepatosplenomegaly, and weight loss. Laboratory diagnosis is established by histopathological examination of tissue samples after staining with Gomori methenamine silver (GMS) stain or hematoxylin and eosin (H&E) for demonstration of large yeast cells with translucent cell walls with multiple buds. (Figure.3)

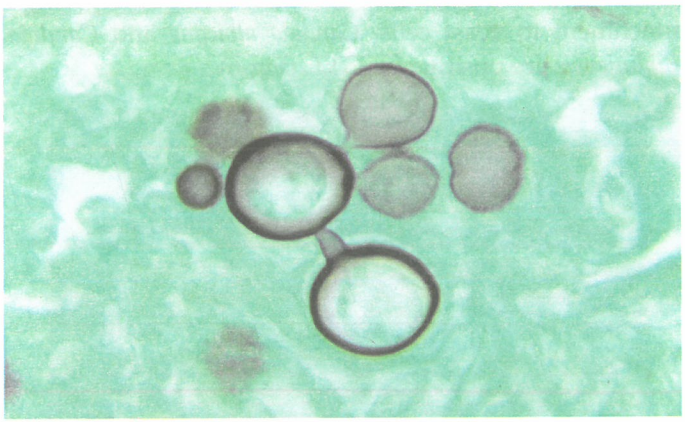


Figure.3 GMS stained tissue section of Paracoccidiodes.
(Source; https://wikipedia.org)

The culture of P. brasiliensis is cumbersome and requires two-four weeks. Demonstration of its ability to grow at room temperature initially (Mycelial form) and, at to 37°C (yeast form) is confirmatory. Antibody detection can help for rapid disease diagnosis and monitoring. Although serological tests are nonspecific, Gel immunodiffusion, Complement fixation can be adopted.

OPPORTUNISTIC FUNGAL PNEUMONIAS

ASPERGILLOSIS

Pulmonary aspergillosis is one of the commonest opportunistic fungal infections associated with significant mortality. The fungi of the genus Aspergillus are widely distributed in the environment. They primarily involve the lungs causing progressive cavitatory lesions however; in 40% of patients, extrapulmonary sites may be affected. Aspergilloma, or fungus ball, can be formed in the preformed lung cavities. The disease can be asymptomatic in 30% of patients and may present with fever, dyspnea, cough, and pleuritic chest pain in others. Pulmonary aspergillosis may also mimic lung neoplasm. Mortality and morbidity can be curtailed by early diagnosis and prompt treatment.

Laboratory Diagnosis

Bronchoalveolar lavague (BAL), blood, and tissue biopsies are suitable for the diagnosis of invasive aspergillosis. Samples are examined for the presence of fungal elements by wet mount preparation in 10% potassium hydroxide. Tissues specimen can be stained by the Periodic acid Schiff (PAS) and hematoxylin and eosin methods. Typical dichotomous branching at an acute angle is characteristic of aspergillus infection.

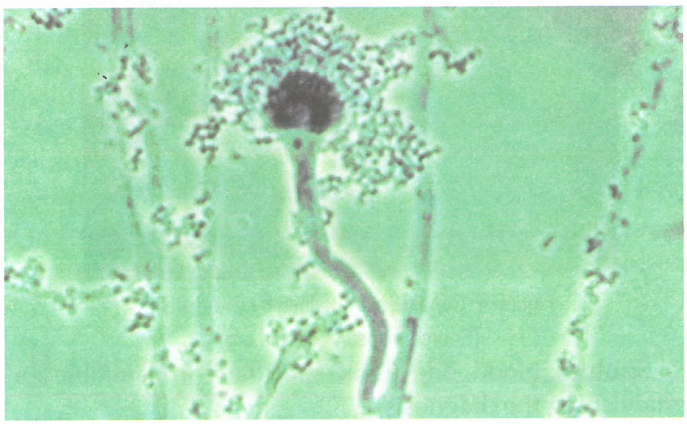


Figure.3 Lactophenol cotton blue stained Aspergillus fumigatus.
(Source; https://wikipedia.org)

Fungal culture on SDA is imperative for specific diagnosis. Demonstration of septate hyphae and

vesicle in the clinical specimen is essential to establish the pathogenicity of clinical isolates in culture. The microscopic appearance of the colony on wet mount preparation stained with lactophenol cotton blue demonstrates the fungal morphology characteristic to the genus and species, helping in specific identification. (Figure. 3)

Detection of galactomannan antigen of Aspergillus in serum is a marker of invasive aspergillosis. The neutrophilic predominance in aspergillus infections is yet another supportive finding.

CANDIDIASIS

Pulmonary candidiasis is rare and mostly occurs as a consequence of disseminated candidiasis in immunocompromised persons. *Candida* spp., are found as normal commensals in the upper respiratory tract and other mucous membranes and can become an opportunistic pathogen in high-risk individuals like those on prolonged antibiotics, anti malignant drugs and corticosteroids. Also the preterm neonates, patients with neutropenia, post-transplantation, diabetes, AIDS, and severe burn wounds are susceptible to pulmonary candidiasis.

Etiopathogenesis

Until recently, Candida albicans was the common causative agent however, non-C. albicans species have gradually increased. C. parapsilosis, C. krusei, C. glabrata, C. tropicalis, and C.guilliermondii are among the frequently isolated noncandida albicans group.

Laboratory Diagnosis

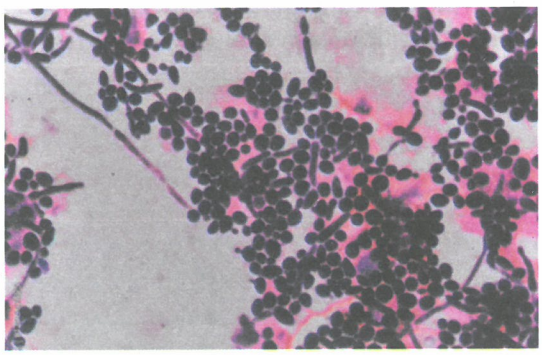


Figure. 4 Candida spp. Stained by Gram stain.
(Source; https://wikipedia.org)

Sputum, blood, and tissue specimens are suitable for establishing the diagnosis.

Direct Microscopy; Gram staining; can demonstrate yeast and pseudohyphae of candida species. The yeast cells are approximately 4-8 µm with budding and pseudohyphae. The presence of pseudo hyphae indicates colonization and tissue invasion hence their demonstration from the direct clinical sample/tissue is highly significant. (Figure. 4)

KOH with calcofluor white can detect the budding yeast-like forms with pseudo hyphae under the fluorescence microscope. It is important to confirm the pathogenicity of the organisms isolated from respiratory secretions since; they can merely represent asymptomatic colonization. Hence, direct demonstration of pseudohyphae from clinical specimens is valuable.

Culture

Clinical specimens are cultured on blood agar or Sabouraud dextrose agar with antibacterial antibiotics and incubated at 25°C and 37°C. Colonies appear in 2-3 days as cream-colored, smooth and pasty. (Fig-5)

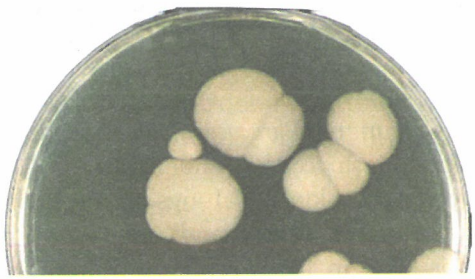


Figure.5. Candida colonies on Sabouraud dextrose agar
(Source; https://wikipedia.org)

Test of species identification; Germ tube test (GTT)/Reynolds Braude phenomenon; It is used for presumptive identification of *Candida albicans*. Candida colonies are treated with bovine, sheep, or human serum and incubated at 37°C for two to four hours. A drop of suspension is examined under the microscope. The germ tubes are seen as long tube-like projections extending from yeast cells. Germ tubes can be differentiated from pseudo hyphae as there is no constriction at the point of attachment to yeast cells. *Candida albicans* and *Candida dubliniensis* are positive for GTT. (Fig-6)

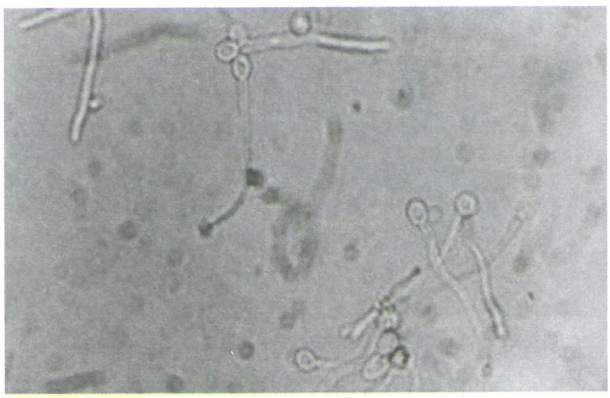


Fig-6. Germ tube test, showing Candida spp. (Source; https://wikipedia.org)

Chlamydospore Formation (Dalmau plate culture); Candida isolates are is grown on Cornmeal agar / Rice starch agar and incubated at 25°C for two-three days. Microscopic observation of culture plate shows large highly refractile, thick-walled, terminal chlamydospores. This test is positive by *C.albicans* and *C.dubliniensis.*

Biochemical tests like sugar fermentation and sugar assimilation are of immense importance for the identification and speciation of the yeast isolates.

Chromogenic media; are used for simultaneous isolation and identification. This medium distinguishes different candida species by distinct color production. Similarly, the ability of Candida species to grow at 45°C differentiates them from other species.

Serological and Molecular tests; Candida-specific antigens such as cell wall mannan and cytoplasmic antigen can be detected by ELISA and specific antibodies can be detected by ELISA and latex agglutination tests. Serological tests are also available for the detection of candida-specific enzymes and metabolites. Molecular tests such as RFLP (restriction fragment length polymorphism), Southern blotting, and, in situ hybridization are used for research purposes.

PNEUMOCYCTOSIS

Pneumocystis pneumonia (PCP) or *pneumocystosis* is caused by the yeast-like fungus Pneumocystis jirovecii (earlier considered as a protozoan) and is known to infect only human beings. Pneumocystis pneumonia is especially seen in people with cancer, HIV/AIDS, and the use of medications that affect the immune system. The risk increases when CD4 + cell counts drop below200 cells/µl.

Symptoms of PCP include fever, dry cough, dyspnea, weight loss, and night sweats. In the minority of cases, pneumocystis can invade other organs.

Laboratory Diagnosis

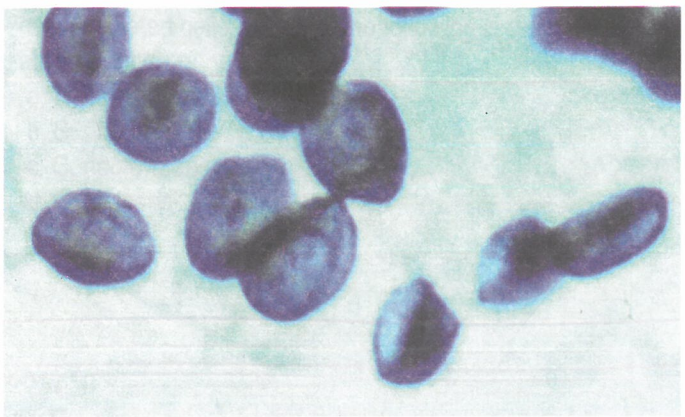


Figure. 7 Pneumocystis jirovecii cysts from bronchoalveolar lavage, stained with Toluidine blue O stain (Source; https://wikipedia.org)

Specimen: Induced sputum, BAL fluid, or lung biopsy

Microscopy: The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or BAL. Staining with toluidine blue, silver stain, periodic-acid Schiff stain, or an immunofluorescence assay will demonstrate the characteristic cysts. The cysts resemble crushed ping-pong balls and are present in bunches of two-eight. (Figure. 7)

Culture: The organism cannot be grown on culture media.

Serology: Complement fixation test, latex agglutination, and ELISA tests can be used.

Molecular tests such as DNA probe, PCR, and Southern blot hybridization can help to detect organisms directly from BAL fluid or sputum.

MUCORMYCOSIS

Mucormycosis is caused by fungi belonging to the phylum Zygomycota which are commonly present in the humid environment. Mucorales from the genera Mucor, Rhizopus, Rhizomucor, and Apophysomyces are pathogenic to humans. Common species are pathogenic to humans. Common species are the Rhizopus *arrhizus, Rhizopus microsporus, Rhizomucor pusillus, and Apophysomyces variabilis..*

Etiopathogenesis

The disease is known to affect individuals with weak immune systems and recently there has been a sudden surge of mucormycosis due to the Covid-19 pandemic. However, mucormycosis has also been reported among immunocompetent individuals particularly, mostly caused by Apophysomyces elegans.

Infection occurs by inhalation of spores in the air or through damaged skin or mucous membranes. Patients with diabetes and immunosuppression, particularly those with monocytic and granulocytic deficiencies and those on glucocorticoid therapy are at higher risk of disease development. Impaired cellular immunity and elevated glucose levels can favor fungal growth. The most common form of the disease is rhino-orbital-cerebral mucormycosis, followed by pulmonary mucormycosis with high mortality. Pulmonary mucormycosis presents with fever, cough, chest pain, and dyspnea.

Laboratory Diagnosis

KOH wet mount and Histopathology examination (H&E and PAS stain) of direct and fixed preparations from BAL, biopsy specimens, and surgical resection specimens shows characteristic broad, non-septate, ribbon-like

hyphae with wide-angle or right-angle branching at irregular intervals.

Culture: Mucormycetes can be easily grown on SDA with antibiotics at 25°C and 37°C. The growth is cottony and dense. The sensitivity of culture is about 50%.

The microscopic appearance of the colony on wet mount preparation stained with lactophenol cotton blue demonstrates the specific fungal morphology characteristic of a particular genus and species, helping in identification.

Although ELISA may be performed to detect antibodies produced in invasive types of infections, there can be cross-reactions between other pathogenic fungi thus, serodiagnosis of mucormycosis is not recommended for routine use.

Molecular tests can be used to directly identify the fungus from tissue samples when the direct examination is positive and cultures are negative in patients with invasive mucormycosis.

CRYPTOCOCCOSIS

The incidence of cryptococcosis is on the rise; it is caused by *Cryptococcus neoformans* and *C. gattii*. The fungi are particularly present in the pigeon droppings and eucalyptus trees.

Pulmonary cryptococcosis is uncommon however, a higher infection rate is reported in HIV-AIDS patients, transplant recipients, and patients treated with anti malignant drugs or corticosteroids. It is an indicator of HIV disease progression to fulminant AIDS. The disease has been rarely reported in immunocompetent individuals as well.

Infection can occur after exposure to pigeon droppings. The presenting symptoms are cough, pleuritic chest pain, low-grade fever, dyspnea, weight loss, and malaise. Laboratory diagnosis is done by demonstration of typical morphology from respiratory secretions by Indian ink staining, growth on Niger seed/ Bird seed agar, and positive urease test. Serological and molecular tests can help in rapid diagnosis.

SPOROTRICHOSIS

Sporotrichosis is also known as rose gardener's disease. It is caused by *Sporothrix schenckii*. The disease is common in farmers and gardeners and usually involves the skin but can affect the lungs, joints, bones, and the brain.

S. schenckii is a dimorphic fungus found in soil and plants. It can enter through small cuts and abrasions in the skin or by inhalation to cause pulmonary sporotrichosis. Symptoms include cough, fever, and hilar lymphadenopathy. The severe disseminated form of the disease is seen in individuals with a compromised immune system.

Laboratory diagnosis is established by histopathological examination of tissue sections for demonstration of characteristic fungal morphology and by culture

Multiple Choice Questions

1. A 55 year old known HIV sero-positive patient was diagnosed with pneumonia and was admitted in the ICU. His CD4 counts were 90/mm^3, his broncho-alveolar lavage (BAL) fluid after staining with GMS showed cysts measuring 4-6 microns. What is the likely organism associated with this disease?
   a. T. gondii
   b. P. jirovecii
   c. H. nana
   d. C. sinensis

2. A 55 year old farmer, a known asthmatic, developed fever and chronic productive cough. He was admitted for evaluation; his chest x-ray shows lobular infiltrates and his sputum sample was sent for culture. Gram stained sputum smear microscopy showed numerous eosinophils and fungal filaments and septate hyphae with 45^0 angle branching. Name the organism associated with this infection.
   a. Aspergillus fumigatus
   b. Candida albicans
   c. Mucor spp.
   d. Cryptococcus neoformans

3. Sputum sample from a HIV reactive patient yielded dimorphic fungus on Saboraud's dextrose agar. LPCB preparation from the colony showed typical brush border appearance of the conidia. Which of the following gives such appearance?
   a. Penicillium marneffei
   b. Blastomyces dermatitidis
   c. Histoplasma capsulatum
   d. Paracoccidioides brasiliensis

4. A HIV reactive patient, on irregular antiretroviral and antitubercular therapy was admitted to the hospital on developing symptoms of pneumonia. His CD4 counts were less than 100/mm^3 and the HIV Viral load was more than 1 lakh copies. Sputum examination after negative staining revealed spherical capsulated cells. Which of the following is the likely causative agent?
   a. H. capsulatum
   b. S. pneumoniae
   c. C. neoformans
   d. C. albicans

5. Which of the following is the commonest of fungal respiratory infections?
   a. Candidiasis
   b. Mucormycosis
   c. Aspergillosis
   d. Cryptococcosis

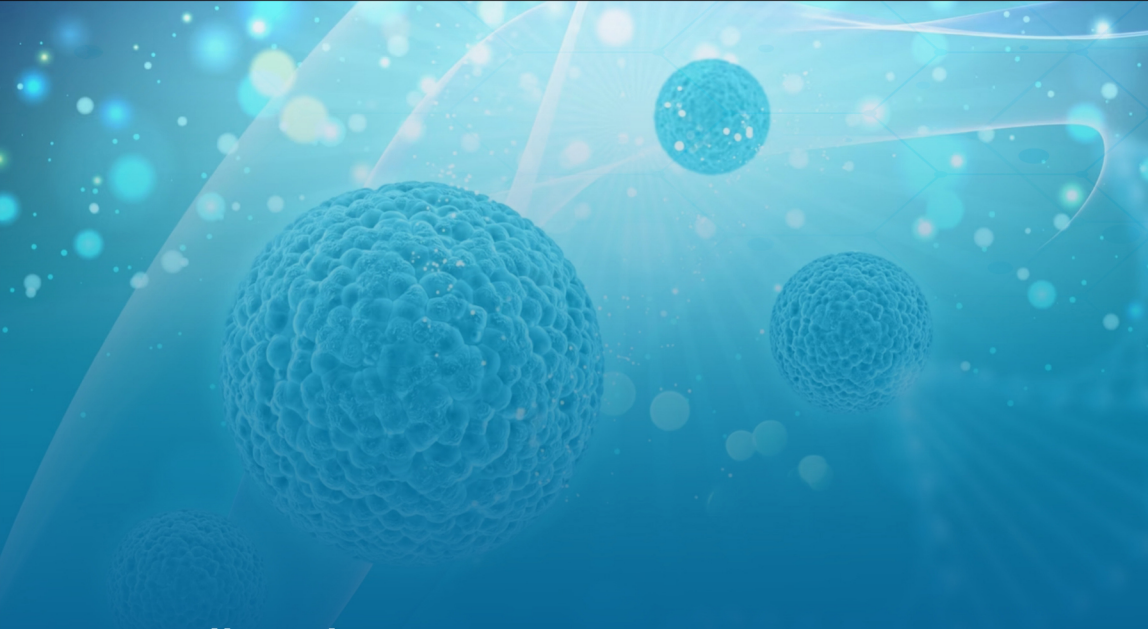
6. Which of the following is known as Darling's disease?
   a. Mucormycosis
   b. Cryptococcosis
   c. Blastomycosis
   d. Histoplasmosis

7. A 72 year old on long term anticancer and steroid therapy developed fever, cough, breathlessness, lymphadenopathy and hepatosplenomegaly. His GMS stained lung tissue specimen showed large yeast cells with translucent cell walls with multiple buds typically appearing as Mariner's wheel. What is the likely diagnosis?
   a. Blastomycosis
   b. Cryptococcosis
   c. Coccidioidomycosis
   d. Paracoccidioidomycosis

8. Which of the following is a marker of invasive pulmonary aspergillosis?
   a. Pseudohyphae on Grams staining
   b. Galactomannan antigen in serum
   c. Fungal hyphae with 'favic chandelier' appearance
   d. Dichotomous branching at acute angles on microscopy

9. Crushed ping-pong ball appearance of the cysts with toluidine blue O stain is characteristic of,
   a. H. capsulatum
   b. C. neoformans
   c. Pneumocystis jirovecii
   d. Blastomyces dermatitidis

10. Which of the following is responsible for causation of Endemic fungal pneumonia?
    a. H. capsulatum
    b. Rhizopus arrhizuz
    c. Cyptococcus neoformans
    d. Sporothrix schenkii



Handbook on MEDICAL EDUCATION

A quick reference to Medical Educators to implement essential teaching and training skills in CBME

VinodKumar Swamy (V.K. Swamy)

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HANDBOOK ON

MEDICAL EDUCATION

(A quick reference to Medical Educators to implement essential teaching and training skills in CBME)

VINODKUMAR SWAMY (V.K. SWAMY)

First Edition: 2023

ISBN: 978-93-80316-871

Published by **Tarun Ahuja**
For **Ahuja Publishing House**
Regd. Office: C-8/124B, Keshav Puram, Delhi-35 (India)
Distributed by **Ahuja Book Company Pvt. Ltd.**
4348/4C, Ansari Road, Darya Ganj, New Delhi-110002 **(India)**
Phones: 91-11-23276564, 23245859, 23289999 Fax : 91-11-23281514
E-mail: info@ahujabooks.com, sales@ahujabooks.com,
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Phones: 91-80-26670322, v26670323 Telefax: 91-80-26670321
E-mail: blr@ahujabooks.com

Printed at: S.K. Offset Shahdara India

ACKNOWLEDGEMENT

Medical education is changing to meet the demands of our evolving healthcare system. One of these changes is the development and implementation of competency-based medical education. The National Medical Commission has rolled out competency-based medical education across the country to ensure that all learners achieve the desired patient-centered outcomes during their training. CBME is an outcomes-based approach to designing, implementing, and evaluating education programs and assessing learners across the continuum that uses competencies or observable abilities. As a result, medical educators play a crucial role in shaping the next generation of healthcare professionals. This book is a valuable resource for educators, providing practical advice and guidance on how to develop and implement effective teaching strategies. It also offers insights into the latest trends and innovations in medical education, from flipped classroom models to online learning platforms.

I acknowledge the contributions of all the authors, and reviewers, who have collaborated to create it and I extend my deepest gratitude and appreciation to all who have devoted their time, expertise, and resources to creating this handbook. This endeavor will undoubtedly help to enhance the knowledge, skills, and abilities of medical professionals, ultimately leading to improved patient care and outcomes.

I sincerely thank our Patrons Sri Dr. Shamanur Shivashankarappa, Honorary Secretary, Bapuji Education Association, Davangere, Karnataka, Sri S. S. Mallikarjun, Joint Secretary, Bapuji Education Association, Davangere, Karnataka, Chairman, S. S. Institute of Medical Sciences and Research Centre, Davangere, Karnataka, Dr. B.S. Prasad, Principal, Dr. Arunkumar A, Medical

Director, Dr. N.K.Kalappanavar, Former Medical Director, Dr. Shashikala P, Vice Principal, Dr. P Nagaraj, Former Principal, Dr. Sampanna Muthalik, Member BEA, Mr. Ravi R.G, Administrative Manager, Dr. Jayasimha V.L, Professor & Head, Department of Microbiology, S. S. Institute of Medical Sciences and Research Centre, Davangere, Karnataka, for always encouraging me to grow in my profession and enduring constant support in all my achievements.

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The Book

As healthcare professionals, we all understand the importance of education in the medical field. The rapidly evolving medical landscape requires us to stay up-to-date with the latest research, technologies, and practices to provide the best possible training for students and care for our patients. In line with this, I am pleased to introduce the Handbook on Medical Education, which is a product of extensive research and collaboration among numerous respected authors and educators in the field. This book comprehensively covers the essential topics and chronicles the latest advancements, making it a valuable resource for healthcare professionals, and educators alike.

I commend the contributors for their dedication, hard work, and commitment to advancing medical education. I am confident that this handbook will serve as a valuable guide for aspiring healthcare professionals and make an outstanding contribution to the field of medical education.

The Author

Dr. VinodKumar Swamy is working as a Professor of Microbiology and Director of Molecular Laboratory at Shamanur Shivashankarappa Institute of Medical Sciences and Research Centre, Davangere, Karnataka. He has 22 years of teaching and research experience in medical colleges. He did his master's from Manipal University, Ph.D. in Microbiology from Gulbarga University, a Ph.D. in Medical Microbiology from St. Johns Medical College, Rajiv Gandhi University of Health Sciences, and a FAIMER fellow from PSG-Coimbatore. He has published 122 research articles in various National and International Journals, handled 12 funded projects (VGST, RGUHS, ICMR, VTU), guided three Ph.D. students, and contributed chapters in academic books. He is the project coordinator for the Centre of Excellence in dengue research. He is the President of the Society of Bacteriophage Research and Therapy, India, and a life member of various associations nationally and internationally. He is the editor of the International Journal of Bacteriophage Research, Journal of Educational Research, and Medical Teacher, Journal of Public Health and Medical Research, and editorial member of the Indian Journal of Immunology and Respiratory Medicine and many more. He is a frequent speaker at various national and international conferences, workshops, symposiums, CMEs, and plenary sessions. He was a member of the State Environmental Appraisal Committee, Government of Karnataka. Representative of CPCSEA, GOI at various institutes for the last 20 years. His area of research includes; AMR, Bacteriophage research, Microbiota, Molecular diagnostic, Educational Research, and Non-communicable diseases. In his illustrious career, he has been the recipient of various awards

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ISBN : 978-93-80316-871

CHAPTER

21

Newer Antiplatelet Agents

Suresh V Patted, Sameer S Ambar, Vijayanand B Metgudmath

ABSTRACT

As the chase for ideal antiplatelet drugs continues for the cardiologist, we appraise the antiplatelet drugs and also upcoming newer antiplatelet drugs along with current approvals in the treatment of ischemic heart disease.

Keywords: P2Y12 receptor antagonists, platelet glycoprotein GP IIb/IIIa, thrombosis, receptor, PAR-1, platelet aggregation.

INTRODUCTION

Antiplatelet medications play a crucial role in treating cardiovascular diseases. Although the currently approved drugs have significantly reduced the morbidity and mortality, still there are signs of undesirable bleeding, recurrent ischemia, and heart attacks. Many of the drugs are manufactured with the aim to target surface receptors or enzymes in the platelet to prevent undesirable clot formation after initial platelet activation. In antiplatelet therapy, the role of aspirin was to target the cyclooxygenase-1 (COX-1).[1] In spite of evolution in alternative drugs to inhibit platelet activity, the pharmacokinetics and pharmacodynamics of those suggest that aspirin will remain a key component of antiplatelet therapy in the future. Currently, a combined regimen of aspirin and clopidogrel is the standard treatment for prevention of thrombosis, platelet activation, and stroke.[2] However, many of the present available antiplatelet drugs have restrictions in their use because of genetic differences in metabolizing prodrugs (such as Clopidogrel) resistance and allergic response as conceded with aspirin. Currently approved antiplatelet agents have a narrow therapeutic window and the efficacy is limited.[3]

CLASSIFICATION OF ANTIPLATELETS[4] (FLOWCHART 1, FIG. 1, AND TABLE 1)[5-8]

Cyclooxygenase Inhibitors

Aspirin is the most widely used drug in medicine. It is also one of the many ancient drugs known to mankind, with the history dating back to the period of Hippocrates and Galen.[9]

In 1971, aspirin's mode of action was discovered. Aspirin irreversibly inhibits cyclooxygenase (COX) and leads to suppression of thromboxane A2.

International Study of Infarct Survival (ISIS-2) trial[10] first demonstrated the role of aspirin in reducing recurrent myocardial infarction (MI) and its mortality. In this study, there was significant reduction in stroke, reinfarction, and 5-week mortality. In ISIS-2 trial, 1,000 patients of acute MI were treated with 1 month of low-dose aspirin. This trail came to conclusion that aspirin therapy prevented 25 deaths and 10–15 nonfatal infarcts and strokes per thousand treated patients.

In 2002, the Antithrombotic Trialists' Collaboration[11] analyzed 16 trials. They analyzed 17,000 patients treated with long-term aspirin with doses ranging from 50 to

Volume 1

Cardiological Society of India

CARDIOLOGY

UPDATE 2023

Editor-in-Chief
Pratap Chandra Rath

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JAYPEE

Tropheryma whipplei Infection (Whipple's Disease) and Hearing Loss

47

Hasan Çetiner, Nihat Susaman, and Nitin R. Ankle

47.1 Introduction

Tropheryma whipplei, a bacterial organism which stains gram-positive, is the probable cause of Whipple's disease [1, 2]. The organism was previously named "Tropheryma whippelii" (note the different spelling). Whipple's disease was first characterised as a malabsorption syndrome that affected the small bowel; however, it is now recognised to be a multi-system disorder which involves the joints and central nervous and circulatory systems. A large number of cases of culture-negative endocarditis are thought to be caused by *T. whipplei* [3]. However, since there are only 1000 cases which have so far been reported in the literature, the evidence base for Whipple's disease remains rather slender [4, 5].

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A. E. Arısoy et al. (eds.), *Hearing Loss in Congenital, Neonatal and Childhood Infections*, Comprehensive ENT, https://doi.org/10.1007/978-3-031-38495-0_47

47.2 Pathophysiological Features

Whipple's disease is a rarely occurring inflammatory disorder that involves multiple organ systems. The various features of the clinical presentation have been linked to invasion of multiple tissues by the *T. whipplei* pathogen. The immune response to the presence of the pathogen is to phagocytose *T. whipplei*, which then remains within the macrophages [5].

The presence of macrophage infiltrates into the tissues is readily observable in histopathological specimens. The sections used are stained with the periodic acid-Schiff (PAS) stain. Although these stained macrophages are seen in Whipple's disease, they are not unique to the condition, since they also occur in several other types of infection, especially if patients are immunosuppressed due to infection with HIV. Similar histological appearances are therefore seen in cases of *Mycobacterium avium intracellulare*, *Cryptococcus*, or parasitic infections [6, 7]. If these alternative infective causes are suspected, the sections should be stained to reveal fungi or acid-fast bacilli.

The *T. whipplei* bacteria can be demonstrated by electron microscopy, where they appear as coccobacilli. In conjunction with polymerase chain reaction (PCR) amplification of bacterial DNA, electron microscopy provides diagnostic confirmation of organ involvement [8–10].

The pathological mechanism which causes malabsorption from the small intestine is considered to result from abnormal function of the intestinal villi. The villi fail to work as expected due to infiltration of the lamina propria by the Whipple organism. Whipple's disease produces systemic symptoms through involvement of many, but not all, of the body's different organ systems [5].

The pathogen has also been detected within the synovial tissues in cases where there is joint involvement wherein pain was a feature [11]. Furthermore, the pathogen was present in cardiac valvular tissue in cases of Whipple's disease in which there were cardiac features, and in the central nervous system when there were neurological features [12–14]. The pathogen has also been detected, albeit infrequently, in the pulmonary tissues [15].

47.3 Aetiology

The pathogenic bacterium *T. whipplei*, in conjunction with a maladaptive host immune reaction, is thought to be the cause of Whipple's disease [16]. It is interesting to observe that Whipple's disease does not appear to occur in HIV+ individuals [5].

There is evidence to indicate that, even where no symptoms occur, patients may carry *T. whipplei* [16–18]. PCR DNA amplification on saliva in such individuals was positive 35% of the time, in a study involving 40 apparently healthy individuals [19]. This result may point to the conclusion that Whipple's disease only occurs due to a dysfunctional immune response to the presence of the bacterium, with the usual

condition being asymptomatic carriage. This may occur in a way analogous to that seen with *Helicobacter pylori* [5].

At present, researchers have been unable to demonstrate that *T. whipplei* causes Whipple disease in a manner satisfying Koch's postulates, i.e. experimental infection of an animal reproduces the features of the original disease. It has proven feasible to culture *T. whipplei* in cell culture, using human fibroblasts (i.e. HEL culture) [2]. Moreover, the organism has been demonstrated to trigger production of specific immunoglobulins of types G and M. In patients with Whipple's disease, the pathogen could be detected in cerebrospinal fluid and vitreous humour and was then cultured in fibroblasts [5].

47.4 Diagnosis

Tissue biopsy of the affected organ is a vital step in confirming the diagnosis. The tissues liable to be biopsied in this way are the small intestine, central nervous system, endocardium, and synovial joints. Small intestinal biopsies show expansion of the villi and multiple PAS-positive staining histiocytes. When these histological appearances are present, the next step is electron microscopy and PCR DNA amplification, to confirm the presence of *T. whipplei* organisms [5].

In all new cases of Whipple's disease, it is important to perform a lumbar puncture to obtain cerebrospinal fluid for a baseline assessment. This applies even in the absence of any apparent neurological features of the disease [5].

47.5 Clinical Feature

Whipple's disease may present with a wide variety of different manifestations [20]. Classically, the disease involves multiple organ systems and manifests as arthralgia, persistent diarrhoea, malabsorption, and unintentional loss of weight. There may also potentially be involvement of several other organ systems. The manifestation of the various features occurs slowly over time, such that arthralgia may occur many years prior to other features, and thus not every case demonstrates the full classic panoply of symptoms. A single organ system may be affected, especially the cardiac valves or the brain and spinal cord, without other features of Whipple's disease being detectable. In a case series involving 52 individuals with the disorder, joint symptoms occurred in 67%, gastrointestinal in 15%, systemic in 14%, while central nervous system involvement was seen in 4% [21]. On average, joint symptoms were complained of 6 years before the diagnosis of Whipple's disease was finally confirmed [20].

Cases have also been reported in which administration of immunosuppressants has either caused a deterioration in the symptoms of Whipple's disease or revealed the disorder as underlying. In certain patients, this led to grave complications, including sepsis or dissemination of the bacterium into multiple organ systems [22].

The improvements in molecular diagnostic techniques have meant that the involvement of *T. whipplei* in other disorders has been detected. One study involving 241 paediatric patients between the ages of 2 and 4 years, suffering from acute gastroenteritis, found that the bacterium was present in 15% of the cases, whereas it was not detected in any of 47 control cases. A further diarrhoeal pathogenic organism was found to co-exist in a third of cases [23]. A study of cases of non-specific pyrexia in a rural west African setting also discovered an association with *T. whipplei* [24, 25]. *T. whipplei* was detected by PCR in the blood of 6.4% of cases ($n = 13$) in a study in Senegal where the patients had pyrexia, but testing for malaria was negative. In the majority of the cases involved, the patient was a child and the symptomatic presentation was of coughing and insomnia [20].

There are also reports concerning asymptomatic carriage of the bacterium in apparently healthy individuals. The presence of the bacterium was confirmed by PCR testing of stool or saliva [17, 19, 26–29]. The frequency of carriage is related to geographical location. European samples taken from the faeces of healthy adults show a prevalence of between 1% and 11% [30]. However, when the prevalence was assessed in a rural setting in Gabon, using the same method of detection, it appeared that 20% of individuals exhibited asymptomatic carriage. The rate in children in this group was even higher [31].

47.5.1 Classical Presentation of Whipple's Disease

The key features of late-presenting Whipple's disease are as follows [21]:

- Joint pain
- Unintentional loss of weight
- Diarrhoeal illness
- Abdominal colicky pain

47.5.2 Involvement of the Central Nervous System

Evidence of central nervous system involvement may be found either in classic Whipple's disease or may indicate that infection has relapsed following initial treatment. The rate of nervous system involvement in cases with the classical manifestation of Whipple's disease is between 10% and 40%. Whipple's disease which only affects the nervous system does occur, but infrequently. The longer the infection continues, the higher the probability that it will involve the central nervous system [32].

The involvement of the central nervous system only rarely results in symptoms. It becomes apparent when PCR for bacterial DNA is performed on CSF. Where symptoms are noted, they generally affect cognition, including irreversible, progressive cognitive decline, and disorientation [33]. There are two signs which are pathognomonic for Whipple's disease, namely oculomasticatory and

oculo-facio-skeletal myorhythmia [21, 33, 34]. The former sign consists of continuous rhythmic action of the ocular convergence reflex and simultaneous action off the muscles of mastication. In both cases there is virtually invariably a concomitant supranuclear vertical gaze palsy [20]. One or both of these signs is/are present in around a fifth of cases.

The frequency of cerebellar ataxia is likely to be higher than was initially claimed in the literature. A study with a retrospective design which reviewed 11 cases of Whipple's disease noted cerebellar ataxia as a presenting feature in 5 patients [35]. In published case series, there have been descriptions of several possible neurological abnormalities, such as myoclonus, hemiparesis, peripheral neuropathy, seizures, and disorders of upper motoneuron type [14]. The bacterium may interfere with the proper functioning of the hypothalamus. In cases where neurological abnormalities present clinically, neuroimaging with CT (computed tomography) or MRI (magnetic resonance imaging) sometimes demonstrates foci of disease of a non-specific type. These foci usually disappear once adequate treatment has been administered [21].

Whipple's disease confined to the nervous system seldom occurs and is challenging to correctly identify. An article which reviewed all the published evidence found 20 cases where Whipple's disease was confined to the central nervous system. Two distinct syndromes were noted to occur in such cases [20, 36]:

- In 72% of the reported cases (i.e. 13 out of 18), there were multiple, varied presenting features of neurological type, such as generalised seizures, ataxia, oculomotor dysfunction, amnesia, SIADH (syndrome of inappropriate anti-diuretic hormone secretion), obstructive sleep apnoea, difficulty sleeping, meningoencephalitis, hemiplegia, irreversible, progressive cognitive decline, etc. Imaging in these patients revealed numerous lesions exhibiting enhancement.
- In 28% of cases (i.e. 5 out of 18), there was an identifiable focus for the abnormality and imaging revealed a single mass lesion.

For cases which do present with neurological signs within Whipple's disease, it is essential to send CSF for analysis. If neurological signs and symptoms are absent, the CSF is generally also reported as normal. Cases where symptoms are present feature abnormalities of the CSF, such as a slight or moderate increase in cell count (between 5 and 100 cells per microlitre). The cells present are typically lymphocytes or monocytes/macrophages. Cytology specimens of CSF stained with PAS may reveal multiple stained macrophages. Furthermore, the protein content may be abnormally high and oligoclonal bands may be detected. In patients prior to treatment, PCR in CSF of *T. whipplei*-affected patients gives a positive result when neurological features are present clinically [20].

Observership at Jean Causse Clinique

Inbox ×

Aakash Rai <aakashrai1995@gmail.com>
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Wed, Jul 12, 7:06 AM

Dear Stephanie,

Greetings Stephanie

My name is Dr Akash Rai, I am currently doing my residency in Otorhino-llaryngology at J.N medical College, KLE Academy of Higher Education and Research (formerly KLE University) ,Belgaum, India.

As discussed with Dr Robert Vincent and My assistant professor Dr Rajesh Havaldar, I would like to express my interest in attending observership programme at Jean Causse Clinique in the month of September.
Kindly guide me further with the Invitation Letter in order for me to apply for the Visa and book my tickets accordingly.

I would like to stay in the hotel of the clinic. Kindly guide me with the procedure for the same.

I look forward to your mail as soon as possible.

Thanking you
Yours sincerely

Dr. Akash Rai

47.6 Deafness/Auditory Impairment

The onset of auditory impairment has been stated to be a possible initial presenting feature of Whipple's disease [37]. However, deafness affecting both ears, associated retinal vasculitis and intestinal features, is not an initial presenting feature. Auditory impairment as a presenting feature is of sensorineural type and affects both ears [38]. A case report by Scheurer et al. [39] describes deafness in both ears affecting the high and mid-frequencies in a patient whose diagnosis of Whipple disease had been confirmed by electronic microscopic examination of the duodenum.

47.7 Management

47.7.1 Susceptibility to Antibiotics

It has been shown in vitro that the *T. whipplei* organisms are sensitive to the following antibiotic agents: doxycycline, macrolides, ketolides, aminoglycosides, penicillin, rifampicin, teicoplanin, chloramphenicol, and the combination of trimethoprim and sulfamethoxazole. The minimum inhibitory concentrations are between 0.25 and 2 μg/mL. This was shown on organisms grown in cell culture and utilised real-time PCR DNA amplification [40–42]. A bactericidal effect has been shown for doxycycline and hydroxychloroquine used concomitantly [41]. For *T. whipplei* organisms within host cells, the cephalosporins, polymyxin, and aztreonam exhibit less efficacy.

T. whipplei is not susceptible to fluoroquinolones. The gyrA and parC genes have been sequenced and shown to possess mutations that have the effect of rendering *Escherichia coli* resistant to fluoroquinolones. It is probable that the same mutations in these genes are what render *T. whipplei* similarly resistant [40].

Furthermore, there is no gene coding section within the *T. whipplei* genome that corresponds to a dihydrofolate reductase. This is the enzyme which trimethoprim inhibits. The fact that *T. whipplei* is susceptible to combined trimethoprim and sulfamethoxazole is thus entirely the result of sulfamethoxazole [20, 42].

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Cough

Pathophysiology, Causes and Management

Nermin Kaplan, Mustafa Altıntaş, and Nitin R. Ankle

Contents

1 Introduction

Coughing may be defined as the process by which air is abruptly expelled from the lungs, often involuntarily, with a distinctive accompanying sound. Despite being considered as a symptom in many conditions affecting the respiratory system, it actually has a protective function in that it both expels harmful substances from the lungs and keeps the airways clear of accumulated secretions. Expectoration

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C. Cingi et al. (eds.), *Airway diseases*,
https://doi.org/10.1007/978-3-031-22483-6_27-1

(i.e., sputum production) then refers to coughing that removes unwanted matter from the airways and to spitting out the said matter [1].

2 Pathophysiology

Coughing gives air-sufficient kinetic energy to sweep matter up from the mucosae and propel it out of the air passages. Coughing may be initiated at will, but for the most part, it is an involuntary act. The physiology of the cough reflex involves coordinated action of various components of a neural arc, including sensory afferents, neural center, efferent motor fibers, and the muscles responsible for expelling the air [1].

It is believed that cough receptors, also termed irritant receptors, can swiftly respond to stimuli. These receptors are found in greater abundance in parts of the respiratory tract liable to exposure to chemical or mechanical irritation, especially the laryngeal mucosa, the carina, tracheal mucosa, and wide portions of the bronchus. These areas also correspond to where it is easiest to clear the airway through initiating coughing. There may be other areas where cough receptors are located, as has been demonstrated or deduced in the throat, peripheral portions of the airway, and some other locations within or even outside the chest, notably the pleural lining, external auditory meatus, ear drum, and even the stomach. The key nerve transporting this afferent sensory input is cranial nerve X, albeit with contributions from cranial nerves IX and V [1].

Coughing, then, is a reflex action that normally protects the airway by allowing removal of pooled secretions and extraneous matter from the respiratory tract [2]. This reflex contains three parts: afferent input from cough receptors, integration of sensory input at a neural center, and an efferent motor response [3].

The afferent portion of the arc consists of fibers in cranial nerves V, IX, and X, with the majority located in the superior laryngeal and pulmonary branches of cranial nerve X.

The irritant receptors are distributed along the whole length of the airways, from the throat to the periphery of the lung, but are most abundant in the larynx and carina and at the points where the greater diameter bronchi fork [4].

There are three key categories of sensory receptor involved [5–7]:

- Rapidly adaptive receptors (RARs). These exhibit sensitivity to mechanical forces, tobacco fumes, ammonia, acid or alkali conditions, saline that is either hypo- or hypertonic, lung congestion, lobar collapse, and narrowing of the bronchi.
- Slowly adapting receptors (SARs).
- Pain receptors within the C-fibers, which are sensitive to chemical stimulation and respond to molecules involved in the immune and inflammatory responses, notably histamine, bradykinin, prostaglandins, substance P, and capsaicin. They also respond to a high hydrogen ion concentration.

Afferent inputs are conveyed to the tussive center within the central nervous system. The tussive center is in the medullary solitary nucleus and is linked to the central pattern generator. The efferent arm then exits the medulla, some fibers travelling within cranial nerve X to the larynx and the trachea and bronchi, while there is innervation of the intercostal muscles, the wall of the abdomen, the diaphragm, and the floor of the pelvis via the motor portions of the phrenic and spinal nerves, which originate at spinal levels C3 to S2 [4].

The tussive reflex has a degree of adaptability, and it has been noted that hypersensitivity of the reflex may occur when the action of coughing itself brings about persistent irritation, with ensuing inflammatory responses and remodeling of the tissues [6]. It is frequent for patients to cough rather more than expected, with the cough becoming persistent. Such coughs may arise from hypersensitivity of the tussive reflex, which may occur either through peripheral events (i.e., the irritant receptors alter their threshold) or central events (i.e., the way sensory input is processed undergoes an alteration) [7].

At the mechanical level, coughing can be seen to consist of the following actions occurring swiftly one after the other: (1) a deep inward intake of breath; (2) the glottis that snaps hard shut, with support by the structures above; (3) the muscles of expiration that contract quickly and powerfully; and (4) the glottis that snaps open abruptly as the breathing muscles keep on contracting. As this maneuver results in a markedly raised pressure in the lungs prior to glottal opening, once the glottis does open, the air rushes out at great speed. Furthermore, since there is a net external pressure on the airways at the fourth stage, they are squeezed shut, becoming smaller bore. Thus a large volume of air exits via a narrow opening at high pressure, and the exiting air may reach a velocity approaching that of sound in air. Any secretions swept up in the blast of air may be conveyed out of the airways with considerable force [1].

Normally the trachea and bronchi produce secretions at a level that they can be comfortably cleared by the mucociliary system. The secretions consist of water; small molecules, including glucose and electrolytes; proteins, including mucoproteins, proteins that pass into the secretion by transudation; and lipids, which have a surfactant role. The mucous secretions of the trachea and bronchus are mainly formed by mucous glandular tissue and goblet cells. This secretion forms a thin layer overlying the epithelium, which bears cilia. The cilia move rhythmically in such a way as to push the mucus in the direction of the pharynx, where deglutition occurs, typically without the individual noticing it. When this system is in equilibrium, the secretions are formed and cleared at equal rates, so that a thin blanket of mucus is always present to catch and deal with unwanted material entering the respiratory tree, but without interference in respiratory function. As long as the mucociliary apparatus is working satisfactorily, coughing has no role to play in the disposal of mucus [1].

3 Acute Cough

One of the most frequent reasons to consult a general practitioner (GP) is an acute cough, often referred to as acute bronchitis. It is the fifth most likely reason for a patient to present newly in primary care, both in Australia [8] and the USA [9]. The data indicate that approximately 50 cases of acute bronchitis present to a GP annually out of each caseload of 1000 individuals [10], while in the USA 10 in 1000 walk-in cases are of this type on an annual basis [11].

Acute bronchitis is generally diagnosed, following taking the history and examining the patient, in cases where a cough with sputum has occurred acutely and has not lasted longer than 21 days. There is generally concern among primary care practitioners not to misdiagnose as acute bronchitis a community-acquired pneumonia (CAP), which results in considerable numbers of deaths, particularly in older individuals [12]. CAP can only be accurately diagnosed when pulmonary consolidation is seen on plain chest x-ray. It is impractical, however, for primary care practitioners to request radiological investigations in every case of sudden onset of cough [13].

Given the absence of any pathognomonic symptom or sign for CAP in those presenting with a new cough, there are various combinations of symptoms and signs that may be taken into account in assessing the probability of CAP [14–16]. However, even in cases where the clinical signs arouse a high degree of suspicion, such as a non-asthmatic individual who presents with pyrexia, raised heart rate, and rales, the algorithms used may still be inadequate to confidently diagnose CAP. In such a case, nonetheless, a chest film is clearly an appropriate investigation [13].

According to the American College of Chest Physicians [17], a chest film is not indicated unless any of the following features of the clinical presentation are observed:

- Tachycardia (i.e., cardiac rate exceeds 100/min).
- Tachypnea (i.e., respiratory rate exceeds 24/min).
- Temperature taken orally exceeds 38 °C.
- Localized consolidation, fremitus, and egophony are noted.

3.1 Treatment

It has been reported that antibiotics are prescribed in approaching 80% of those who do not smoke and 90% of those who do, presenting with acute productive cough [18, 19]. Several studies have examined the effectiveness of antibiotic treatment in cases of acute bronchitis. The conclusion in 50% of studies was that antibiotic treatment offers no advantage, while the other 50% of studies found at most modest benefit to antibiotic therapy, in comparison with placebo. The latter group of studies also involved a review undertaken by the Cochrane Collaboration [20]. Prescription of antibiotics is associated with a reduction in symptoms of approximately half a day and allows patients to return to work on average 1/3 of a day sooner. Clinicians need

to consider the potential benefits, which are slight, against the very real chance of side effects associated with antibiotic usage and consider that benefit may only be seen in a subgroup of patients, in any case [13].

4 Persistent Cough

There are a large number of conditions which may lead to a persistent cough, encompassing the whole respiratory tree from the nose, via the nasopharynx, to the periphery of the lung itself. Certain reasons for persistent cough are readily diagnosed on the basis of the history alone, such as tobacco use or a side effect of ACEi (angiotensin-converting enzyme inhibitor) therapy [2].

Research that employed a prospective methodology indicates that between 92% and 100% of cases of persistent cough in individuals whose chest x-ray is normal, who do not smoke and who have no deficiency of immune functioning, are down to just three disorders, as follows [21]:

- Upper airway cough syndrome (UACS). This condition was earlier termed postnasal drip syndrome (PNDS). It is the most common.
- Asthma.
- Gastro-esophageal reflux disease (GORD). This is the least common.

These three disorders are collectively referred to as the "pathogenic triad" of persistent coughing.

Alongside the pathogenic triad, it is worth including in the differential diagnosis non-asthmatic eosinophilic bronchitis (NAEB); since it occurs frequently, the diagnosis is straightforward, and its presence should be excluded at the initial stage of diagnostic workup.

A further way that causes of chronic cough can be separated is into those involving eosinophilic infiltration of the airways (such as asthma and NAEB) and those without eosinophilic involvement [22]. Disorders of eosinophilic type feature an eosinophilic inflammatory reaction in the airways. Sputum contains high levels of eosinophils, and there is an increased concentration of nitric oxide in exhaled air, features which may be used diagnostically. Eosinophilic disorders, in addition, may be effectively treated with corticosteroids [22].

4.1 Upper Airway Cough Syndrome

UACS is characterized by the patient perceiving nasal or sinusal secretion dripping into the nasopharynx and leads to rhinorrhea and the need to keep clearing the throat. This diagnosis is largely based on how patients describe their symptoms, and there is a regrettable absence of objective findings to back up the diagnosis in many cases. Furthermore, some 20% of those whose cough is attributable to UACS actually do not perceive the secretions dripping from the nose or, if they do, fail to associate it

with coughing [23]. Mucus may be observed in the oropharynx, and the throat may reveal cobblestones, but these signs are not specific for UACS, nor do they occur in every case [21].

The concept of postnasal drip has now been enlarged in the UACS clinical entity, which encompasses a wide variety of conditions affecting the nose and sinuses that may cause coughing. Some such disorders are [21]:

- Postnasal drip
- Acute sinusitis secondary to bacterial infection
- Allergic sinusitis secondary to fungal infection
- Allergic rhinitis
- The various categories of nonallergic rhinitis, namely:
  - Nonallergic rhinitis with eosinophilia (NARES)
  - Occupational rhinitis
  - Post-infectious rhinitis
  - Rhinitis secondary to anatomical anomaly
  - Rhinitis secondary to physical or chemical irritation
  - Rhinitis medicamentosa
  - Rhinitis of pregnancy
  - Vasomotor rhinitis

4.2 Asthma

Asthma is characterized by a varying degree of blockage to the airways and hypersensitivity of the airways. This leads to dyspnea, wheeze, difficulty drawing breath, and coughing. While cough is an invariable symptom in asthma, in a few patients it is the sole symptom. This variant of asthma is termed cough-variant asthma (CVA). All variants of asthma are treated with beta-2-blockers and steroid therapy [2].

4.2.1 Gastro-Esophageal Reflux Disease

It has been proposed that coughing in GORD arise because of either [24]:

1. Acid irritation to the inferior esophagus, triggering a cough reflex that involves the tenth cranial nerve and links the esophagus to the trachea and bronchi.
2. There may be minute quantities of material aspirated from the esophagus into the larynx, trachea, or bronchi, provoking a cough.

This second possibility is termed laryngopharyngeal reflux (LPR) or extra-esophageal GORD. Unlike in GORD generally, this variant does not give rise to burning indigestion, and symptoms are usually felt when the patient sits up rather than when recumbent. Up to 75% of cases of persistent cough may actually be due to latent LPR [25].

4.3 Non-asthmatic Eosinophilic Bronchitis(NAEB)

It has been suggested that between 13% and 33% of cases of persistent cough are due to NAEB [21]. In this condition, eosinophilic inflammation does surround the bronchi, but the airways fail to exhibit hyper-responsivity, and there are no changes in airflow through the airways. NAEB responds very well to treatment with steroid inhalers.

4.4 Other Causes

There are multiple other conditions which together explain the other 5–10% of cases of chronic cough. These conditions include [2]:

- Bronchiectasis
- Bronchiolitis
- Malignant neoplasm of the bronchus
- Chronic aspiration
- Chronic obstructive pulmonary disease (COPD)
- Congestive cardiac failure (CCF)
- Foreign body obstructing the airway
- Interstitial pulmonary disorders
- Neuromuscular disease
- Whooping cough
- Coughing due to psychological disturbance
- Sarcoidosis
- Tracheo-esophageal fistula
- Tuberculosis
- Zenker diverticulum

4.5 Management

The first step in treating chronic cough is to advise the patient to quit smoking or to stop ACEi treatment, if those are the causes identified. Patients who quit smoking usually find their cough stops within 4 weeks of their last cigarette [21]. While stopping an ACEi generally brings relief in a fortnight or less, there are reports that the median period prior to resolution is 26 days [21].

Where there is an abnormality on chest x-ray appearances, the next step hinges on the nature of the abnormality detected. Where a lung lesion is detected, computed tomography, bronchoscopy, core biopsy, and sputum examination are all possible next steps [2].

If a patient does not use tobacco, is not on ACEi therapy, and has no deficiency of the immune system, successful diagnosis depends on systematically going through a differential diagnosis and being open to the possibility that there may be multiple

etiologies. There is an abundance of published evidence to support particular therapeutic decisions. If the patient responds well to therapy, this supports the diagnosis given. It makes most sense for economic and scientific reasons to address the pathogenic triad initially, rather than begin with in-depth investigations [26, 27]. Moreover, additional treatment modalities may be attempted if the cough appears to be multifactorial in origin, as is frequently the case.

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CHAPTER

102 Adiponectin the Molecule of the Millennium

VA Kothiwale

INTRODUCTION

Adiponectin is one of the most important adipokines synthesized mainly by the adipose tissue. To begin with, it was presumed that adiponectin was solely produced only by adipose tissue. However, later it was found that adiponectin is expressed in other tissues which include human and murine osteoblasts, liver parenchyma cells, myocytes, epithelial cells, endothelial cells, and placental tissue. It is a fat-derived hormone that is found to play a crucial role in protecting against obesity, diabetes, atherosclerosis, and cardiovascular disease. It structurally belongs to complement 1q family and functions like a hormone. A new role of adiponectin as a "starvation gene" has been proposed where it was found to play a central role in homeostasis via its action through the hypothalamus. Adiponectin was discovered in 1995–1996, since the past two decades research regarding its structure, function, and possible therapeutic uses is on the rise.

Adiponectin is a bioactive peptide composed of 244-amino acid protein which is present in the body in three oligomeric complexes—trimer (67kDa), hexamer (140 kDa), and a high-molecular-weight (300 Dka) adiponectin. High-molecular-weight adiponectin is considered to be the most common and most active form. These entities are encoded by the *Adipo Q* gene on chromosome locus 3q27. Biochemically, the adiponectin protein comprises an NH2-terminal hypervariable region, a collagenous area of 22 Gly-XY repeats, and COOH terminal C1q-like globular domain. Extensive post-translational modifications of adiponectin are essential for efficient maturation, oligomerization, and secretion of adiponectin which contributes to its stability in the circulation. The activity of adiponectin also depends on the appropriate ratio of low- to high-molecular-weight adiponectin.

Adiponectin undergoes minimal degradation during its passage through the body. It has a half-life ranging from 45 to 75 minutes. Clearance of the molecule is principally via the liver, although it can also bind to pancreatic beta cells, kidney, and heart cells.

Adiponectin mainly acts via the adiponectin receptors:

- *AdipoR1:*
  - High affinity receptor for globular isoform and low affinity receptor for full-length adiponectin
  - Abundantly found in the skeletal muscle
- *AdipoR2:*
  - Recognizes the full-length adiponectin
  - Expressed mainly in the liver
- *T-cadherin*: It acts as a receptor for only hexameric and high-molecular-weight forms.

APPL1 is an adaptor protein which mediates the adiponectin signaling by binding to the adiponectin receptors. Interactions of adiponectin with its receptors result in activation of multiple signaling pathways including IRS1/2, AMPK, and p38 MAPK.

PHYSIOLOGICAL EFFECTS OF ADIPONECTIN

Skeletal Tissue

Adiponectin acts via two major signaling pathways in the muscle AMPK and p38 mitogen-activated protein kinase pathways. In the muscle, its action leads to fatty acid oxidation, glucose uptake, and the glucose transporter type 4 (GLUT 4) translocation into the muscle.

Vascular Endothelium

Vasculoprotective and angiogenic action of adiponectin is carried out via the ability to increase nitric oxide production through the activation of eNOS in an AMPK-dependent manner. Adiponectin supplementation reduces TNF-alpha-mediated vascular cell adhesion molecule-1 and interleukin-8 by suppressing the nuclear factor kappa-β activation in endothelial cells. It is also found to improve the endothelial function by increasing the cyclo-oxygenase expression. Studies have shown that adiponectin supplementation attenuates the neointimal thickening in mechanically injured arteries through its suppressive action on the proliferation and migration of vascular smooth

muscles and thereby protecting from hypertension, left ventricular hypertrophy, and myocardial infarction.

Adipose Tissue

Adiponectin increases the oxidation of fatty acids reducing the triacylglycerol stores and producing a hypolipidemic effect. It was found that insulin-resistant humans have low adiponectin receptor expression on visceral adipocytes. Activation of peroxisome proliferator-activated receptor alpha (PPAR-α) leads to adiponectin and its receptor upregulation, thereby decreasing the insulin resistance. Overexpression of adiponectin protects from acute and chronic effects of high fat diet–induced lipotoxic effects of lipid accumulation.

Liver

Adiponectin primarily acts via suppression of gluconeogenesis and glycogenolysis, thus having a glucose-lowering effect. The insulin sensitizing effect of adiponectin is mediated via PPAR-α. Research has shown that other beneficial effects of adiponectin supplementation include its ability to alleviate the alcohol and obesity-induced hepatosteatosis.

Factors Affecting the Adiponectin Levels

- *Sex*: Women have a higher level of adiponectin compared to males which is mainly due to the presence of different sex hormones and also because of the variation in fat distribution.
- *Genetics*: Concentration of adiponectin in an individual is inherited by up to 55%.
- *Body mass index (BMI) and weight*: Adiponectin is negatively correlated with the degree of obesity in obese people. Interesting results were obtained in the Pounds Lost Trial that revealed statistically significant correlation between adiponectin concentration body composition and adipose tissue distribution. Visceral adipose tissue was inversely related to the total adiponectin concentration.
- *Dietary pattern*: Mediterranean diet, DASH diet, and plant-based diet have positive effect on the adiponectin concentration via the anti-inflammatory and anti-antioxidant properties of bioactive components in the respective foods. Monounsaturated fatty acids, polyunsaturated omega 3 fatty acids, dietary fiber, polyphenols, and moderate quantity of alcohol and milk products increase the adiponectin concentration. Low-energy and low-calorie diet have beneficial effect on adiponectin concentration.
- *Exercise*: Acute bout of aerobic exercise has a significant increase in the adiponectin levels in abdominally obese individuals.

ADIPONECTIN AND CANCER

Adiponectin reduces cancer cell migration and invasion abilities, stops their growth and proliferation, and helps triggering apoptosis in them. Low levels of adiponectin are associated with a number of cancers such as ovarian, endometrial, and papillary thyroid cancer.

A meta-analysis of 11 studies showed the 6% increase in risk of kidney cancer in men and 7% in women per unit BMI increase with an average of 36% higher risk in individuals with BMI > 30 kg/m^2. Largergran et al. reported a positive correlation of esophageal carcinoma with increased BMI along with a higher risk in BMI > 30 kg/m^2. The strongest correlation of cancer and adiponectin is breast cancer. The mammary epithelial cells are in close contact with cocktail of adipokines produced by adipose tissue and any imbalance in the hormonal milieu renders the breast susceptible to tumorigenesis. Reduced levels of total and high-molecular-weight adiponectin have been shown to be associated with breast cancer irrespective of age, BMI, and hormone status.

ADIPONECTIN AND OBESITY

Adiponectin controls lipid metabolism by promoting the transport of fatty acids and oxidation in muscle by inhibiting hepatic lipogenesis and by stimulating the storage function of adipose tissue. It, therefore, induces a lipid-lowering effect in body. It increases the transport of fatty acids into the muscle cells by stimulating the expression of fatty acid translocase and also promotes the catabolism of fatty acid by inducing the activity and expression of fatty acid translocase. It regulates the transcription of many genes involved in lipid metabolism such as *ACO*, *FABP3*, and *CPT-1* by inducing the expression of the transcription factor PPAR-α. It has seen to inhibit the expression of 30 hepatic genes encoding proteins involved in the transport of fatty acids and lipogenesis. Adiponectin is inversely proportional to the visceral fat concentration, and its concentration differs with respect to the distribution of fat in the body. From the above-mentioned theory, it is clear that adiponectin protects against obesity and higher is its concentration, lesser is the visceral fat. Some clinical trials have shown that statins such as pravastatin, simvastatin, rosuvastatin, and atorvastatin have reported to increase the adiponectin levels. Drugs such as fenofibrate and Zetia, and non-thiazolidinedione (TZD) antidiabetic drugs such as acarbose, glimepiride, and sulfonylureas are also effective in increasing the high-molecular-weight adiponectin.

ADIPONECTIN IN DIABETES MELLITUS

Various studies and meta-analyses showed that the risk of T2DM is strongly associated with low levels of adiponectin. Adiponectin plays a key role in decreasing insulin resistance. Hepatic gluconeogenesis and increased glucose transport in the muscle are the primary factors behind the insulin-sensitizing action of adiponectin. Other mechanisms include higher energy consumption and oxidation of fatty acids in peripheral tissues which help increase the production of adenosine triphosphate (ATP). The glucose-lowering effect of adiponectin has been shown to be due in part to its activation of the AMP-activated protein kinase (AMPK) cascade.

AMPK, a likely target for metformin and other antidiabetic drugs as well as for exercise-related glucose transport, is an insulin-independent, phylogenetically ancient mechanism of stimulating glucose transport. Best thought of as a means of maintaining intracellular energy levels, AMPK stimulates both the catabolism of the existing intracellular energy stores, such as triglycerides, and an insulin-independent influx of extracellular energy sources, such as glucose. Two adiponectin receptors have been cloned and shown to mediate increased fatty acid oxidation in the muscle and increased glucose uptake in the liver. Adiponectin also exerts a glucose-lowering effect via the improved secretion of insulin. This has been demonstrated to act against fatty acid– and cytokine-induced β-cell dysfunction. Recently, many small-scale studies report an antagonistic association between adiponectin and proinflammatory markers. Hence, a future use of adiponectin as a biomarker could be used to predict the development of diabetes when it is low, at least in the case of nonsmoking subjects.

The insulin-sensitizing effects of new antidiabetic molecules such as PPAR-γ nuclear agonist and thiazolidines such as rosiglitazone and pioglitazone are accompanied by an increase in adiponectin levels. Troglitazone, an oral antihyperglycemic agent, increases the adiponectin production in isolated human adipocytes. The insulin-sensitizing effects of these drugs have been mediated by the acceleration of adiponectin production. PPAR-α/γ agonist increases the concentration of adiponectin in nondiabetic volunteers.

ADIPONECTIN AND CARDIOVASCULAR SYSTEM (ANTIATHEROSCLEROTIC EFFECT)

There is a close relationship between hypoadiponectinemia and peripheral arterial dysfunction. The biosynthesis of nitric oxide (NO) is performed by AMPK and is mediated by adiponectin-induced phosphorylation of eNOS. Adiponectin inhibits the interaction between leukocytes and endothelial cells by reducing E-selectin and vascular cell adhesion molecule-1 induced by TNF-α, resistin, and IL-8 and by increasing endothelial NO, which results in the attenuation of monocyte attachment to endothelial cells.

Elevated serum TG levels are an independent predictor of endothelial dysfunction. Lowering circulating TG levels by adiponectin may improve the endothelial function. The increase of TG and decrease of HDL reduce the activity and expression of eNOS and disrupt the integrity of the vascular endothelium due to oxidative stress; therefore, reduction of TG, elevation of HDL, and improvement of glucose metabolism may ameliorate the endothelial function.

Adiponectin blocks the proliferation and migration of human aortic smooth muscle cells (SMCs) by inhibiting several atherogenic growth factors, including platelet-derived growth factor, basic fibroblast growth factor, and heparin-binding epidermal growth factor.

ABCA1 receptors have been identified as important membrane receptors to generate HDL by cholesterol efflux from foam cells. Adiponectin has been reported to upregulate the expression of ABCA1 in human macrophages and enhance apo-AI-mediated cholesterol efflux from macrophages. Adiponectin markedly suppresses foam cell formation in oxidized low-density lipoprotein (LDL)-treated macrophages from diabetic subjects, which was mainly attributed to an increase in cholesterol efflux. In addition, a deletion of adipoR1 in macrophages from diabetic patients accelerated foam cell formation induced by oxidized LDL. Studies have shown that adiponectin has a negative relationship with the ratio of metalloproteinase 9/tissue inhibitor of metalloproteinase 1 (MMP9/TIMP-1) in patients with acute coronary syndromes and that the MMP9/TIMP-1 ratio is an independent predictor of the stability of atherosclerotic plaque and severity of coronary atherosclerosis.

Reports suggest high-molecular-weight adiponectin to be a better independent risk factor than the total adiponectin for cardiovascular disease.

Physiological actions of adiponectin on various tissues would be a possible way to treat various metabolic diseases. AdipoRon, a synthetic analog of adiponectin, can bind the adiponectin receptors and help in treating various metabolic conditions. However, similar to most biologics, the mass production of functional adiponectin is challenging since in the biological system it is in intense post-transcriptional and post-translational modification which are hard to mimic in vivo. The short half-life of adiponectin in circulation makes the administration of recombinant adiponectin a nonfeasible approach. Therefore, the only practical approach is boosting the endogenous production of adiponectin by natural methods such as weight loss or pharmacologic intervention.

CONCLUSION

Adiponectin is the most important adipokine synthesised majorly by the adipose tissue among the various other sources being osteoblasts, liver cells and placental cells. Adiponectin acts via the adiponectin receptors to produce various physiological effects on the body which include hypolipidemic, hypoglycaemic, insulin sensitizing, anti-artherosclerotic.The vascular protective and angiogenic action is carried out via its ability to increase nitric oxide production by activating epithelial nitric oxide synthase in an AMPK dependent manner and by increasing the cyclooxygenase expression.The hypolipidemic action is caused by the ability of adiponectin to increase the fatty acid oxidation and reduce the triacylglycerol stores. Adiponectin concentration being inversely proportional to the visceral fat concentration, in obesity the visceral fat being high the adiponectin concentration is low which is responsible to the various negative effects.It has glucose lowering and insulin sensitizing effect on body by the suppression of gluconeogenesis and glycogenolysis via the PPAR receptor action. Adiponectin is protective against various cancers and as its low concentration is associated with ovarian, endometrial and papillary thyroid cancer.

We have understood why adiponectin is rightly called the molecule of the millennial as it is protective against obesity, diabetes mellitus, peripheral arterial dysfunction and various neoplasms and also importantly its physiological actions would be a possible way to treat various metabolic diseases in the near future.

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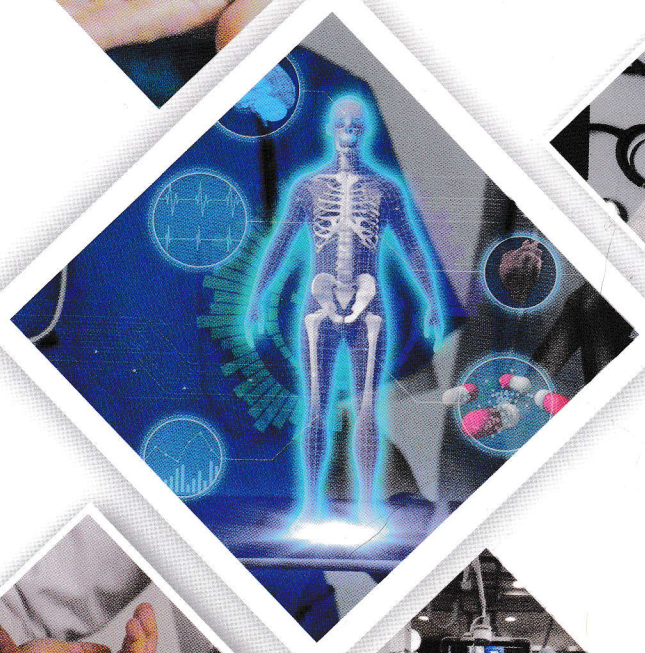
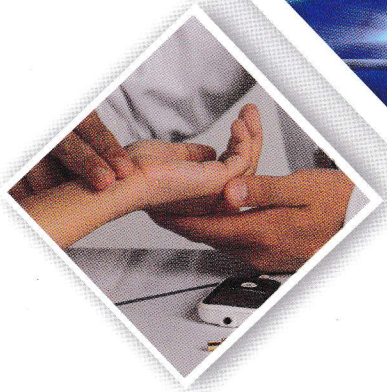
SECTION 5: ENDOCRINOLOGY

Sailesh Lodha, Dheeraj Kapoor

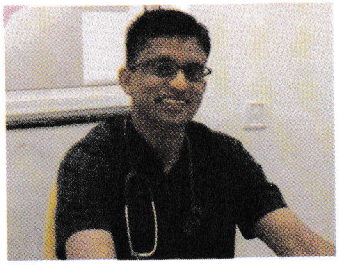
Clinical Manual of Medicine





Dr. Raju H. Badiger

PREFACE



The most difficult/important for all UG (MBBS, BDS & BPT) & PG students is to pass & score good marks in practical exam.

To prepare for the same presently there are many books & students have to refer different books for different topics.

Keeping in view the same, this "Summarized Clinical Manual" is prepared after referring standard textbooks of medicine. The important topics have been covered completely and precisely.

Studying this book will not only help to score good marks in practical exams but also will help students in preparing for Objective type questions (E.g.: NEET PG).

I sincerely thank all my teachers.

I would like to thank Mr. Vinayak Badiger for editing and other technical work.

I hope you enjoy reading the book and I warmly welcome critical comments and constructive suggestions.

Please convey your thoughts and suggestions via email to badigerraju@yahoo.com.

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CHAPTER

Evoked Potentials

Karkal Ravishankar Naik, Aralikatte Onkarappa Saroja

INTRODUCTION

Evoked potentials (EPs) are the electrical responses from within the central nervous system to external stimulus. Majority of the EPs recorded from scalp and peripheral electrodes represent near-field potentials. Far-field potentials originating in deeper subcortical and brainstem structures are recorded using referential montages. Generators of these centrally-conducting volley of action potentials and synaptic potentials correlate with anatomical data, clinicopathological states, and neuroradiologic data. Recording during surgical procedures have provided confirmation of neural source generators of the EPs.

These potentials generally range from 0.01 to 10 μV and are much smaller than the simultaneously recorded electroencephalogram (EEG) from which they have to be extracted. Apart from the photic drive response from luminance-induced occipital responses in EEG, other EPs are not discernible in the raw EEG. Dawson described the use of signal averaging for extracting the somatosensory-EPs from the raw EEG in 1954. Introduction of signal processing and averaging paralleled by improvements in digital computations has made the EP extraction from EEG and other biological signals a simpler task. The responses to stimulations (signal) are time-locked to the stimulus and occur with each stimulus. The random electrical activities from nervous system (noise) are not time-locked to the stimulus. Averaging of multiple stimulus epochs removes the random noise leaving only the signal of interest which is time-locked. Signal-to-noise ratio (SNR) is proportional to the square root of the number of stimulus epochs. Increasing the number of stimulus epochs, therefore, increases the clarity of the signal by increasing the SNR (Fig. 1). Averaging >1,000 epochs is needed for eliciting the small-amplitude (<0.5 μV) auditory evoked potentials (AEPs) whereas the larger-amplitude visual evoked potentials (VEPs) can be recorded with <100 stimulations. The stimulation should be continued till the EP waveform is robust and at least two trials should be averaged to demonstrate consistency.

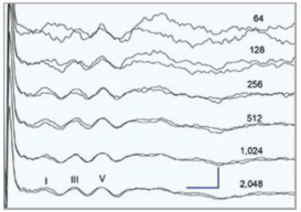


FIG. 1: The use of averaging to reduce noise in evoked potential recording with number of stimulus epochs ranging from 64 to 2,048; with increasing number of stimulations, the evoked potential waveform becomes well delineated due to progressive elimination of noise. Calibration 2 msec, 0.5 μV.

Laboratories performing EPs should obtain their normative data using guideline-based recording and use recommended parameters and nomenclature of the waveforms. It is recommended to use 2.5–3 standard deviations above the mean for latencies and intervals; and 2.5–3 standard deviations below the mean amplitude to avoid labeling a normal observation as abnormal.[1,2] It is customary to display the potentials with negativity upward in clinical neurophysiology laboratories. However, most ophthalmic and audiology electrophysiologists display positive activity above the baseline.

Auditory evoked potentials, VEPs, and somatosensory evoked potentials (SSEPs) are the routinely recorded EPs in clinical neurophysiology practice. Other EPs including electroretinograms (ERGs), vestibular evoked myogenic potentials (VEMPs) and event-related cognitive evoked potentials are evaluated less frequently. Intraoperative monitoring (IOM) of nervous system using EPs monitoring in special situations has contributed to better surgical outcome. Despite the advances in magnetic resonance imaging (MRI), including diffusion tensor imaging and functional imaging, EPs have important role in the diagnosis and monitoring of neurological disorders.

VISUAL EVOKED POTENTIALS

Visual evoked potentials are the averaged potentials from EEG recorded over the scalp overlying the visual cortex in response to visual stimuli. Adrian and Mathews demonstrated occipital EEG response to strobe flash in 1934. Visual stimuli used to record VEPs have evolved through stroboscopic flash, light-emitting diodes (LEDs), pattern onset–offset, and pattern reversal/shift to multifocal stimulation protocols. VEP is a complex response with many overlapping responses from the visual pathway. Primary visual cortex is located in the medial occipital lobe. Foveal visual field is in the calcarine fissure away from the occipital pole. Due to interindividual variations in visual-cortical representation, surface-recorded P100 amplitude varies between the midline and lateral electrodes. Generally, the surface-recorded VEP from hemifield stimulations have higher

Chapter

Diagnosis and Treatment Planning in Surgery First Approach

Adithi Rao and Shreya Mantri

Abstract

Surgery first approach is evolving as a better accepted treatment modality in contemporary orthognathic treatment. It has gained popularity gradually over the traditional orthognathic surgery as it involves performing of orthognathic surgery with minimal or no presurgical orthodontic phase. A correct diagnosis is the fundamentals of a precise treatment outcome. The present chapter discusses in detail about the diagnosis and treatment planning in surgery first approach as they lay the foundation for the best clinical outcome. This chapter is intended to provide an insight into the orthodontic and surgical consideration in surgery first approach. It entails the conventional as well as advanced diagnostic tools and treatment strategies in surgery first approach. It also encompasses the strategic planning of cases based on the specific requirements and objectives which further helps in execution of appropriate treatment plan. This chapter would thus be an essential guide for trainees and practicing clinicians in maxillofacial surgery and orthodontics.

Keywords: surgery first approach, diagnosis, treatment planning, skeletal anchorage system, pre-surgical orthodontics, post-surgical orthodontics

1. Introduction

The primary indication for surgical orthodontic treatment is severe skeletal malocclusion with jaw discrepancy such that the camouflage orthodontic treatment alone is insufficient to obtain acceptable results.

The concept of envelop of discrepancy introduced by Ackerman and Proffit, delineates the limits of different types of orthodontic treatment and thus helps in deciding the preliminary line of treatment. The essence of this concept is as follows. When a moderate skeletal discrepancy exists and there is no potential for further growth, orthodontic camouflage should be considered as the treatment option. Extraction of some teeth will usually be required so that enough space in the arch can be created to allow required movement of other teeth. The treatment should result in reasonable occlusal stability and pleasing aesthetics. For a severe skeletal discrepancy,

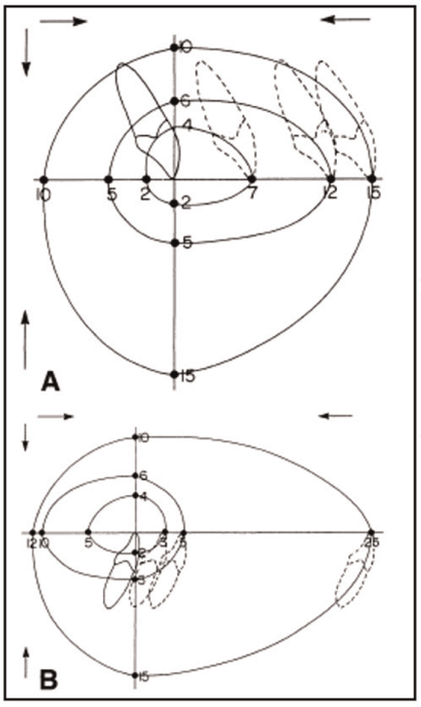
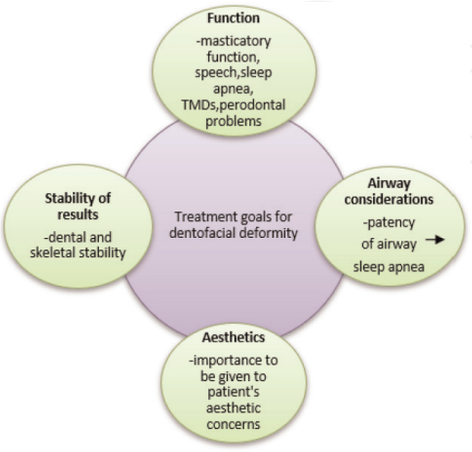


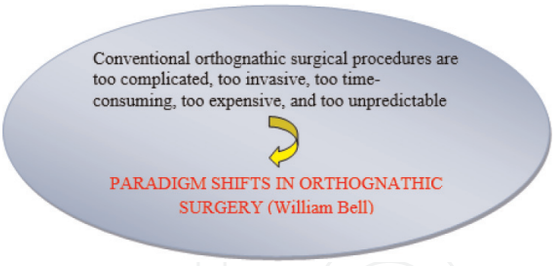
Figure 1.
The envelopes of discrepancy, showing the amount of change in the antero-posterior and vertical planes of space. Inner envelope: change from orthodontics alone. Middle envelope: orthodontic tooth movement combined with growth modification. Outer envelope: orthognathic surgery [1].

the final treatment option is orthognathic surgery and orthodontic treatment. Once growth has ceased, surgery becomes the only means of correcting a severe jaw discrepancy (**Figure 1**) [1].

The conventional approach to orthognathic surgery requires a variable length of preoperative orthodontic preparation, the surgery, and a relatively stable period of postoperative orthodontics. It involves progressive deterioration of facial esthetics and dental function, and causes significant patient discouragement and discomfort [2].



In the recent years, a drift towards revising the line of treatment that achieves immediate improvement in the facial esthetics has arisen. Hence, a different approach, the surgery-first approach, is to proceed with the orthognathic surgery in the beginning without presurgical orthodontic preparation, and most of the orthodontic treatment is performed postoperatively.



The concept of Surgery-first was introduced by Brachovogel in 1991, with the goal of reducing some of the disadvantages and inconveniences of pre-surgical orthodontics [3]. This concept of "surgery-first and orthodontics second" is called "SFOA" (Surgery-First-Orthognathic-Approach) or "SFA" (Surgery-First approach) no requirement of tooth movement or minimal decompensation of tooth for a short period of time in clinical scenarios with occlusal interference, usage of surgery to fasten the achievement of improvement of facial aesthetics which is patient's primary concern.

It reduces total treatment time due to RAP (rapid acceleratory phenomenon) along with improvement in upper airway constriction [4]. These factors improve the quality of care and lead to high patient satisfaction rates from the early stages of treatment and improved cooperation during postsurgical orthodontics and thus has a positive psychosocial effect on patients [5]. The proposed benefits of surgery first have led to a growing acceptance in surgical and orthodontic communities toward these protocols. Surgery first approach is thus exhibiting a paradigm shift in the field of jaw surgery.

An illustration of computer assisted simulation of conventional orthognathic surgery and surgery first approach is shown here **Figures 2–4**.

Indications of SFOA

Malocclusion	• Skeletal class III malocclusion
Intra-arch discrepancy	• Minimal crowding • Minor tranverse discrepancy • Midly proclined/retroclined maxillary /mandibular incisors
Curve of Spee	Flat to mild Curve of Spee
Pateint's psychological perspective	• Patients with low self esteem desiring to experience immediate soft tissue corrections,satisfying the other indications of SFOA

2. Diagnosis

Diagnosis is the definition of the problem. Treatment planning is based on diagnosis and is the process of planning needed to eliminate the problems. Diagnosis of a surgical case does not differ for conventional and surgery first approach. Diagnosis provides guidance to the surgeon and the orthodontist regarding the needs of the case. Study models, clinical examination, and soft tissue cephalometrics have all been used to guide facial treatment [6]. Though SFA can be considered as an advantageous procedure it also has certain disadvantages associated with it to overcome the

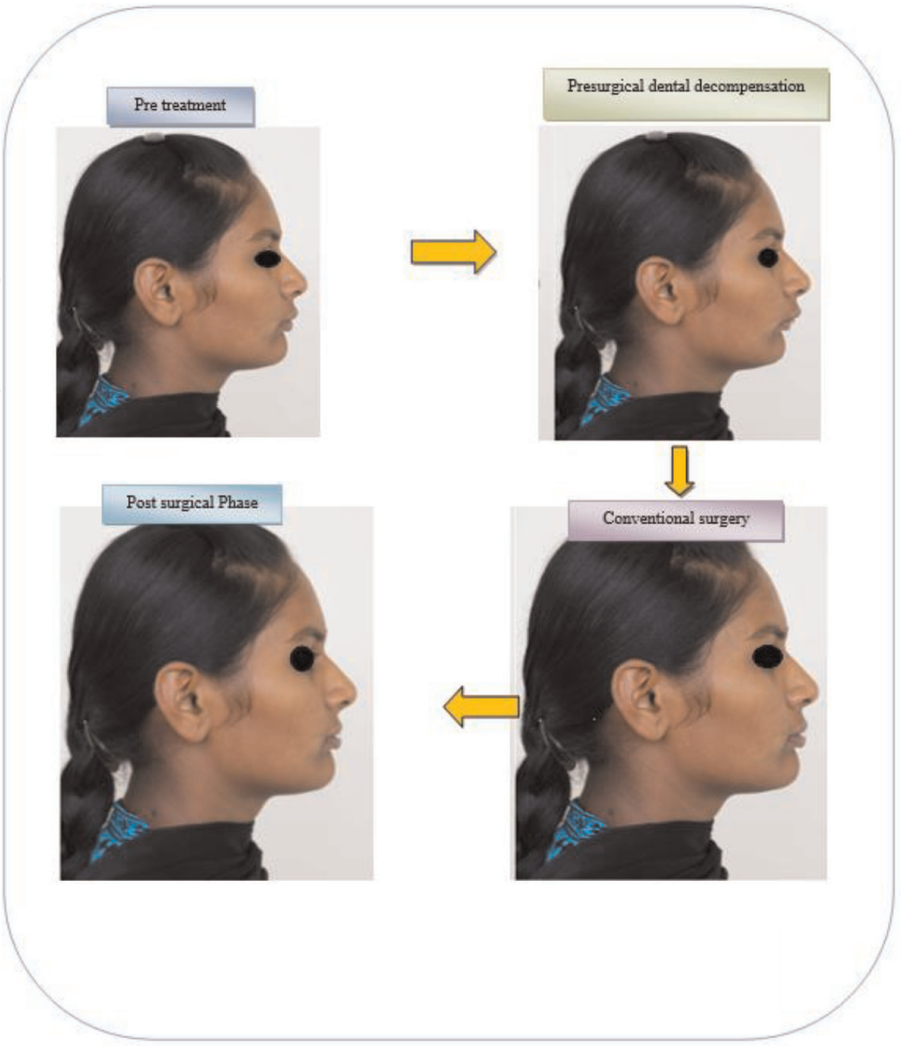


Figure 2.
Conventional orthognathic surgery approach.

problems. The occlusion cannot be used as a reference for determining the treatment goal hence the final occlusion interpretation is challenging. Post operative occlusion immediately achieved after SFA is mostly unstable. Due to such problems this concept requires an accurate diagnosis and meticulous treatment planning for beginners, cases with minimal dental discrepancies, in sagittal, vertical, and transverse planes, could be ideal cases to start with for SFOA.

2.1 Intended transitional malocclusion (ITM)

In the model surgery procedure, the crucial step is to predict the intended transitional malocclusion (ITM), to fabricate surgical splint and later facilitate the postsurgical movement of the teeth [7]. For predictable splint fabrication and skeletal movements ITM attained should have enough stability and 3-point contact between upper and lower models is a pre-requisite. In some cases, initiation of some orthodontic movement to resolve occlusal interferences and allow stable transitional malocclusion maybe required when such temporary occlusion cannot be established [8, 9].

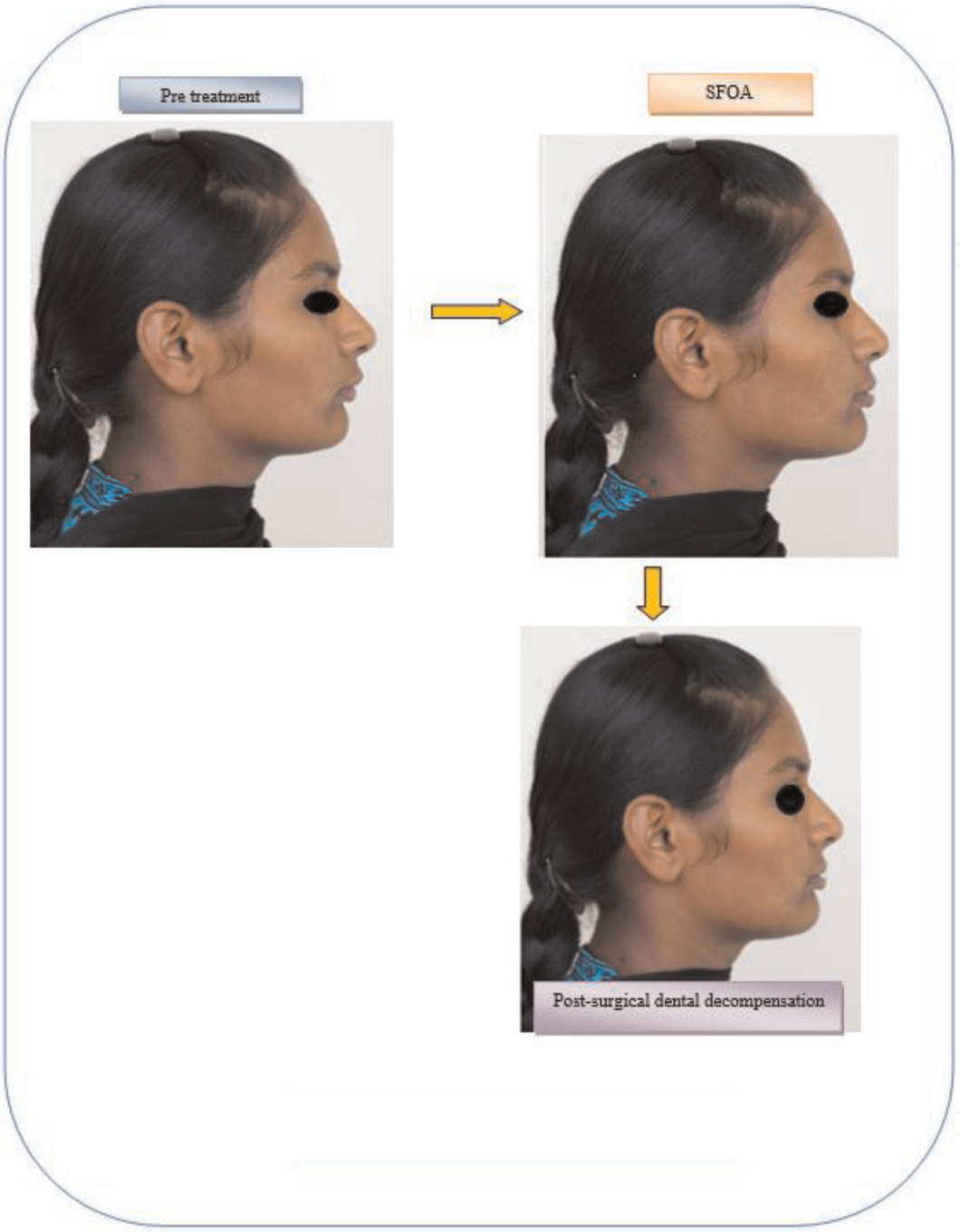


Figure 3.
Surgery first approach.

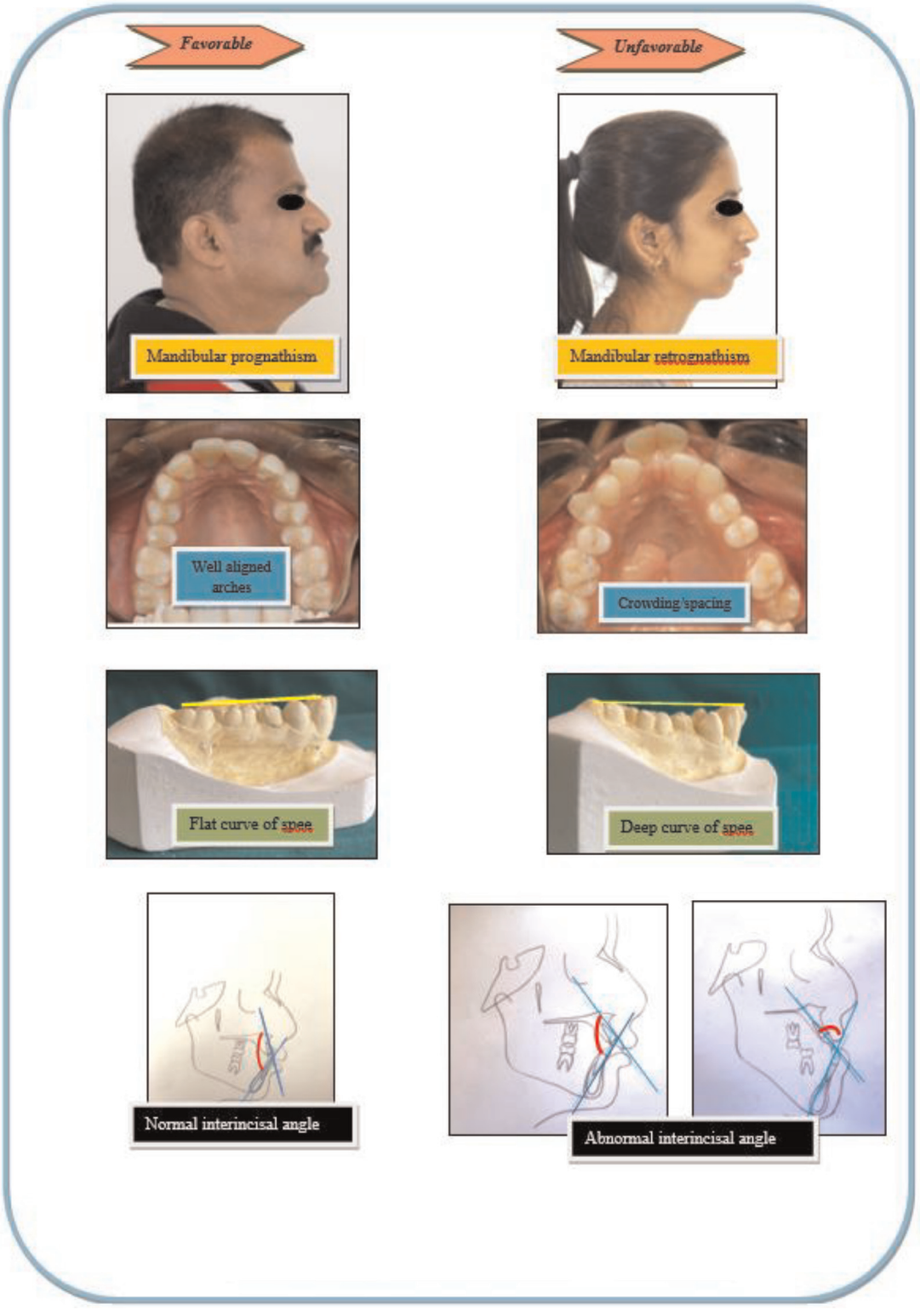
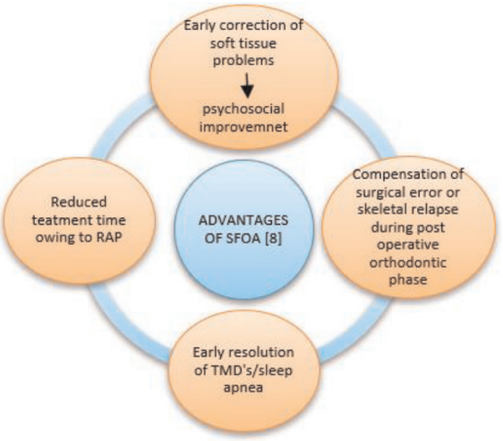


Figure 4.
Favorable and unfavorable case scenarios for SFOA (Liou et al. [6]).

2.2 Advantages of surgery first approach



Both conventional and 3D surgical planning is discussed in this chapter.

2.3 Methods for planning and predicting surgical outcome using cephalometrics

There are various methods available for planning and predicting surgical outcomes such as [10]:

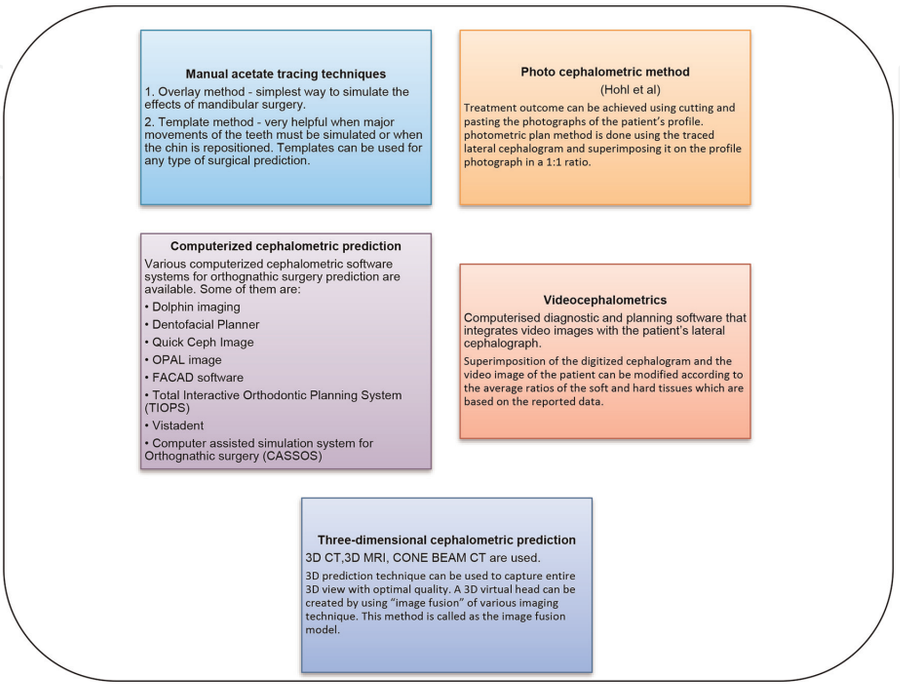
1. Manual acetate tracing techniques.

2. Photo cephalometric method.

3. Computerized cephalometric prediction.

4. Videocephalometrics.

5. Three-dimensional cephalometric prediction.



2.4 Pre-surgical planning through manual cephalometric prediction

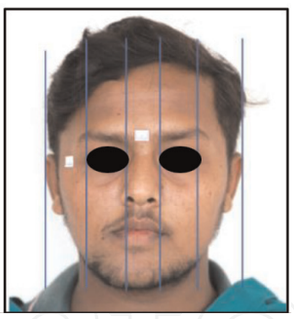
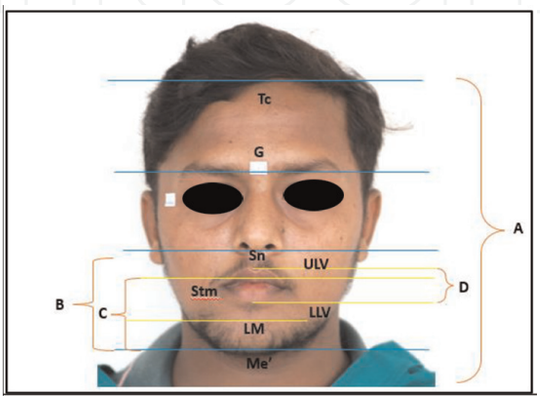
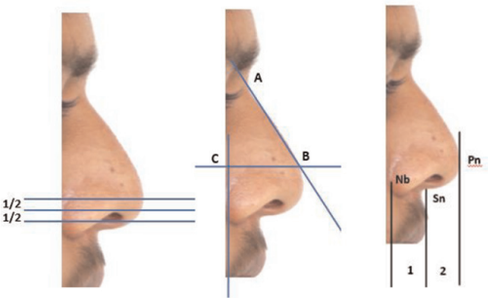
Model surgery and paper surgery furnishes a secure method of designing a treatment plan for a surgical patient, using the fundamental diagnostic tools such as photographs, study models and cephalograms.

After a detailed clinical and radiographic assessment, the data obtained is integrated in the paper surgery to set up a surgical plan. Further, the model surgery is reproduced on a face-bow transfer, transferred on articulator which facilitates surgical splint creation. The treatment plan, when using 2D data, is essentially a composite of clinical evaluation and cephalometric (both lateral and posteroanterior cephalograph) assessment using Schwarz's 'gnathic profile field (GPF)' [9].

3. 2D planning

3.1 Clinical Evaluation

See **Table 1**

Frontal view	**Profile view**
Facial form: Ratio of facial width to facial height is calculated to check the facial harmony [11].	Orbit: Projection of globe of the eye from infraorbital rim and distance of bridge of nose from globes is measured
Transverse facial dimensions: Rule of fifth to evaluate the transverse proportion of the face. 	Paranasal area: Flatness or fullness of paranasal sinus area indicates middle third deficiency/mandibular anteroposterior excess.
Vertical evaluation: Vertical thirds to evaluate the equivalence of face. 	Nose: (a) nostril Show, and (b) nasal projection 
Ferretti-Reyneke Analysis: Five zones of soft tissue facial integument that are under the influence of the	Cheeks: Cheekbone-nasal base-lip curve line should be smooth. Interruption of the curve at MxP (maxillary plane) indicates

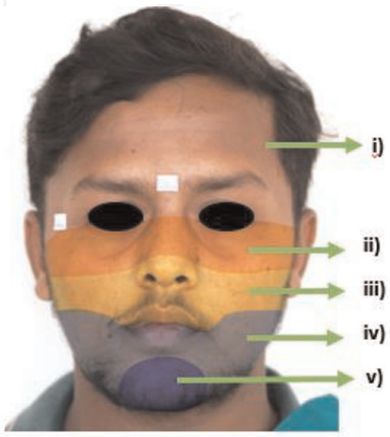
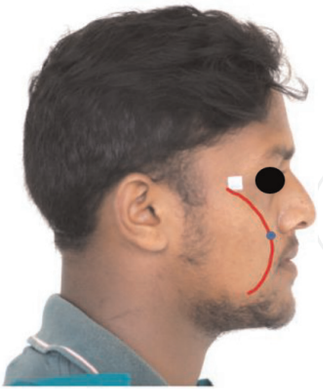
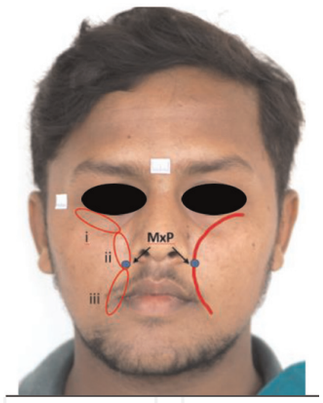
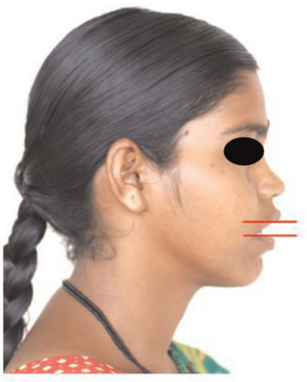
Frontal view	**Profile view**
corresponding underlying skeleton i. Forehead zone ii. Occlusonasal zone iii. Upper maxillary component iv. Lower mandibular component v. Mental subunit 	maxillary anteroposterior deficiency. 
Cheeks: Cheekbone-nasal base-lip curve line should be smooth. Interruption of the curve at MxP (maxillary plane) indicates maxillary anteroposterior deficiency. 	Lips: Upper lip length, interlabial gap, lower lip position 
Facial symmetry: Facial midline is the reference line. Asymmetry is checked in chin, mandible/maxilla or combination of structures	Chin: Height, vermilion exposure, labiomental fold, lower lip chin position, S shaped curvature, chin-Throat Length, labiomental angle, lip chin throat angle
Lips: Symmetry, interlabial gap 	

Table 1.
Clinical evaluation in surgical patients.

3.2 Occlusion and study cast evaluation

1. Occlusal functional evaluation [6]:

   The functional analysis is performed to analyze the centric occlusion and centric relation; any discrepancy between CR CO, bite of convenience or occlusal slide; and interocclusal rest space is noted.

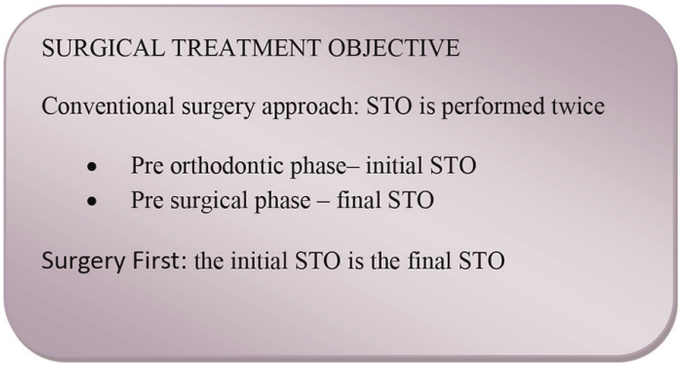
2. Study cast analysis

3.3 Temporomandibular joint evaluation

An evaluation of temporomandibular joint before the orthognathic surgery is essential with regard to diagnostic and prognostic aspect. Mandibular movements along with maximum mouth opening, deviation and TMJ signs if any are recorded. Correct positioning of the condyle in the fossa is a critical part of the orthognathic surgical procedure and information obtained during the pre-treatment evaluation may be useful during the surgery [11].

3.4 Lateral cephalometric radiographic evaluation

The clinical examination along with cephalometric evaluation constitutes the important diagnostic criteria. The information from lateral and posteroanterior cephalometric radiographs forms a crucial part of the database for orthognathic surgical treatment planning. With the help of cephalometrics orthodontists can create a treatment plan through a visual and surgical treatment objective and it also helps to keep a track of the progress of the treatment. Soft tissue cephalometrics is a way of calibrating the facial deformity and identifying its underlying causes. The soft tissue parameters and profile at the end of treatment is greatly influenced by how the orthodontist and surgeon manage the dentoskeletal components (**Figure 5**) [6].



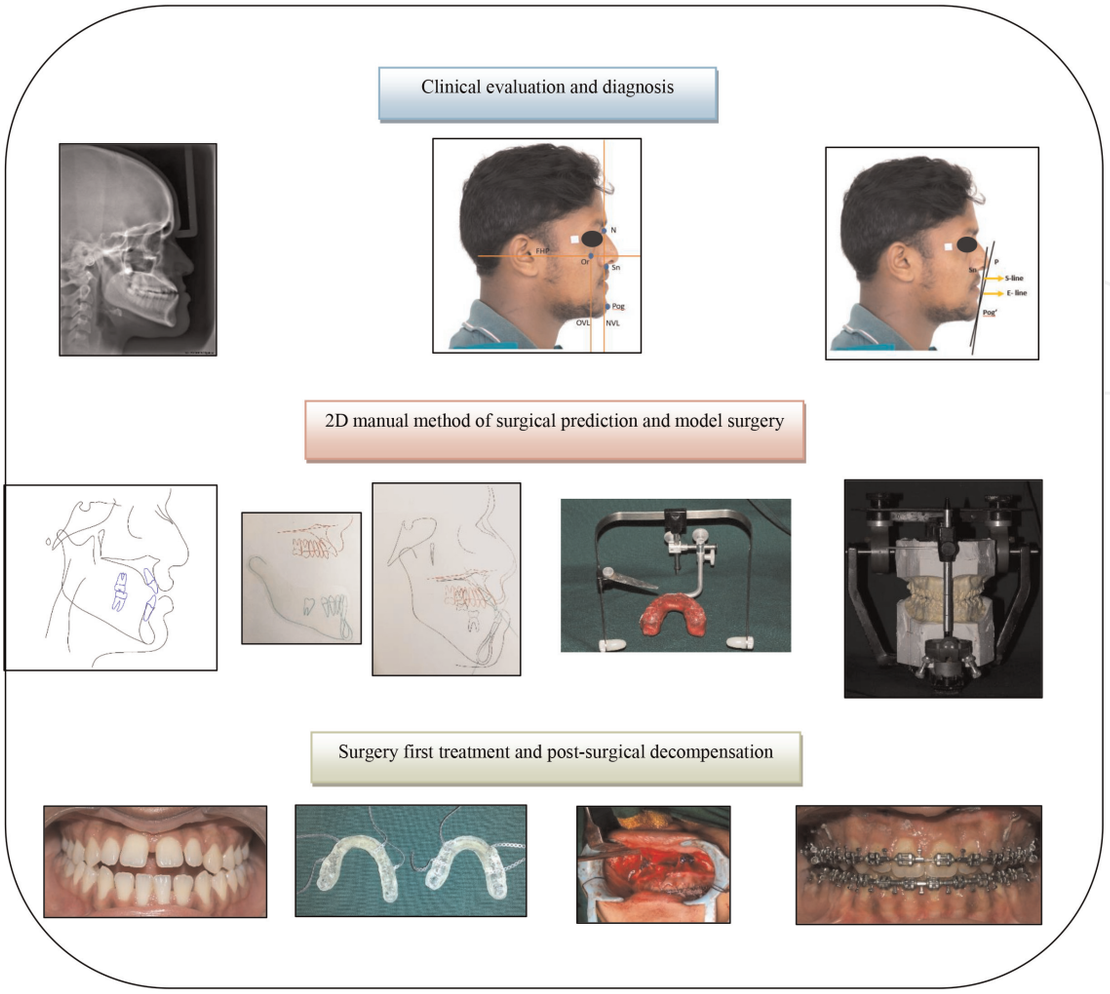
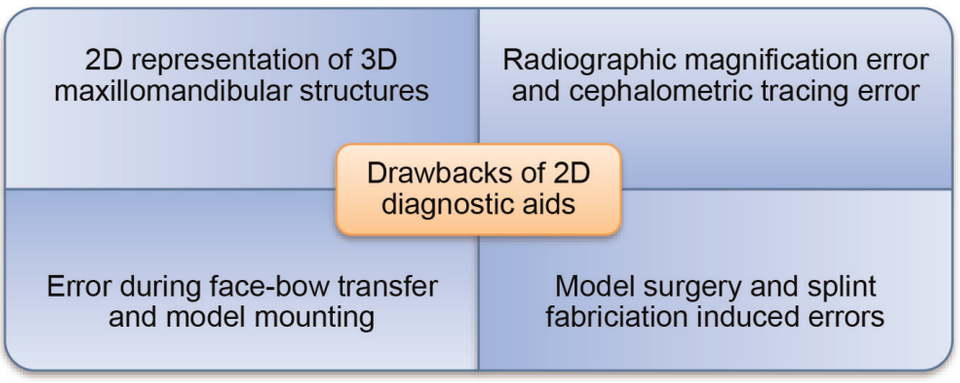


Figure 5.
Summary of 2D evaluation.

Drawbacks of 2D diagnostic aids in SFOA [12]



4. 3D planning

Three-dimensional computer-aided surgical planning techniques for craniofacial deformities were introduced by Xia et al and Swennen et al. For accurate diagnosis and meticulous virtual surgical treatment planning, obtaining precise data from the imaging of the orofacial region in 3 dimensions is absolutely necessary to complement

the clinical examination particularly when treating complex malocclusions with maxillo-mandibular orthognathic surgery [12].

Cone-beam computed tomography (CBCT) for imaging the craniofacial region heralds a true paradigm shift from a 2-dimensional to a 3-dimensional (3D) approach which diagnoses the problem in all 3 spatial planes considering pitch, roll and yaw [13, 14].

CBCT permits a 3D display of the craniofacial structures with possibilities of image segmentation, thereby augmenting the role of imaging from diagnosis to simulation of the orthognathic surgical procedures and fabrication of the computer-manufactured surgical splints surgical splints for effective treatment outcome [12].

It is also possible to visualize the virtual patient by creating an integral fusion model combining the data from all 3 important tissue groups using a CBCT reconstructed bony volume, digital dental models, and a textured facial soft tissue image. The rapid prototyping technology combined with SFOA has aided in virtual setup, treatment simulations and surgical splint fabrication, leading to improved treatment accuracy by eliminating the error. The 3D techniques have profoundly improved the surgery first treatment outcomes, but have disadvantages of increased radiation dose, technique sensitive procedure and high cost.

However, the potential glitch in discrepancies between virtually planned orthodontic movements and actual ones cannot be eliminated totally with introduction of 3D virtual orthodontic set up technology (**Figure 6**) [15].

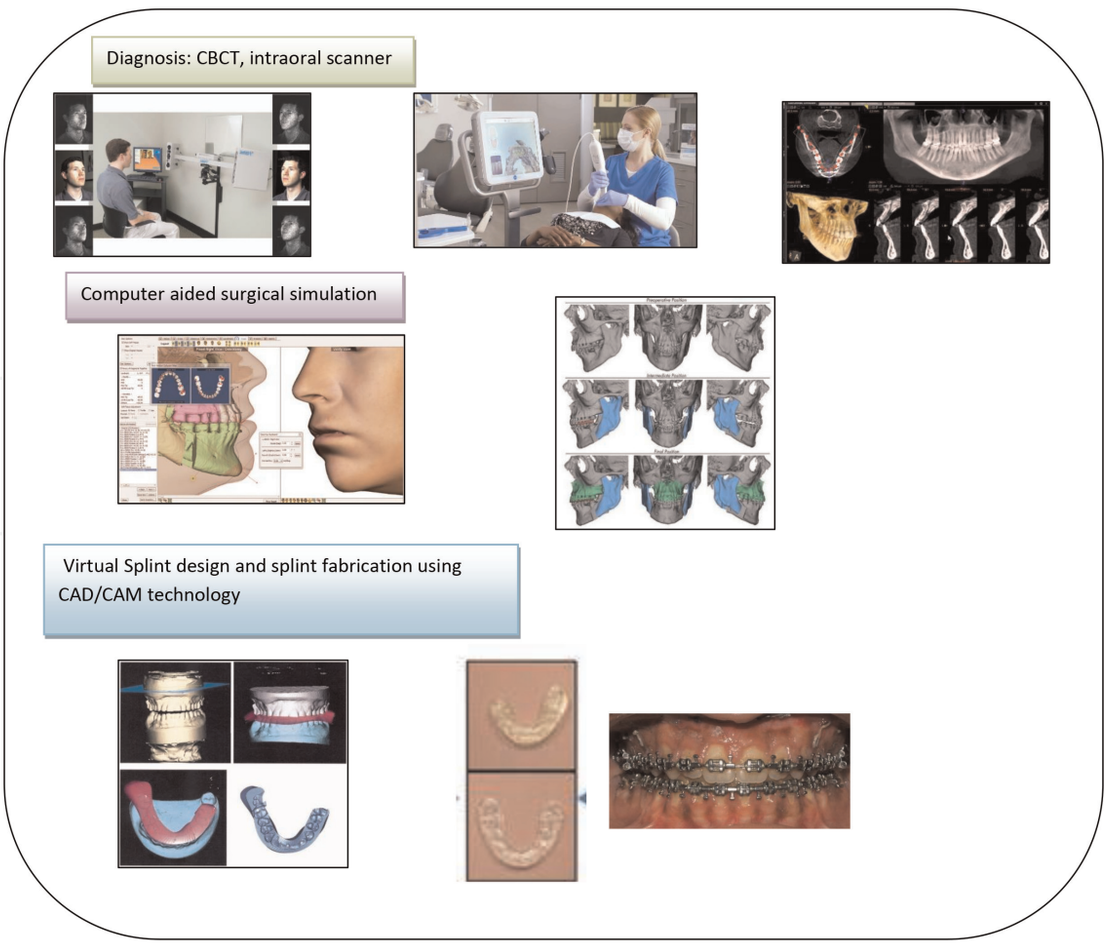


Figure 6.
Summary of 3D evaluation.

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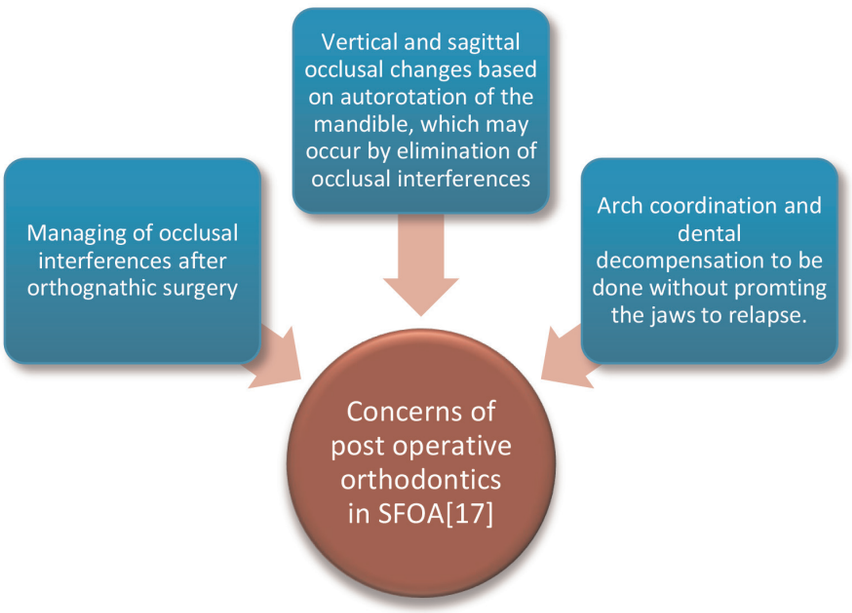
5. SFOA approaches

SFOA procedure incorporates the following steps which are meticulous treatment planning, accurate demonstration of the model surgery and definite post-surgical orthodontics. The 2 approaches are i) surgical driven and ii) orthodontic driven. First approach corrects jaw and dental problems via the surgical procedure and second approach corrects the jaw deformity through surgery and dentition through skeletal anchorage system (SAS) (**Table 2**) [16, 17].

Goals of post-operative orthodontics in surgery-first orthognathics
(according to Lio et al)

- Decompensate the malocclusion
- Detail the occlusion
- Ensure skeletal stability.

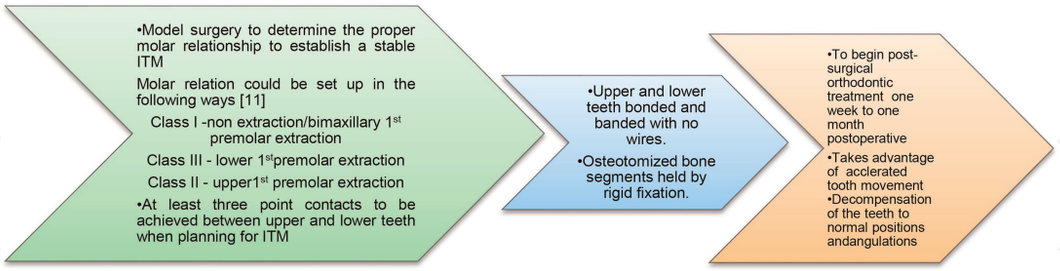


Features	Orthodontic driven	Surgery driven
Background	Technique was given by Sugawara et al of Japan and termed it as 'Sendai surgery first' (SSF) for correction of skeletal and dental deformities using surgery followed by SAS	Skeletal and majority of dental deformities are corrected using surgical approach
Post-surgical orthodontics	Done using SAS which corrects multiple dental complexities	Done with routine orthodontic biomechanics as the complex dental problems are surgically corrected

Table 2.
Two types of SFOA approach.

6. Guidelines for surgery first approach

6.1 General guidelines

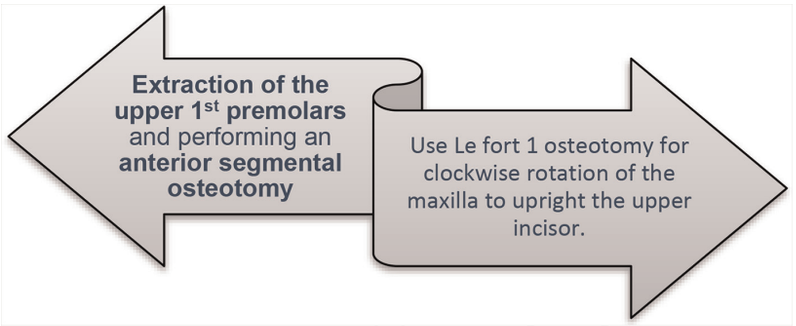


6.2 Specific guidelines

6.2.1 Antero-posterior and vertical decompensation in Class III cases

In Surgery first approach, the incisors can be positioned either orthodontically or surgically after the surgery, in contrast to positioning them orthodontically in a proper inclination in the supporting bone to show the true extent of skeletal discrepancy (decompensation) before surgery in conventional surgery [11].

1. For proclined maxillary incisors: the correction of inclination can be done by 2 methods.



Lack of occlusal antagonist in the mandibular 2nd molar maybe a drawback of the first approach. Hence the second approach is recommended.

Incisor inclination decides the need for extraction

For proclined incisor:

.Extraction considered when upper incisor to occlusal plane angle < 53-55°

. Making occlusal plane steeper by changing the position of maxilla to upright the incisor

. Distalize the maxillary posterior segments using zygomatic plates to gain space to retrocline the maxillary incisors

2. For retroclined and crowded lower incisors:

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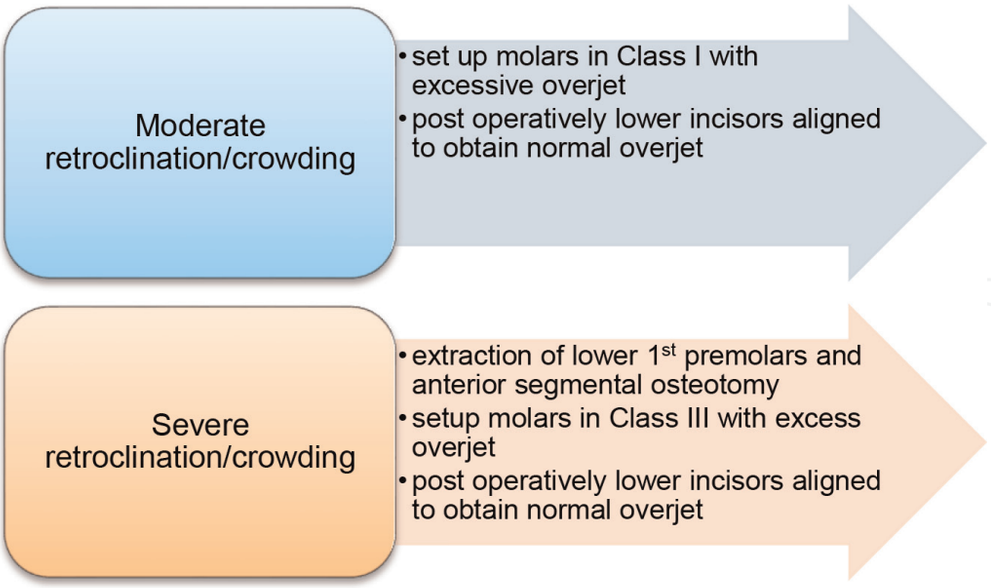


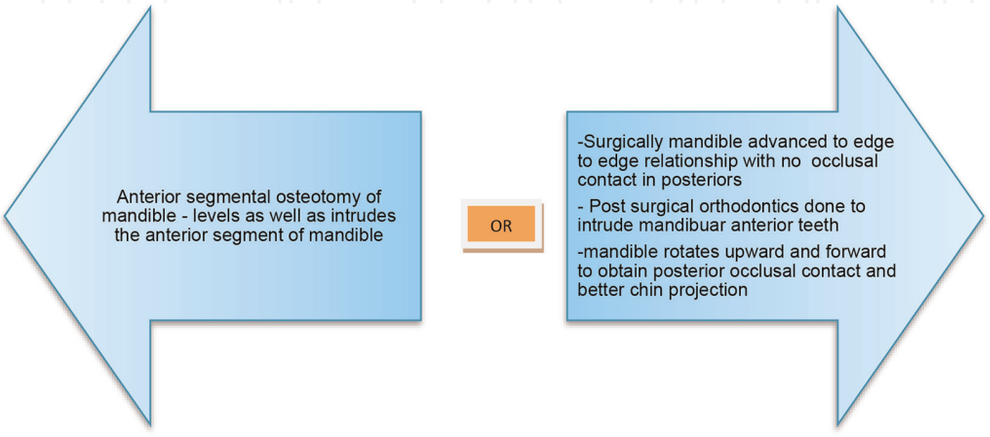
3. Class III case with moderate to steep curve of spee:

   For prevention of post operative forward and upward rotation of the mandible it is levelled pre operatively or by anterior segmental osteotomy surgical procedure. Through upward and forward rotation of the mandible there is improvement of chin projection in case of class II mandibular retrognathism, but it worsens in case of class III mandibular prognathism. Intrusion of lower incisors and extrusion of upper incisors can be done to prevent post operative upward and forward rotation on the mandible.

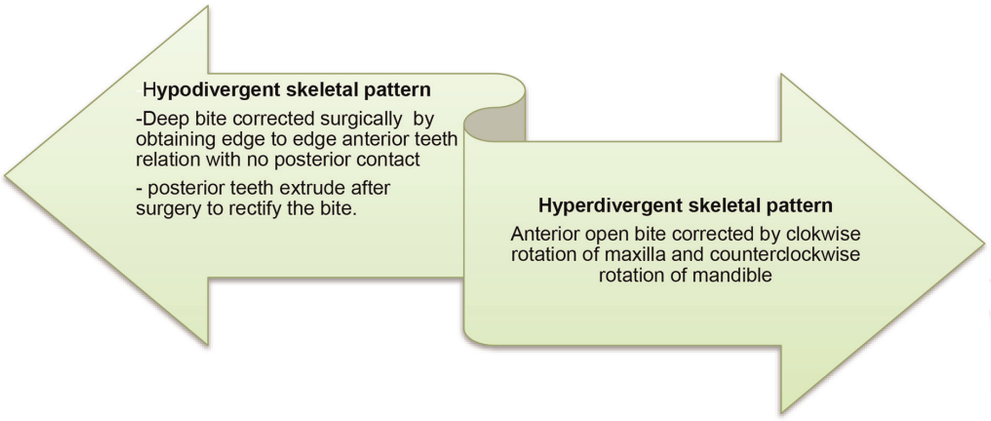
4. In order to prevent relapse of mandibular skeletal malocclusion a chin cup can be applied post operatively in initial 3 months.

6.2.2 Antero-posterior and vertical decompensation in Class II cases

In class II mandibular retrognathism with a moderate to steep curve of spee and proclined mandibular incisors:

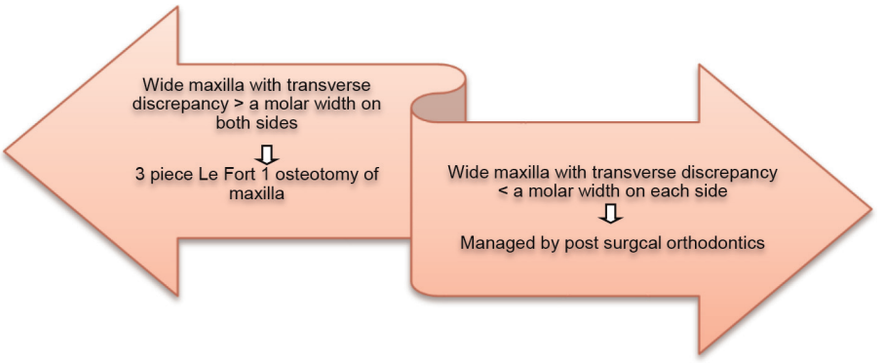


In Class II division 2 cases, a short-term period of minimal orthodontics to upright the incisors or to overcorrect the jaw deformity to Class III relations is indicated to provide sufficient overjet for surgical correction.



6.2.3 Transverse arch coordination

In surgery-first approach, the intercanine and intermolar widths of the upper and lower dentitions are coordinated by either surgery or postoperative orthodontic tooth movement in contrast to conventional surgery where the transverse arch coordination is managed either during pre-surgical orthodontics or during the surgery.



The excessive buccal overjet would be solved postoperatively by the occlusal force or vertical chin cap or orthodontically by a 0.032-inch Beta-titanium constricting transpalatal arch in a short period of time because of the RAP. The transverse dimension often poses a special challenge when performing model surgery in surgery first cases. Depending on the degree of discrepancy between the two arches, the orthodontist can resolve this issue by planning for segmental osteotomies in more severe cases or possibly plan on resolving the issue post-surgically by arch coordination and elastics.

6.3 Surgery first approach with SAS

Recent innovative developments and the relevance of temporary anchorage devices (TADs) or skeletal anchorage system (SAS) in the orthodontics have made postsurgical orthodontic treatment more predictable and scalable.

The outcome of post orthodontic results is based on the orthodontist's expertise towards the conduct of the model surgery [18].

The use of temporary anchorage devices in the post-surgical phase that includes extractions or segmented osteotomies can correct the disparities which are encountered during the challenging surgical phase [8]. In addition, SAS

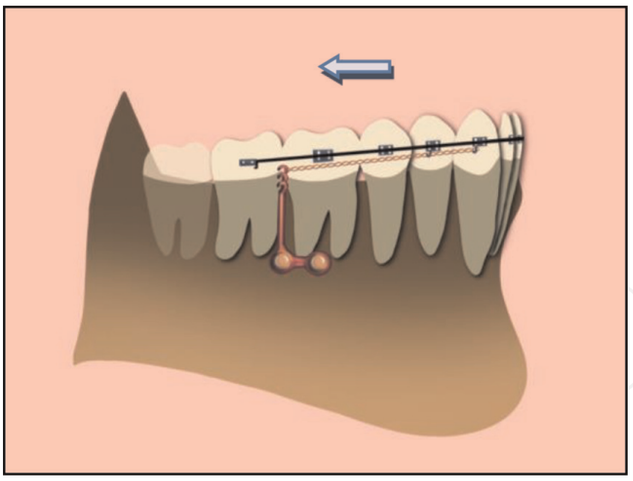


Figure 7.
Orthodontic mechanics used to distalize entire mandibular dentition with miniplate anchorage.

mechanics with SFA can be used to compensate for any surgical errors or skeletal relapse (**Figure 7**).

Diagnosis and treatment planning for surgical orthodontic treatment of patients with skeletal class II relationship with a deep bite pattern and short anterior face is quite challenging. Traditionally the treatment would include pre surgical orthodontics, incisor decompensation, tooth alignment as well as arch coordination. In patients who have short face with deep bite often have heavy occlusal forces due to strong muscles, which may make all these processes more complex.

When surgery is performed first in such cases, the facial height is increased, but the Class II malocclusion worsens to Class III, with an edge-to-edge incisor relationship immediately after surgery. This situation therefore requires the use of Class III orthodontic mechanics. Because it can predictably distalize the mandibular molars in nongrowing patients, the SAS makes it possible to correct a Class III malocclusion and lower incisor proclination without premolar extractions. At the same time mandibular arch can be leveled by extruding the premolars [19].

The TAD permits a wider range of orthodontic vectors and avoids premature bracket loading with secondary troublesome dental extrusion. Interdental corticotomies can augment the tooth movement through RAP and further enhance the orthodontic treatment outcome [20].

7. Conclusion

SFOA has biological, psychological and functional advantages over the conventional orthognathic surgical treatment. SFOA is commonly performed for Class III patients but with precise diagnosis and meticulous treatment planning, it can be adapted for treating Class II patients with retrognathic mandible, one advanced way being the use of SAS along with SFOA.

The future of SFOA technique lies in using augmented skull models, virtual orthodontic set-up to replace the mounted study model set-up and the computer-aided design and computer-aided manufacturing fabrication of surgical splints [19].

3D planning technologies are a clinical reality today. Interpretation of patient's expectations and co relation of this with proper diagnosis and preparation and execution of accurate treatment plan forms the basis for successful orthognathic surgery. Though virtual 3D planning is an additional aid in diagnosis and surgical planning, it is the responsibility of the orthodontist to continue to be experts in traditional approaches of cephalometry as well [11].

According to Pelo et. al Initial therapeutic process as well as Greater part of the responsibility regarding the final result must also be undertaken by the surgeon. Hence the orthodontist does not condition the surgeons work any longer which is contrary to the traditional approach.

Acronyms and abbreviations

SFOA	surgery first orthognathic approach
SFA	surgery first approach
SAS	skeletal anchorage system
ITM	intended transitional malocclusion

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Advances in Dental Sciences

Volume - 9

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AkiNik Publications®
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Published By: AkiNik Publications

AkiNik Publications
169, C-11, Sector - 3,
Rohini, Delhi-110085, India
Toll Free (India) – 18001234070
Phone No.: 9711224068, 9911215212
Website: www.akinik.com
Email: akinikbooks@gmail.com

Chief Editor: Dr. Harkanwal Preet Singh

Publication Year: 2023

Pages: 75

ISBN: 978-93-5570-592-1

Book DOI: https://doi.org/10.22271/ed.book.2118

Price: ₹ 685/-

Registration Details

- Printing Press License No.: F.1 (A-4) press 2016
- Trade Mark Registered Under
  - Class 16 (Regd. No.: 5070429)
  - Class 35 (Regd. No.: 5070426)
  - Class 41 (Regd. No.: 5070427)
  - Class 42 (Regd. No.: 5070428)

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Chapter - 1

Legacy Studies in Epidemiology

Pallvi Sharma, Archita Bhardwaj, Rumeet Kaur, Dr. Sahil Thakar and Dr. Mohit Bansal

Abstract

Epidemiology is the study of health and disease in populations. It emphasizes a descriptive component that captures patterns of disease by person, place, and time and an etiological component that identifies causes of disease. The descriptive element of epidemiology comprises tracking of health and disease indicators and population risk factors (surveillance).

The etiological activities such as searching for the factors responsible and the origin of the disease involved, primarily case control and cohort studies. Epidemiological research encompasses intervention studies both randomized and non-randomized in the assignment of protective measures such as vaccination or other interventions.

This chapter composed of studies done prior to the release of drug into the market. The whole study can be summed up in different phases which can be categorized as:

1) Animal and Human experiments.
2) *In vitro*, *In vivo* & In silico studies.
3) RCT and Non RCT/Non experimental trials.

Keywords: Epidemiology, legacy studies, clinical trials, randomized controlled trials, non-randomized controlled trials.

Introduction

According to John M. Last epidemiology is the study of the distribution and determinants of health related states or events in a specific population, and the use of this study in controlling health problems [1].

The prior studies conducted for a drug which is currently being studied are known as legacy studies.

There are three types of epidemiological studies or methods; Descriptive, Analytical and Experimental. The descriptive and analytical studies are often called observational studies.

Descriptive studies are mostly the first phase of any epidemiological investigation. These studies are concerned with observation and distribution of the disease or any health related events in the human population and identification of its characteristics [2]. It describes the pattern of development of a disease or condition in relation to other features of the population [3]. It aids in quantification of the disease status of a community.

The second major type of epidemiological study is Analytical study. It focuses more on the individual rather than the population. It primarily establishes the cause of the disease by investigating association between exposure to a risk factor and the occurrence of the disease [2]. The analytical study is further divided into; Case control study and cohort study. The objective of an analytical study in epidemiology is to recognize and evaluate the relationship between exposure and a health outcome. The hallmark of such a study is the presence of at least two groups, one of which serves as a comparison group.

The third type of epidemiological study is the Experimental study. These are the trial studies which are in direct control of an investigator. In such type of studies some alterations are done in experimental group while keeping the control group constant followed by observing and comparing the outcome of the experiment in both the groups [4]. These are usually conducted on animals or human beings.

Legacy studies are concerned with Experimental studies only as the drug under study is first tried on an animal or a human and the outcome of the drug is then studied [4].

Aim of legacy studies include

1. To provide a scientific proof of causative factors which allow modification or control of diseases [2].
2. To provide a method of measuring the potency and competence of health services for the prevention, control and treatment of diseased condition and overall health refinement of the community [3].

Experimental epidemiology (Experimental studies)

It is also called as intervention study. This is carried out under direct control of investigator. This study include-Action and Intervention/ manipulation.

This means in tensional application or removal of a suspected cause or changing one variable in the causative chain in experimental group, while making no change in the control group and observing and comparing result of the experiment in both the groups [5].

Aims

1. To have access to scientific proof of risk factors that permit the modification and control of disease.
2. To impart method of computing the effectiveness and efficiency of health services for prevention, control and treatment of disease and to improve the health of a group of individuals [5].

Categories

1. Animal and Human experiment.
2. *In vitro*, *In vivo* and In silico studies.
3. RCT and Non RCT/Non experimental trials.

Animal experiment

Uses

1. For etiological hypothesis (reproduction of disease in animals [6].
2. Study of pathogenic phenomena & complete the history.
3. Test the efficacy of prevention and therapeutic measures [7].

Advantages

1. Animals are bred in lab and manipulated easily.
2. They multiply rapidly and useful for certain experiments.

Limitation

1. All diseases cannot be reproduced.
2. All derived studies cannot be applicable to human [5].

Human experiments

***In vitro* studies:** Procedure done in test tube/ controlled environment outside the living organism.

Advantage: Faster, cheaper, few ethics and safety concerns and allow isolation of specific cells without distraction.

Disadvantage: Fails to replicate precise condition and results may not interpret to real life.

***In vivo* studies:** Done within the living organisms. It has 2 forms

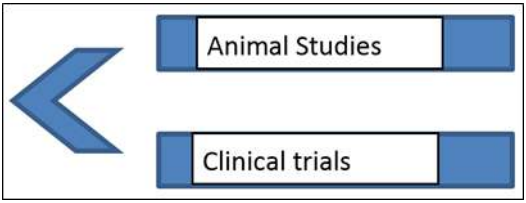

Fig 1: Two forms of *in vivo* studies i.e. Animal studies and Clinical studies

Advantages

1. It has the capability to offer conclusive rights about nature of medicine and disease.
2. These studies are better for observation and overall outcomes of an experiment on living subject.

Disadvantages: Short term benefit but long term harm may result in ethical and safety concerns.

In silico Studies: Performed on computer or by computer stimulation.

Randomized controlled trials (RCT)-(Basic steps)

1) Drawing up a protocol [4].
2) Selecting reference and experimental populations [4].
3) Randomization [4].
4) Manipulation/intervention.
5) Follow up.
6) Assessment of outcome.

Drawing of a protocol: It specifies the design of the study, criteria for the preference of study and control groups, size of the sample, the procedure for allocation of subjects into the study and control groups' treatment to be given and working schedule up to the stage of evaluation of outcome of the study.

Selecting reference and experimental populations: Reference or target population is in which the findings of the trial, if found successful, is expected to be applicable.

Experimental or study population is the real population that participates in the experimental study and it is obtained from the reference population.

Randomisation: It is a statistical procedure by which the participants are divided into groups which are mostly called 'study' and 'control' on the basis of whether to receive or not receive an experimental preventive or therapeutic procedure or intervention.

Randomisation attempts in eliminating bias and it allows comparability so that every individual can get an equal chance of being allocated into either group.

Bias is the error of assessment arising from the outcome of human element. The three sources of bias are as follows

a) **Participant bias:** It happens when participants feel better or report improvement if they know that they are receiving a new form of treatment.
b) **Observer bias:** It happens when the investigator estimating the outcome of a therapeutic trial may be influenced if he knows beforehand, the particular procedure or therapy which is administered to the patient.
c) **Evaluation bias:** It happens when the investigator gives a favourable report of the outcome of the trial.

In randomized controlled trials blinding is important in order to avoid any source of bias.

Blinding can be done in three ways

1. **Single blind trial:** The trial is planned in such a way that the participant will not be knowing whether he is allocated to the study group or control group.
2. **Double blind trial:** The trial is so planned that neither the investigator nor the participant is aware of the group allocation and the treatment received.
3. **Triple blind trial:** This goes one step. Further the participant, the investigator and the person analyzing the data for all blind idly of course treble brining should be used but double bending is the most frequently used method when a blind trial is conducted.

Manipulation/intervention: The next step is to intervene or manipulate the study group by deliberately applying or withdrawing or reducing the suspected casual factors as laid down in the protocol.

Follow-up: It is the examination of the experimental and control group under identical circumstances till final assessment of outcome.

Assessment of the outcome: This is the final step of randomized controlled trials. Positive results are said when experimental measures show reduced incidents or severity of the disease, and negative results are said when there is severity and frequency of side-effects and complications including death.

Study designs

1. Concurrent parallel study

Two randomly assigned groups, one group exposed to specific treatment and other group not exposed.

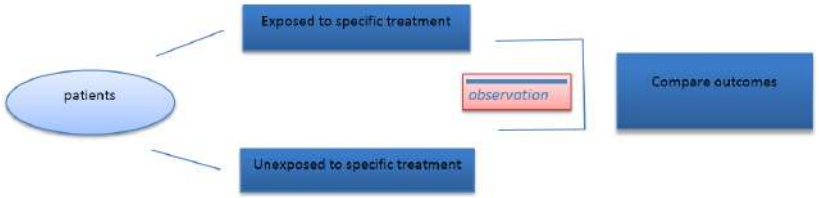

Fig 2: Design of concurrent parallel study

2. Cross over type of study

Each patient serves as his own control [8].

Study: Receives treatment under considerations.

Control: Another form of active treatment/placebo.

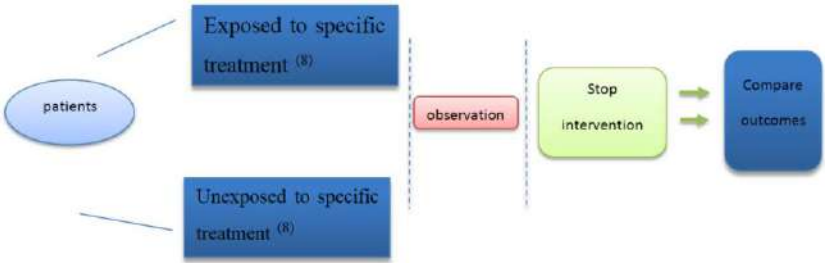

Fig 3: Design of cross over type of study

Types of randomized controlled trials

1) **Clinical trails:** Some common types of clinical trails are-

- Prophylactic trails-Immunization.
- Therapeutic trails-drug treatment, surgical procedures.
- Safety trails-side effects of oral contraceptives.
- Risk factor trails-smoking.

- **Phases of clinical trails:** There are four phases, mainly used for therapeutic agents.

The drug passes through Phase 1, Phase 2, Phase 3 it will be approved by national regulatory authority for use in general population [6]. While Phase 4 includes post approval studies.

Before clinical trails, pre-clinical study [9] is done to evaluate efficacy, toxicity and pharmacokinetic information.

Phase 0 (inspecting if and how a new drug works)

- Recent designation for exploratory.
- Also called as human microdosing studies
- Outline to speed up the growth of a promising drug/imaging agents [6].
- This includes application of single sub therapeutic doses of study design to small number of subjects (10-15) [6].
- It provides no data on safety or effectiveness [6].
- Drug Development Company carry out this to rank drugs in order to decide the best pharmacokinetic parameter.
- They enable go/no-go decision.
- This is not an essential part of testing a new drug.

Phase 1 (To determine if the treatment is safe?)

- First stage of testing human subjects, it includes small groups (20-100) healthy volunteers [6].
- It is planned to access safety, tolerability, pharmacokinetics, pharmacodynamics of a drug [6].
- Subjects receive a fraction of anticipated dose and are then monitored.
- The subjects are observed by full time staff.
- Also called as dose escalation study as it identifies best and safest dose and poisonous dose [6].
- It includes healthy volunteers, in some cases real patients e.g.- patient having HIV/ any other disease can be part of this survey [6].
- It is of short duration of about 1-2 months, volunteers are paid convenience fee according to the length of participation [6].

Phase 2 (to determine if the treatment works?)

- Here the dose is determined then the biological effects are noted.
- Trials are conducted on a larger group and then the effectiveness of drugs is accessed [10] to know the appropriate dose and its safety.
- It is used to continue phase 1 safety assessment in large group of volunteers divided into two parts [6].

Phase 2a: Designed to access dosing requirement.

Phase 2b: Designed to access efficacy of drug.

Phase 3: Clinical trails

- It is better than what already is available in the market.
- These are randomized controlled multi centre trials conducted on big groups (300-3000) and are aimed at conclusive judgment of how effective the drug is in comparison to gold standard treatment. [6].
- It is most time consuming, expensive, difficult especially in chronic medical cases.
- Once approved satisfactory results are combined to large documents.
- This makes up regulatory submission for review in different countries [6] which gives approval for marketing of a drug.
- Most of the drugs are marketed under FDA norms and guidelines by NDA (New Drug Administration) [6].
- In case of any adverse effect the drug is recalled immediately from the market [6].
- Results from this phase are used to evaluate a product to be licensed for general public use.

Phase 4 (What else do we need to know)

- Also called as post marketing surveillance trials [6].
- It involves safety inspection and proceeding technical support of a drug [6].
- It is required by regulatory authorities for competitive reasons [6].
- The surveillance detect any rare or long term adverse effects over a large populations over a long time (Approximately 12-18years) [6].

Phase 5 (Has the new therapy integrated into wide clinical practice)

- In this phase research is done and evaluated and the patient are not monitored.
- It determines integration of new therapy into clinical trails.

2) Preventive Trials

- These are done to prevent disease.

- These are most common type.
- Under this are-vaccine trials and chemo prophylactic drug [6].
- The trial is applied to group of subjects instead of to individual subjects.
- As they require great number of individuals, in longer time span, there may be increased practical problems in organization and execution of the obtained results.

3) Risk factor trials

The investigator intercede to break the usual order of the development of the disease for more susceptible individuals.

It often involves modification of the risk factors.

4) Cessation experiment

A preventive trial is an attempt which is made to estimate the termination of a habit which is casually linked to a disease.

This trial causes reduction in the disease.

5) Trial of etiological agents

Since the diseases are mostly fatal or disabling, human experiments to know the etiological hypothesis are seldom possible [7].

6) Evaluation of health services

Here we choose the services according to priorities and resources which contribute to welfare of the society. The necessity of priorities arise from the fact that resources are limited in the society.

7) Community intervention trials

Carried out in hospitals or clinics and in group with specific health condition. E.g.: testing of vaccine.

The communities should be similar as much as possible, as only small number of individuals are selected. As blinding is not possible in these types of studies, contamination & co intervention may occur.

Some types of such trials involve:-

a) Community diagnosis, which evaluate the assessment or analysis of needs.

b) Design evaluation which evaluates the outline of a health service.

c) Effectiveness or evaluation of a process, which evaluate the performance and effectiveness of delivery of the services.

d) System evaluation relating to the inputs and control of program which includes cost benefit analysis.

Non Randomised Trials (Quasi-experiments)

Non experimental methods are used for practical purpose

Ex-induction of cancer by virus (The history is long but frequency of disease is low) [1] that is why we depend on other study designs. Here degree of comparison is low

Ex-

Uncontrolled trails

Natural experiments.

Before and after comparison studies [7].

Conclusion

These are the studies done before introduction of certain drug into the market. It involves humans, animals in certain environment to see the effects of the drugs.

It is important as it shows how a drug can have a effect on certain disease and on the living organism [10].

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Chapter - 2
A Novel Development in Intra-Oral Bone Conduction Hearing Aid: Molar Mic or Soundbite Hearing System

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Chapter - 2

A Novel Development in Intra-Oral Bone Conduction Hearing Aid: Molar Mic or SoundBite Hearing System

Dr. Vishal Mehrotra, Dr. Asheesh Sawhny and Dr. Karuna Singh Sawhny

Abstract

In this world of technology, we as medical and dental specialists are interdependent on each other when it comes to the treatment of number of diseases affecting humans. One of such condition often affecting the human population is hearing loss or much specifically the single sided deafness. Single Sided Deafness (SSD) is the term given to significant or total hearing loss in only one ear. SSD is usually a permanent condition which impairs one's ability to tell the direction a sound is coming from. It can also be responsible for difficulty understanding speech or conversations on the deaf ear side, particularly in a noisy environment. The SoundBite hearing system allows people with single-sided deafness to wear an intraoral device and a small microphone in the deaf ear to regain lost hearing. Unlike implantable bone conduction hearing aids, SoundBite requires no surgery. Rather, it is the world's first removable and non-surgical hearing solution to use the well-established principle of bone conduction to imperceptibly transmit sound via the teeth. Custom made for each patient, SoundBite is simple, removable, and totally non-invasive. Further, no dental alterations to the teeth are necessary, and the device is virtually invisible. SoundBite has been clinically proven to improve one's ability to hear and understand speech, even in noisy environments. The goal of this article is to introduce and highlight the importance of this noninvasive system to the dental surgeons, orthodontists and audiologist, and help them in making use of this appliance for treatment ofpatients with single sided deafness

Keywords: SoundBite, Bone-anchored hearing aid, Sensorineural, Single Sided Deafness

Introduction

Hearing loss is a significant and common disability that affects approximately 9% of the Canadian population [1]. Overall it is estimated that

16% of UK adults and 50% of those over 75 are affected by some level of hearing loss [2]. This disability is more prevalent in older populations and if uncorrected can lead to social isolation and communication difficulties [3, 4].

Hearing loss can be broadly classified as sensorineural (inner ear), conductive (external and middle ear), or mixed hearing loss. In sensorineural hearing loss, the auditory cranial nerve or part of the bone of the inner ear is defective due to aging, heredity, viral or bacterial infection and other conditions. Single sided deafness is another term used for unilateral sensorineural deafness [5].

It is a condition where the inner ear on one side has difficulty sending signals to the brain, but the outer and middle parts of this ear function normally [2]. It is estimated that at least 70% of those with single-sided sensorineural hearing loss will experience difficulty localising the source of a sound and picking out sound in background noise [6]. This may cause feelings of isolation, difficulties with employment, and problems as a pedestrian or driver [7].

In conductive hearing loss the sound waves' path through the ear canal, past the ear drum, and into the inner ear is impeded by a physical or mechanical blockage, e.g., a totally blocked ear canal at birth (atresia), tumors in the ear canal, long-term infections of the ear canal (otitis externa) or ear drum (otitis media, tympanic cavity infection), or severe skin problems in the ear canal, such as dermatitis [5], glue ear, wax build up, a burst ear drum and abnormal growth of bones in the middle ear [2].

Mixed hearing loss is a combination of both conditions. The degree of hearing loss is defined as mild (26 to 40 decibels (dB) hearing loss), moderate (41 to 55 dB hearing loss), moderately severe (56 to 70), severe (71 to 90 dB hearing loss), and profound (91 dB or more hearing loss) [5].

Air-conduction hearing aids (ACHAs) are the standard treatment for hearing loss that cannot be medically or surgically corrected. This technology assessment focuses on the use of semi-implantable electromagnetic hearing aids and bone-anchored hearing aids as an alternativeto ACHAs for the treatment of hearing loss [8].

Semi-implantable electromagnetic hearing aids use the periodic attraction and repulsion of two magnetic fields, one electromagnetic and the other static magnetic, to cause vibration of the ossicles and transmission of sound to the inner ear. When the external sound processor receives sound, it is transformed into electrical signals, which are then amplified and transmitted to a magnetic device that is surgically implanted into the middle

ear. The implant's vibrations directly drive the ossicles' movement, producing amplified sound perception. By mimicking the natural vibrations of the ossicular chain, an enhanced signal is sent to the cochlea, resulting in a clearer sound that can be increased without the volume amplification required by ACHAs. In addition, since the air pressure on each side of the sound processor is the same, the wearer does not experience the feeling of occlusion that is common with standard hearing aids [8].

While conductive hearing loss can often be treated with ACHAs, in some cases (e.g., those resulting from the congenital malformation of the external ear canal, pinna and middle ear structures) the use of ACHAs is precluded. In these cases, a standard bone conducting hearing aid (BCHA) is required. A bone-anchored hearing aid (BAHA) is an alternative to a standard BCHA [8].

BAHA devices take advantage of the physical property of bone to conduct sound. The device plays a vital role in treatment of conductive hearing loss and unilateral sensorineural hearing loss [9]. The BAHA system consists of three components: a titanium post implant, an external abutment and an electronic sound processor. It is important to note that the BAHA system requires surgical implantation of the titanium post followed by the integration of the implant into the bony architecture. The device works by transmitting sound through bone to the inner ear thus, skipping both the external auditory canal and the middle ear [3, 9]. In the case of unilateral sensorineural hearing loss the sound is transmitted transcranially and stimulates the cochlear fluid of the unaffected inner ear. The titanium screw is implanted directly into the mastoid bone in order to overcome the loss of energy during the transcutaneous transmission of sound. The electronic sound processor is responsible for the transmission of sound vibrations via the external abutment to the titanium implant [10]. There are a number of complications associated with the BAHA device. The most common complication is skin irritation at the site of the implant. A more serious complication is the failure of the titanium post to osseointegrate. This complication can lead to poor function or failure of the implant. In addition, several less common but potentially dangerous complications such as skin flap necrosis, wound dehiscence; bleeding and pain have been reported [10, 11].

Bone conduction hearing aids are used in very young children who are not candidates for air conduction hearing aids. Bone conduction hearing aids may be uncomfortable to wear because they are comprised of a bone conduction transducer held in place by a steel springband over the head. A

potential alternative to conventional bone conduction hearing aids are bone-anchored hearing aids held in place by a headband. Use of a headband allows the bone- anchored hearing aid to be held against the skin behind the ear. In this application there is no implantation surgery; rather, the sound processor is attached firmly to the head using either a hard or soft headband, and the amplified vibrational sound is transmitted transcutaneously to the bones of the skull for transmission to the cochlea. Children may use a headband until their temporal bone is mature enough for implantation of a bone anchored hearing aid. For adults, a headband is often used to determine whether they might benefit from bone conduction hearing technology [8].

Semi-implantable electromagnetic hearing aids and bone-anchored hearing aids are classified by the U.S. Food and Drug Administration (FDA) as hearing aids [8].

Totally implantable hearing systems are also being evaluated in patients with hearing loss. This form of device is totally implanted behind the outer ear and in the middle ear. Unlike hearing aids, this device does not use a microphone or a speaker. Three implanted components comprise the system: a sound processor, a sensor and a driver that converts electrical signals transmitted by the sound processor to the inner ear, where they are perceived as sound. The device is powered with a maintenance-free battery that may last up to nine years and requires no recharging. Another totally implantable active middle ear device uses a microphone implanted beneath the skin. Sound is picked up by the microphone and transmitted to a transducer in the middle ear. The transducer vibrates the bones of the middle ear allowing vibrations to enter the cochlea [8].[8]

The sound conduction property of bone exploited in the BAHA technology has also been applied in the most recent technological advancement for the treatment of unilateral sensorineural hearing loss; the SoundBite Hearing Aid [12].

The soundbite hearing system

A unique technological approach for the treatment of unilateral sensorineural hearing loss is the use of a removable oral device called the SoundBite hearing system developed by Sonitus Medical [4].

The SoundBite hearing system also makes use of the sound conduction properties of bone; yet, unlike the BAHA system, does not require the use of surgery [4, 13]. This system uses a microphone unit housing a receiver and wireless transmitter to receive sound (Figure1). The microphone portion of the unit sits in the affected ear canal to take advantage of the ability of the

ear's pinna and external ear canal to capture and direct sound into the microphone, while the receiver and the transmitter sit in a unit behind the affected ear [4, 13]. The unit then transmits the captured sound wirelessly to a removable oral device similar to a retainer that sits over the maxillary molars in the mouth (Figure 2). The oral device touches several structures in the mouth including the gingiva, teeth and the inner cheek (Figure3). The electrical signal from the behind the ear transmitter is captured by the oral device and is transduced into vibrational energy using a piezoelectric transducer [13]. The vibrations are conducted by way of the teeth to the bone and transcranially to the cochlea of the ear. One of the advantages of the piezoelectric transducer is that it allows a much wider frequency range to be conducted through the teeth than the traditional electrodynamic transducers used in the BAHA systems [13].

The SoundBite intraoral device is similar to a retainer or partial denture worn in the maxillary arch. Parts of the SoundBite touch the gingiva, teeth, and inner cheek. An actuator on the buccal side of the device has a round post that fits typically between the 2 most distal teeth; this is the part that creates the sound. The battery and electronic components are on the lingual surface and connect to the actuator via a wire from the buccal to the lingual aspects along the distal surface of the most distal tooth.

A proper intraoral examination should be done by the dentist before fitting a SoundBite appliance; this includes visual as well as radiographic examination and probing to make sure that the teeth are healthy. The SoundBite is a removable device, and the abutment teeth are usually the last three in maxillary arch. There can be no active caries or periodontal or endodontic conditions affecting the abutment teeth. SoundBite has been successfully used on teeth with fillings, crowns, or implants or those have had endodontic treatment. Anatomy and orthodontic placement must be considered. If a tooth is worn or a crown poorly contoured, the SoundBite might not have enough retention, if the position of the teeth is poor, then the patient might not derive the full benefit from the device. Orthodontic treatment might be needed to align the teeth before usingthe device [4].

Since the device vibrates the maxillary molars to transmit vibrations to the bone, this force of the oral device is four orders of magnitude lower than the forces exerted on the teeth by normal mastication and is within the force range of normal orthodontic devices and does not damage the surface of the maxillary molars [13]. Moreover, the oral device is comfortable, well tolerated in most patients, does not affect the speech and can even be worn while eating [4, 13].

Some of the disadvantages of the Soundbite system are: the patient cannot drink alcohol while wearing the oral device, risk of aspiration/swallowing of the oral device if the patients physical responses are impaired, and the most important is that healthy teeth are needed to fit the device properly and good oral anatomy for full benefit; the last three teeth in the maxillary arch are usually the abutment teeth and must be free of active caries, periodontal and endodontic conditions [12].

There are several advantages of the SoundBite hearing system compared to bone anchored hearing aids (BAHA)which include: avoidance of surgery and surgical complications, no need to wait 3 months before use since osseointegration is not required, discreet oral device and discreet behind the ear unit with optimized microphone location does not cause discomfort, the device helps in delivering high fidelity sound with a wide frequency range and lastly the removable nature of the device is patient friendly [12].

Conclusion

We live in an exciting time in the world of medicine and dentistry in which we can truly be part of the health of the total patient. The SoundBite is a new hearing prosthesis that delivers bone conduction energy. It is a nonsurgical, noninvasive treatment for SSD. It requires the expertise of at least 3 health care specialists: a physician, an audiologist, and a dentist. The patient must have healthy teeth with acceptable alignment and good undercuts for the appliance to have the right amount of retention. The SoundBite has significantly provided an improvement in ease of communication, hearing in background noise, sound reverberation, and an overall global hearing benefit.

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Chapter - 3
Evidence Based Decision Making in Dentistry

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Chapter - 3

Evidence Based Decision Making in Dentistry

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Abstract

Evidence Based Decision-Making relates to the idea that effective decisions are formulated on the analysis of information and data, rather than anyone's instinct or assumptions. Evidence based decision making is the consolidation of best evidence available with clinical practice for the best outcome. It can thus act as a vital guide in clinical practice to provide best patient care thereby helping in refining the quality of healthcare.

Keywords: Research, clinical practice, healthcare, evidence-based, dentistry

Introduction

"If our ideas are not evolving with verifiable evidence, they are not reliable ideas"

-C.A.A. Savastano

Evidence is basically the data from which a judgement or a conclusion can be postulated. Evidence Based Decision-Making relates to the idea that effective decisions are formulated on the analysis of information and data, rather than anyone's instinct or assumptions. Evidence based decision making basically involves making decisions concerning a practice or program by virtue of scientific evidence, which can be research based, experience based and relevance based. Addressing a problem with what research says and with evidence base, has become a new way of life in majority of the fields. Appropriate foundation for decision making includes the contributions from various researchers and practitioners in the field in order to put forward a more complete and concise view of evidence. Hence in short; Evidence based decision making is a way to introduce the best research in patient care and practice [1].

The basic foundation of evidence-based decision making is high quality research and the use of evidence.

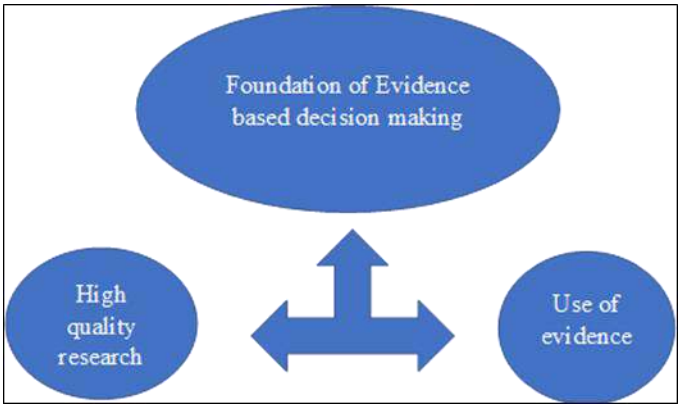

Fig 1: Foundation of Evidence- based decision- making

Each profession has its own inherent principles. Clinical care forms the corner stone in healthcare profession. Healthcare profession takes decision on clinical care for successful treatment outcome. To enhance this success, it is essential to take the support of the available scientific evidence. Hence the usage of immense wealth of research information must be included in the clinical practice. And Evidence-based practice is such an advent which blends the research and evidence into clinical practice and patient care to get the best treatment outcome. So, it is the integration and application of best accessible research evidence to provide relevant inputs for decision making in clinical practice. Evidence based decision making has a great impact in clinical practice and outcome. This approach amalgamates critical thinking and the best available evidence.

A good knowledge of the current evidence or the potentiality to search the literature and evaluate the content and its relevance is an essential requirement for Evidence-based decision making. This evaluated evidence should not be taken as the resort for the decisions of individual patients. Clinical experience as well as patient preferences have to be considered along with the evidence in order to make righteous decisions. Many hardships have been faced in recouping and evaluating the evidence. Hence along with evidence, clinical experience and patient opinions and preferences stand together in the right decision making.

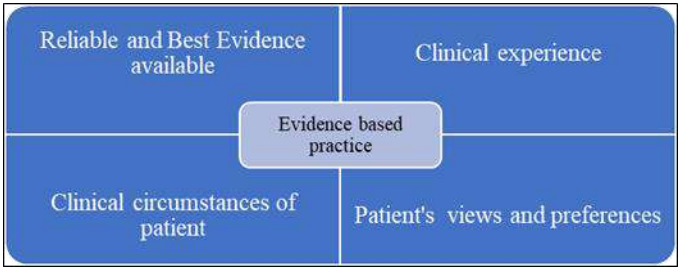

Fig 2: Pillars of Evidence- based decision- making in clinical practice

Prior to evidence-based practice

Prior to evidence based practice, health professionals took the advice of more senior and experienced colleagues, their intuition and what they were taught during their student time-frame. But experience can have flaws and what studied before as students become outdated. Hence instead of depending on clinical experience alone for decision making, it is always better to use evidence-based information.

What is the need for evidence based decision making?

First and the foremost, evidence-based decision-making plays great role in providing quality health care. Secondly, variations in the practice patterns and the longer gap of clinicians to update their knowledge also demands an evidence-based decision making in clinical practice. It helps in demonstrating the best use of limited information, which the clinical practitioners can use to keep them updated and apply it in their routine clinical practice. This precious tool, helps in improving the efficiency of health care practitioners as well as in developing confidence among them and a self-motivated learning, thus creating better practitioners.

Evidence based practice aims to give the most effective patient outcomes with a promise of patient care. Patients can look for potent individual care rooted on the best available evidence. Hence the clinical practice will be based on the best available evidence ensuring that finite health resources are used judiciously.

Major aspects of evidence

Taking into consideration about the quality of research, it should be noted that all researches may not have sufficient quality to guide in clinical decision-making process. Hence, critical appraisal of evidence is a must before using it in clinical decision making. The three main aspects of evidence which we are supposed to critically appraise include its validity, impact and its applicability.

Validity-Whether you can trust it??

Impact-Results are clinically important?

Applicability-Whether you can apply it on your patient?

Levels of evidence

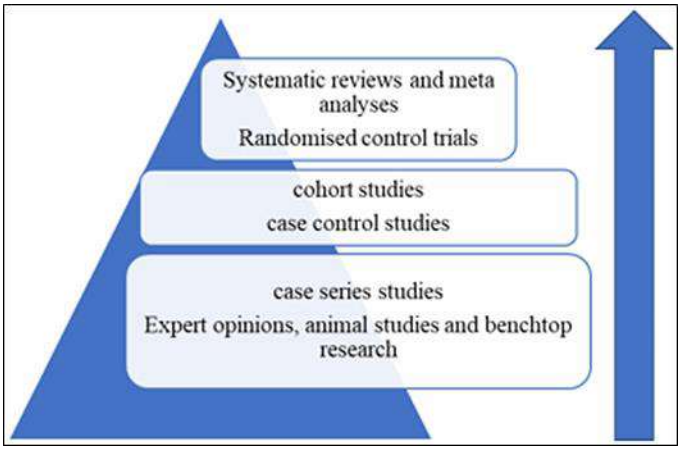

Fig 3: Levels of evidence

This pyramid depicts the hierarchy of evidence, showing the strength of evidence; with bottom (expert opinions, animal studies and bench top research) showing the weakest evidence and the topmost (systematic reviews and meta-analysis) showing the strongest evidence that can be considered [2].

Stages of the decision-making

Stages of evidence based decision-making process starts with the recognition of knowledge gap. The process continues by involving mainly gathering, assimilating, interpreting, applying of the evidences and information and finally evaluating the effects.

Gathering evidence basically is to seek out the best available research evidence and collecting contextual information required mainly for the decision. The highest quality evidence is considered apt to be used. But if it does not exist, lower levels of evidence will be taken into consideration. But in such cases, the research design is more susceptible to bias and data will be less reliable.

How to assimilate the scientific evidence?

Extensive search for the scientific evidence using electronic databases like MEDLINE (PubMed) and the Cochrane Library, by scientific articles.

Attending courses and conferences

From these, benefits are borne by the practitioners and the patients.

Next comes interpreting of evidence by considering the experience, views and preferences of stakeholders. Ensuring the accuracy, reliability and accessibility of the research data and information gathered is very important. All these strategies must fit the location and population affected by the decision. Considering the different evidences (best available evidence, contextual evidence, experiential evidence) should be done in order to provide the best practice. Lastly, evaluation of the effects has to be carried out to analyse and confirm the expected outcome.

In clinical practice, as evidence-based decision making starts with the identification of the knowledge gap, it gives a question for further relevant information search. After information search, both the internal and external validity of the research must be considered [1, 3].

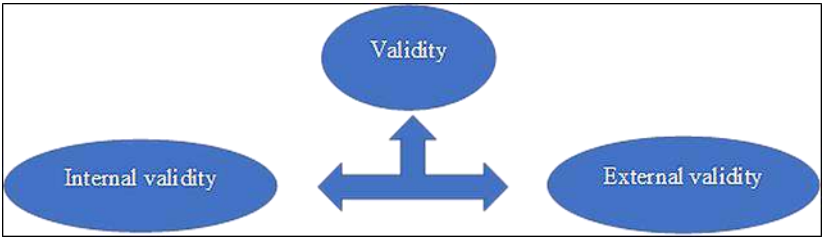

Fig 4: Validity of Research

Internal validity mainly focuses on the method of research and external validity hinge on the generalization of the findings outside the study. This external validity is affected by the way of treatment given. Like the time period of treatment rendered and the inclusion criteria may affect the external validity. After collecting and assessing the research, it has to be applied clinically and later the results must be evaluated to unveil the efficacy of it in achieving successful and expected outcome [1].

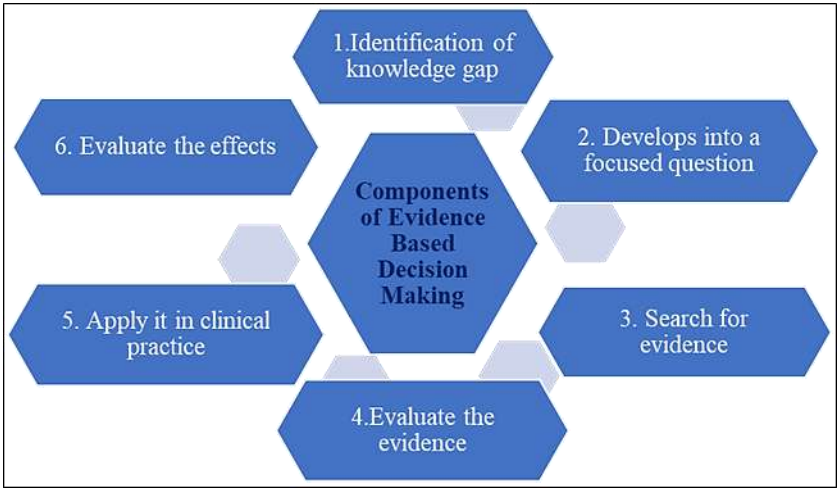

Fig 5: Components of Evidence- based decision- making

Qualities of decision making

Evidence based decision making thrives at attaining all of the qualities to achieve successful outcomes. The qualities include-Transparency, participation, openness, facilitation and defined process. Each decision-making is unique and the attainment of these qualities differ in each situation.

Even though Evidence based decision making has unique qualities which can give good outcome in the treatment as well as help the health care professionals and patients, there are certain misconceptions and limitations which has to be mentioned.

Misconceptions include

- It is limited to clinical research.
- It ignores patient's preferences and opinions.
- It criticizes clinical practice.
- It fosters reasonless clinical practice.

Limitations include

- Less scientific evidence availability.
- Less resources and less time to search and understand research findings.
- Difficulties in applying evidence in individual treatment of patients.
- Less evidence that evidence-based decision-making works.

- Requirement of new skills or limited searching skills.
- Hinderance to practice high-quality medicine.

Future considerations

As in any other field, healthcare field is experiencing many changes due to extensive research works and developmental activities. Evidence based decision making leads to performances with a more desirable effect with less bias, as it uses high quality data and experiential evidence to make decision and get better outcomes. In healthcare professions, professionals work with much scientific and objective data on the health conditions of the patients even though some believe that clinical practices have too long subjective in nature.

Sufficient literature searching knowledge is very much essential to obtain current, accurate and relevant evidence. Training in evidence-based decision making or evidence-based practice is a must to support the goal [4]. Evidence based practice is gaining popularity because of its great potential to deal clinical issues effectively and provide better individual patient care. Being open to learn from comparing and contrasting views and refining our skills is very important to upgrade evidence-based practices. Using evidence-based practice can help in reducing the shortcomings of conventional standard care.

Conclusion

High quality research and the usage of evidence form the key for evidence-based decision making. This approach has a great hand to modify clinical practice in a better way as it uses a strong appeal to address the strengths as well as flaws of the evidence. It takes the effort to gather all available data as well as reduce the bias in condensing the data. Evidence based decision making is thus the consolidation of best evidence available with clinical practice for the best outcome. It can thus act as a vital guide in clinical practice to provide best patient care thereby helping in refining the quality of healthcare.

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Chapter - 4
Laminar Optical Tomography (Lot): A New Revolution

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Chapter - 4

Laminar Optical Tomography (Lot): A New Revolution

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Abstract

Laminar optical tomography (LOT) is an optical imaging technique capable of making depth- resolved measurements of absorption and fluorescence contrast in scattering tissue. The technique combines a non-contact laser scanning geometry, similar to a low magnification confocal microscope, with the imaging principles of diffuse optical tomography (DOT). Laminar Optical Tomography (LOT) is a new medical imaging modality for high-resolution, depth-resolved, functional imaging of superficial tissue such as rodent cortex, skin and the retina. LOT uses visible laser light to image to depths of >2mm (far deeper than microscopy) and is highly sensitive to absorption and fluorescence contrast, enabling spectroscopic functional information such as hemoglobin oxygenation to be imaged with 100-200 micron resolution. LOT has been used to image the hemodynamic response to stimulus in the somatosensory cortex of rats. The resulting three-dimensional (3D) images through the depth of the cortex can be used to delineate the arterial, capillary and venous responses, revealing new information about the intricacies of the oxygenation and blood flow dynamics related to neuronal activation. Additional applications of LOT are being explored, including the integration of 3D Voltage Sensitive Dye fluorescence imaging. LOT imaging uses a system similar to a confocal microscope, quickly scanning a focused beam of light over the surface of the tissue (~8Hz frame rate). Light is detected from both the focus of the scanning beam, and also at increasing distances from the beam's focus. This scattered light has penetrated more deeply into the tissue, and allows features at different depths to be distinguished. An algorithm that includes photon migration modeling of light scattering converts the raw data into 3D images.

Keywords: Tomography, optical, confocal, microscopy, imaging

Introduction

The ability of light to probe biological materials stems from the numerous interactions light undergoes with its environment. In biological

tissues, these interactions include, among others, absorption, scattering, and fluorescence. While scattering can be used as a source of optical contrast, it also presents a significant challenge to optical imaging as it limits the penetration depth of optical techniques by attenuating light and introducing uncertainty in the path that the light travels. In the past few decades, advanced optical imaging techniques have been developed to exploit the value of optical contrast while maximizing resolution and penetration depth. Techniques such as confocal microscopy offer increased resolution and contrast (compared to conventional fluorescence microscopy) by rejecting out of focus light while techniques such as diffuse optical tomography push the penetration depth of optical imaging through innovative instrumentation and advanced tomography algorithms.

Laminar optical tomography (LOT) was developed to record depth sensitive measurements of light in order probe optical properties of tissues beyond the depths of conventional microscopy and with resolution exceeding that of diffuse optical techniques. The technique relies upon scattering to collect backscattered light and is sensitive to absorption and fluorescence contrast.

As light travels through biological tissues, several light-tissue interactions may occur, including absorption, scattering, and fluorescence. The degree to which these interactions occur is governed by the optical properties of the tissue with local differences in optical properties serving as the source of contrast in optical imaging [1].

Optical imaging provides unparalleled sensitivity to functional parameters such as hemoglobin oxygenation, membrane potential and metabolic processes. In-vivo optical imaging of superficial tissues using CCD cameras has provided valuable insights into the underlying physiology of both healthy and diseased tissues.

Laminar optical tomography is a new optical imaging modality which allows high-resolution, depth-resolved optical imaging of tissue to depths of >2mm, with resolution of 100- 200 microns, at the frequency of approximately 8 Hz frame rate [1]. It is a completely non-contact technique so additional imaging or point measurement can be made simultaneously such electrophysiology recordings or speckle flow imaging. LOT measures light that has emitted from the tissue at some distance offset from the source position. Confocal Microscopy measures ballistic light, limiting its penetration depth but allowing high resolution imaging [2]. DOT detects diffuse light, allowing it to probe deeper into the depths but with poorer resolution. The light measured by LOT is from the region in tissue in which

light has multiply scattered but is not yet diffuse. By measure this light, LOT offers a compromise between the two techniques: providing proper penetration than confocal microscopy and higher resolution than the DOT [3].

Lot basic principle

The working principle of LOT is based on light transport in tissues [4], which includes three primary physical processes: scattering, absorption, and fluorescence. The relative probability of occurrence for each process depends upon the type of sample imaged and the wavelength of light used [5]. For in vivo brain imaging, scattering is the prevalent phenomenon. During light propagation, some of the photons will scatter out from the surface of the tissue. These photons will be captured by the detectors near the tissue surface with various separations from the light illumination/entrance position (source-detector separations). The light emerging at greater distances (i.e., larger source-detector separation) has a higher statistical probability of having travelled deeper into the tissue. By detecting the emerging light for a range of positions with different source-detector separations, it is possible to perform depth-resolved imaging of subsurface tissue structures through a proportional relationship between the source-detector separations and the average investigation depths [6]. Shows the cross-sectional diagram of a typical LOT source detector configuration and representative photon paths. The detection geometry used in LOT is similar to the detection geometry used in DOT. In contrast to DOT, where source-detector separations are typically several centimeters [7], LOT utilizes smaller source-detector separations (from several tens of microns to a few millimeters). As a result of this difference, information from a relatively shallow depth (millimeter or mesoscopic scale) is collected by the detectors, enabling tomographic imaging with a higher resolution compared to that of DOT [8].

Optical design

LOT uses a system similar in design to a confocal microscope, raster scanning a focused laser beam over the surface of the tissue being imaged. It detects both confocal and multiply scattered light. Light that emerges light that has been multiply scattered emerges a distance away from the focus of the scanning spot. The further away that the light emerges, the deeper on average it has travelled. LOT measures the scattered light at 7 different distances away from the scanning point [9]. LOT has seven different pieces of information for each spot scanned, each with differently weighed depth sensitivity. These measurements are combined with an image reconstruction algorithm which incorporates a mathematical model of light propagation in

scattering to convert raw measurements into 3D IMAGES. In the confocal type design light from one of the two lasers is emitted from the optical fiber and collimated. This light passes through a polarizing beam splitter and onto galvanometer scanning mirrors which steer the collimated beam through a scan lens. The scan lens focuses the beam at an intermediate image plane, which is imaged onto the surface of the tissue using an objective lens. Light being remitted from the tissue then passes back through the objective, through the scan lens and is de-scanned by the galvanometers. Since the incident laser lights are strongly polarized, specular reflections from optics and from the surface of the tissue will maintainthis polarization [10].

OCT is an important tool for depth- resolved imaging of living tissue, and is capable of penetrating beyond a millimeter into the scattering tissue with very high resolution. It suffers from poor sensitivity to absorption contrast, and cannot be used to measure fluorescence contrast. This is because OCT deliberately isolates only coherently backscattered light [11]. Can image both absorbing and fluorescent contrast and is hence strongly sensitive to parameters such as haemoglobin oxygenation and can be used to image molecular andenvironment sensitive fluorescent probes [10].

Image reconstruction

The probable paths travelled by light in scattering tissues can be stimulated using radiative transport equation. Diffuse optical tomography is an established technique for imaging large volumes of scattering tissue using near infrared light. LOT uses similar image reconstruction approaches as DOT with main difference that LOT cannot use diffusion approximation to RTE, since the length scales considered are comparable to the scattering length of the tissue, and at visible wavelengths, absorbtion is more higher than NIR wavelengths [12].

LOT has lower resolution than conventional scanning microscopy methods and OCT, it has the advantage that there are no significant physical limit to its depth sensitivity. It also has the advantage of being highly sensitive to both absorption and fluorescence contrast [10].

Instrumentation

The incident light is shown as solid lines originating from an optical fiber. The light is collimated and passed through a beam splitter before being reflected by a set of galvanometer mirrors. These mirrors are computer controlled to raster scan the beam. The beam then passes through a scan lens, collimator detector lens detector image plane x-galvanometer y-galvanometer scan lens mirror microscope objective intermediate image plane sample

plane beam splitter laser photodetectors which convert the angular deviation of the collimated light into lateral translation of the scanning spot [13].

LOT was the first demonstrated in 2004 by Hillman *et al.* where it was shown that the technique could allow high-resolution 3D imaging in a scattering medium over depths of 0-2.5 mm. it was limited in its speed, signal to noise, and was unable to image multiple wavelengths and florescence in parallel [10].

Applications of laminar optical tomography

The advances made to LOT overcame the shortcomings and improves upon many other aspects of the system including faster acquisition rate, larger field of view, and higher measurement density. It is better suited for *in vivo* imaging as it can capture faster responses, measure additional sources of contrast and have fewer motion artifacts [14].

LOT imaging of skin cancer could provide valuable information for skin cancer screening and treatment planning. The ability of LOT to probe beyond the dermal epidermal junction could reveal changes in vasculature beneath lesions which could help deter dermal invasion has occurred or assist in the excision margin determination. The depth sensitive measurement could help determine the lesion depth, an important prognostic factor and parameter for surgical planning. Further it can be used for selecting a region to biopsy within larger lesions [15].

High-dynamic-range fluorescence laminar optical tomography (HDR-FLOT)

In the FLOT system configuration, a charge-coupled device (CCD) or electron multiplying CCD (EMCCD) can be used as the array detector since either one has a higher sampling density in comparison to a photomultiplier tube (PMT) array or an avalanche photodiode (APD) array [8, 16]. During signal collection in FLOT with reflectance imaging mode, the photons collected at larger source-detector separations have a higher statistical probability of travelling through deeper tissues. In general, the detector with a larger source-detector separation collects a lower signal compared to a detector closer to the illumination source, indicating that the deeper area will have a low signal-to-noise ratio (SNR), which will limit reconstruction accuracy [8]. We can increase either the excitation power or exposure time to enhance the collected signals from deeper regions. However, all pixels acquired from CCD/EMCCD have the same gain or exposure time, meaning that increasing the excitation power or exposure time will saturate the pixels near the illumination source very quickly.

Another scenario occurs when imaging fluorescent samples with a large concentration difference (e.g., inhomogeneous dye loading, tumors at different stages), and the area with higher fluorescence concentrations will easily become saturated, while areas with a low fluorescence concentration will have a low SNR, which may affect the quantitative accuracy of FLOT. Ultimately, the insufficient dynamic range of the CCD/EMCCD limits the penetration depth and quantitative accuracy of FLOT. A high-dynamic range (HDR) method based on a multiple-exposure scheme is widely used in digital cameras and smartphones [17, 18, 19]. Taking advantage of the multiple-exposure-based HDR method, HDR optical projection tomography (HDROPT), HDR laser-scanning microscopy (HDR-LSM), and HDR fluorescence molecular tomography (HDR-FMT) were recently reported [20, 21, 22]. Localization of fluorescent targets with a large concentration difference is effectively improved with HDR-FMT. Good quantitative accuracy was demonstrated in both the phantom and in vivo animal experiments [20]. In this paper, we present an HDR-FLOT method to increase both its dynamic range and penetration depth. To assess the potential of this method, we first fabricated an agar phantom in which three 150-μm capillaries filled with different concentrations of Cy 5.5 solution were inserted at similar depths. Then, we obliquely inserted one capillary within the brain of a mouse in vivo to illustrate the improved penetration depth of HDR-FLOT for brain imaging. Our data demonstrated the feasibility of HDR-FLOT in increasing the dynamic range and penetration ability of FLOT, and provide a potentially improved mesoscopic tomography method for imaging neuronal activities.

Conclusion

LOT is a new technique for medical imaging, allowing high resolution imaging to depths much greater than possible with microscopy, and with enhanced sensitivity to absorption and fluorescence compared to OCT. Currently the studies of vascular dynamics using a self-built video rat two photon microscopy systems are being extended [23]. In addition studies are being performed to allow the comparison of these results with those functional MRI to investigate the impact of our observations on interpretation of high blood oxygen level dependent signal. Plans are being made to extend these studies by investigating neurovascular coupling in 3D [24].

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Chapter - 5
Health Benefits of Basil Seeds in Dentistry

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Chapter - 5

Health Benefits of Basil Seeds in Dentistry

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Abstract

Basil is a group of aromatic plant that contains a wide variety of distinct herb and shrubs from the genus species Ocimum Lamiaceae. The term basil is originated from the classic word King. For many years, the leaves of basil plant (*Ocimum basilicum* L.) were frequently used in cooking. These types of plant are referred as Tulsi in many countries i.e., India and Nepal, a number of Ocimum species are utilized in Ayurvedic and other conventional medical systems. Basil is found all over the world and is used in the food, drug and cosmetic sectors. Little is known about the nutritive and functional qualities of the foods. In addition, their use is linked with a number of health benefits, such as prevention of type-2 diabetes mellitus, oxidation inhibitor cardiovascular safety, antibacterial actions, anti-inflammatory, antiulcer and anticoagulant as well as anti-depressant properties. The goal of this review was to explore the existing state of knowledge and the huge potential of basil seeds as a food with therapeutic properties and a source of useful substances for dietary component.

Keywords: Basil seed; nutritional value, novel food, anti-inflammatory, antimicrobial.

Introduction

Basil Seeds belonging to Labiatae family [1] (named as *Ocimum basilicum* L) are designed to be a nutritious food due to the immense qualities, it endowed with many chemical components and therapeutic purposes [2]. They are black in colour with oval shape. The term basil is originated from the classic word “Basileus” means “Royal” and commonly called as “King of the herbs” because it has so many uses in the domains of food, beauty products, and the pharmaceutical industry [1]. These basil seeds have ability to submerged in water, they expand and produce a gelatinous mass because the outer epidermis wall of seed has a poly saccharide layer.[3] Basil seeds has two major fractions of poly saccharides i.e. glucomannan and xylan and have a little portion of glucan [4].

Though basil seeds are not generally used as food but it is considered to be superfood because they have tremendous properties such as prevent to cause inflammation, oxidation inhibitor, stomachic, antiviral, analgesic, antidiabetic, antimicrobial, antimutagenic, antitumor, anticancer, anti-stress, antipyretic, diuretic and emmenagogue properties [5]. This makes the aromatic extracts and the basic oils from basil seeds a crucial component of numerous dental goods, therapeutics, cosmetics, and flavoring compounds [6-9].

Background of basil seeds

Many cultures have utilized basil for a long time as a culinary herb. It is accepted that Basil has originate in India, though the herb has been cultivated for more than 5000 years [5] with its influence extending to every part of the world. Through India, it made its way to England and then in the 1600s, it made a visit to the US [9]. Several Asian nations, including India, Thailand, China, Vietnam and Sri Lanka grow basil because of its superior dietary qualities [10].

Uses

It is used as food and Ayurvedic medicine in India.[9] Additionally, basil has a long history of usage in herbal remedies for the alleviation of stress and headache, the treatment of respiratory gastrointestinal and kidney ailments as well as bleeding disorders [8, 9].

Nutritional values of sweet basil seeds

1. It contains large quantity of antioxidants such as beta carotene, lutein as well as zeaxanthin, Vitamin A and Vitamin K. Basil seeds serve as protective scavengers against free radicals generated from oxygen and reactive oxygen species that act as a process of ageing and other diseases [11].
2. It contains a yellow colour carotenoid compound known as Zeaxanthin, is specifically taken up by the macula lutea of the retina, where it has been discovered to filter dangerous UV radiation before they reach the retinas. Studies indicate that they serve as oxidation inhibition, assist in prevention of diseases like age-related macular disease, particularly in the elderly [12].
3. They have significant amounts of minerals such as calcium, magnesium, potassium and copper as well as vitamins C and folates. In addition to being an essential part of physiological fluids and cells, Potassium also assists to control the blood pressure and heart rate. Manganese serves as a co-enzyme in the body's usage of the oxidation inhibition enzyme such as superoxide dismutase [13].

4. It has high iron content as to 40% recommended dietary allowance per 100 grams. It is considered to be a key element that controls the ability of blood to carry oxygen and is found to be a fundamental part of hemoglobin in red blood cells [14].
5. Contains nearly 25% fats, 20% proteins and 42% carbs [15].
6. Rich fiber contents: more fiber is present in 4 grams of Sweet Basil Seeds than in a whole lettuce bulb.
7. Alpha-linolenic acid is present and have less calories. Due to the presence of Omega-3 fatty acids, it is very advantageous [16].
8. They have significant amount of folic acid such as 78% recommended dietary allowance and vitamin E such as 53% recommended dietary allowance as well as calcium (24.4% of RDD), magnesium (17.8% RDD), iron (49.9% RDD) and potassium (56% RDD) [17].

Uses of sweet basil seeds

Basil Seeds have many uses along with medicinal values, nutritional facts and surprising health benefits such as follows:

1) **Useful for treating hyperacidity:** They possess many beneficial properties like cooling and calming property that aids the benefit on the digestive tract. When paired with basil seeds, rose petal jam also relieves acid reflux [18].
2) **Useful for treating Diabetes mellitus:** The seeds are highly effective at regulating blood sugar in patients with Type 2 diabetes [18].
3) **Can be used as diuretics:** They have ability to swell. As a result, it encourages diuresis, or the increase of urine production [19].
4) **Useful for treating cold:** Fever, cold, flu and bronchitis can all be treated with basil seeds [20].
5) **Useful for treating arthritis:** It is used to relieve sore and inflamed joints. Basil contains necessary oil as eugenol, demonstrated to have anti-inflammatory actions by inhibiting the activity of the enzyme cyclooxygenase. People with inflammatory illness like rheumatoid arthritis as well as inflammatory bowel disease can utilize basil seed as a medication to reduce their symptoms [21].
6) Useful for the treatment of Migraine and depression [21].
7) Useful for the treatment of asthma and respiratory disorders [18].

8) **Useful to reduce the genitourinary infections:** They can use in infections of the vagina and bladder as a medication to reduce their symptoms [21].

9) **Useful to lower the risk of cardiovascular diseases:** By limiting the accumulation of plaque in artery walls, basil seeds reduce the chance of developing cardiovascular diseases [19].

10) **Used as an anti-cancer:** Sweet basil seeds have omega-3 fatty acids and the antioxidants, lower the body's generation of free radicals and prevent degenerative illnesses such as carcinomas as well as Alzheimer's diseases and many more [19].

11) **Utilize as a preventative therapy:** Oils are produced through the direct compression of basil seeds. These oils prevent the growth of numerous harmful bacteria including Staphylococcus, Enterococci, Shigella and Pseudomonas [20].

12) **Used for relieve of bowel dysfunction:** When consumed drenched basil Seeds, they could significantly aid to amend the entire stomach. It facilitates simple bowel movement and assist with the elimination of toxins with in the abdomen. Additionally, to alleviate bowel movements, take it in the night with milk [17].

13) **Used for appetite control:** The soaked fibrous seed's causes satiety, which eventually aids along with suppression in hungriness and loss of weight [17].

14) **Used for stress relief:** The use of Sweet Basil Seeds is thought to improve mood and alleviate mental tiredness [21].

15) **Used as coolant in drinks:** They facilitate the action of cooling by lowering the body temperature. It is a crucial component of several summertime beverages, including 'Alooda-A Mauritian Specialty', 'Falooda in Asian Countries', 'Indian lemonade' and 'Indian Lemon water'. Anyone who needs to revitalizing will love these flavorful, appetizing and invigorating drinks [21].

16) **Used for weight loss:** It serves as a tool for managing weight. It has high fiber content thus it fills up the stomach and prevents from feeling hungry for a while. Basil Seeds (fig. 1) have the expansion ability up to 30 times their initial size (fig. 2) when soaked in water, making them a fantastic natural diet supplement [21].

Fig 1: Basil seeds **Fig 2:** Soaked basil seeds

17) **Used as hair nourishment:** They have essential elements such as amount of vitamin K, protein and iron. These elements are much needed for maintaining the healthy and shiny hair [17].

18) **Used for healthy skin:** Coconut oil and basil seeds work well together to treat a variety of skin conditions [18].

19) **Used to improve memory:** They have poly unsaturated fats i.e. omega-3 fats, which are much needed for the development of cerebrum. It is an essential nutrient for the health of the brain and memory [19].

20) Used as an Aphrodisiac (increase sexual desire) [17].

21) Used as Diaphoretic, carminative and stimulant (Leaves of Tukmaria) [17]

22) The seeds and Roots of Sweet Basil are used as antidote to snake poison and reduce the fever.

23) **Used as an insectifuge:** Basil oil have very good effect of insecticide. It has been discovered that basil is an insecticide and larvicide. In storage, it serves as an as insecticide fumigant [19].

24) Used for sore eyes and night-blindness.

25) Used to promote longevity.

26) These seeds are useful in enhancing breast milk production in nursing moms [19].

Properties

1) **Antioxidant activity:** The consumption of phenol compounds has been shown to have protective effects against major diseases including cancer and cardiovascular disease. Phenolic chemicals serve a number of physiological roles in plants [20].

2) **Antimicrobial Activity:** Gram-positive as well as Gram-negative bacteria both are resistant to the antibacterial effects of basil seed oil. Nine clinical pathogens have been demonstrated to be resistant to it [21].

3) **Anti-inflammatory capacity:** Eugenol, citronellol, linalool, limonene, citral and terpineol are just a few of the necessary oils found in basil seeds. They have benefits for reducing inflammation and bacteria [13, 14, 15, 16]. Basil contains an essential oil called eugenol, which possess anti-inflammatory properties via blocking the action of enzyme cyclooxygenase. Basil can be used as treatment for symptomatic alleviation in people with inflammatory health conditions [22].

Biochemical and nutritional content of basil seeds

1) **Carbohydrate content:** Carbohydrates serve as main source of energy in human metabolism. This element has intricated molecular structures and serves a variety of physiological purposes in body. They have significant effects on controlling the gut microbiota through their prebiotic properties. These outcomes cover the defence of mucosa in intestine, the control of inflammation progenitors, reduction of lipogenesis, and an increase in satiety hormones. Therefore, basil seed considered as significant source of carbs, its advantages are mostly related to their nutritional profile [17].

2) **Protein content:** Basil seeds contain high protein, which ranges from 10-22.5%. They have high level of essential amino acids, with the exception of S-containing types and tryptophan, this makes it particularly attractive from a nutritional perspective in terms of diet consumption recommendations [18].

3) **Lipid content:** Basil seeds contains fat ranges from 9.7% and 33.0% demonstrating that the seeds have significant amount of this supermolecule. They have an excellent source of essential acids of fat, considered as primary nutrient included in cooking oils. The research indicates that certain acids which are present in fat that facilitates the positive effects in living system. Polyunsaturated (n-3) fatty acids as well as other fatty acids including linoleic (LA), linolenic (ALA) and arachidic fatty acids, help naturally prevent cardiovascular disease and other health issues. The most prevalent saturated acids were stearic acid (2.0-6.6%) and palmitic acid (4.9-11.0%). Due to its high content of ALA (C18:3), basil oil has

considered as significant amount of Omega 3 fatty acid for all dietary people [21].

4) **Mineral content:** Mineral content is important for nutrition and are regarded as inorganic element of plant materials. Basil seeds found as significant amount of minerals [20]. The basil seeds contain numerous essential minerals for the human body are substances like phosphorus, potassium, calcium, magnesium, iron, zinc, copper and manganese therefore they play crucial roles in the disease emergence and protection [21].

Future prospective for dentistry

Since basil seeds have so many beneficial effects. It can be used in dentistry as systemically or topical both uses. It can be used in preparations of local drug delivery. Throughout the ages, people have used herbs to treat and prevent illnesses. Herbs are effective medicines due to their interaction with particular chemical receptors in the living system. People who use verdant remedies, they avoided the numerous adverse conditions that are typically associated with traditional pharmacy; however, this does not imply that unfavorable consequences do not take place. Only skilled medical clinician can recommend the needful treatment and their appropriate application. The term "traditional" currently refers to medicines, while "alternative" refers to herbal remedies. Now a days numerous well known commonly used drugs were inspired by plants in the society. Herbal products might vary in their potency. There are numerous herbs including bloodroot, Caraway, Chamomile, Echinacea, Myrrh, Peppermint, Rosemary, Sage, Thyme, Aloe Vera, Propolis and curcumin have been commonly found in dental treatment, as it has numerous therapeutic properties. Therefore, Basil seeds can be considered as good alternative in current treatment trends for oral and general health problems because it has the same property as above-mentioned herbs.

Conclusion

One of the earliest and most well-known medicinal plants, sweet basil is known as the king of herbs, which is brimming with potent curative properties**.** In addition to proteins, omega 3 fatty acids and dietary fiber, basil seeds also include minerals, flavonoids as well as polyphenols, all of them have desirable characteristics for food manufacturer and food buyer. The usage of herbal remedies is still growing rapidly on a global scale. In various national healthcare settings, various people increasingly use herbal remedies for their health. In dentistry, herbal extracts have been utilized as antimicrobial plaque agents, analgesics, antiseptics, antioxidants, antifungals, antibacterial and

antiviral agents, in addition to reduce inflammation and limiting histamine release. They promote healing and are efficiently control microbial plaque in gingivitis and periodontitis, which enhances immunity. Therefore, Basil Seeds is considered as superfood because they have a variety of healthy properties that promote wellness and disease prevention.

Conflict of interest- Nil

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Chapter - 6
Music Therapy and Patient Care in Dentistry

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Chapter - 6

Music Therapy and Patient Care in Dentistry

Saundrya Kaushal, Dr. Nidhi Gupta, Dr. Sahil Thakar and Dr. Abhinav Bhasker

Abstract

In the modern scenario, providing excellent oral health care plays a significant role in dentistry and is always better if it is patient oriented. When the oral health care is patient-centered, it leads to patient satisfaction, better outcomes and enhances the oral health status. These benefits are desirable both by the patient and the dental professional. Different interventional methods are adopted by various health care providers including the dentists for better patient care. Music Therapy is one such intervention.

Keywords: Music therapy, oral health care, patient care, dentistry, interventional methods

Introduction

Dentophobia, or the fearing the dentists is not only confined to the young patients but is significantly seen in the elderly too. Dental anxiety and phobia amongst patients adds on to the already persistent negligence and negative attitude of the patients towards dental treatment [1].

This, in turn, offers a big challenge to the dentists in providing the patients with good patient care. Dental fear, being the most difficult fear to get over; becomes a hugely faced challenge by the dentists in their practice. Moreover, lack of patient co-operation due to apprehension may lead to a compromised treatment [2].

A wide range of methods have been adopted by various clinicians over a period of years with an aim of providing a proper patient care. However, Music Therapy has proven to be a highly effective approach towards managing apprehensive patients. Music Therapy has become a burgeoning field and is ever-flourishing and is greatly effective towards excellent management of uncooperative or apprehensive patients in a dental clinic.

What is music therapy?

As per the American Music Therapy Association (AMTA), “Music Therapy is the clinical and evidence-based use of music interventions to

accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program".

This chapter emphasises over the need for the utilisation of this non-pharmacological intervention in dental practice.

Music therapy actually is a profession constituted by music therapists who are well trained. However, if one cannot offer full-fledged employment to one such professional in his/her office, one can at least use this intervention through other modes and enjoy its rewards. Using an additional and feasible intervention like this one comes with no harm but countless rewards.

"Music is a mystical therapy!"

A dentist is no less a therapist and musical intervention is no less a magical wand that is capable to quickly soothe the mind and calm the anxiety. Music Therapy is purely a mystical therapy that can even relax the most jittery minds.

The moment a patient sits on the dental chair or enters a dental office; a lot of thoughts begin to ponder within their brains. Thousands of "ifs" and "buts" start arising, which may leave the patient tensed, anxious and reluctant regarding the treatment. Music acts as a wonderful natural remedy for decluttering and tranquillizing the mind.

Music therapy and its anxiolytic effects

Dental anxiety many a times leads to avoidance of dental care, which may lead to a significant deterioration of oral and dental health. Certain anxiety management interventional methods like listening to recorded music by the patient, are being adopted by the dentists worldwide but yet not many Indian practitioners have brought this into their practice.

Undoubtedly, the efficacy for music's anxiety relieving benefits is well known for treating preoperative anxiety. However, in some cases, using music for distracting might not prove to be sufficient for exacting children and some adults who are extremely anxious. In such cases, musical aids through a music therapist who is well-trained in his field might be required to enhance the anxiolytic impact of the music. Music interventions are specified to a particular patient's presenting needs and are focused at optimizing a patient's voluntary active indulgence in managing anxiety [3, 4].

Music interventions may be in the form of

- Refocusing the attention actively.

- Music-guided deep breathing.
- Music-assisted relaxation.
- Audio-imagery or Music-guided imagery.

I. **Actively refocusing one's attention:** It is easily achieved when the therapist is present there during the treatment, majorly in case of more anxious patients. This permits therapists to modulate the music as per the presenting requirements of the patient at that very moment, instruct verbally for refocussing, and periodically changing the track to avoid habituality. Anyhow, for patients who have slight anxiety or moderate anxiety, focusing techniques that are based on music can absolutely be learned just before the procedure can be implemented later in the treatment.

II. **Deep breathing guided by music:** It is a method which we can easily teach the adults or the children but needs to be practiced before starting the dental procedure. Music-guided inhaling and exhaling actively brings a patient in a relaxed state much better, rather than listening music to divert mind.

III. **Effective relaxation guided by music**: It is a method of training in which we use music to foster decrease in already elevated heart rate or respiratory rate. Despite of making the patient listen a previously selected list of tracks of calm or soft music, a music therapist is eligible to perform live music.

IV. **Audio-Imagery or Music-guided imagery:** It helps to manage both anxiety and pain. It depends upon the type of music played that what quality of the imagery is created, the patient's indulgence into the imagery, and the kind of experience achieved. Hence, it is necessary to select previously recorded music or try to improve the music quality to create visual imagery or experience that a patient enjoys the most (e.g. taking a walk in the nature, birds chirping, hearing the winds moving or the waves swirling, etc.)

Also, a music therapist can

- Teach patients some ways to manage anxiety before the treatment begins based upon music.
- Let the patients express how do they feel about the upcoming procedure.
- Make them feel that they have an access to control and safety.

Dentophobia may lead to negligence in oral health care which leads to its complete deterioration and such deterioration raises dental care costs sharply . Moreover, anxiety or phobia while dental treatment calls for a prolonged duration of appointments in a dental office [5].

The highest amount of dental anxiety is found in children, but it decreases remarkably with increasing age. It is very important to manage a child's fear to make him a cooperative patient as it is very crucial for the treatment to become successful. Children are a subject to dental anxiety mainly because of the fear of pain. So, managing the pain becomes like managing the root cause. Also, fear or anxiety are proven hurdles in a good dental care, be it in adults or children or those who are specially abled. For instance, it is found in some reports that some adults who have Autism Spectrum Disorder (ASD) present with raised anxiety levels than those who don't have ASD when being treated in a clinic [6].

In the specially-abled and in small children, an apprehensive and resistant behavior is found more oftenly, which somewhere hampers safe provision of dental care. Lack of knowledge and understanding about dental procedures and forcibly bringing such patients to dental clinics are the two main reasons that instill such an anxiety in these patients [7].

In severely anxious patients, conscious sedation using nitrous oxide and various anxiolytic drugs can be additionally used.

Music therapy in comparison with other pharmacological interventions

According to various studies adult patients and the parents or the guardians of the young pediatric patients who present with dental anxiety go for non-pharmacological aids. They choose these because of their perception of associated medical risks. Also, pharmacological interventions make a dental treatment way more expensive. That is why, most of the dentists switch to behaviour management methods and non-pharmacological interventions [8].

It has been proven that behavioral management is always safe and better over the use of drugs to subside anxiety and offers no side effects at all. Music is such an intervention and is easily and widely accepted by parents, pediatric and adult patients and also by the clinicians. It even helps to subside anticipatory anxiety situations that induce stress such as right before a clinical examination or when in waiting area waiting for an upcoming surgery. Studies quote that music has almost similar anxiolytic effects when compared to benzodiazepines or can even render more effectiveness [9].

Musical aids for patient care are listed as a "continuum of care", as it can range from either listening to some music by patients on their own, to listening to some recorded music as given by the professional for management of certain symptoms and then, to music customised for an individual offered by a trained music therapy professional.

In oral health care, making use of music interventions is yet restricted to **"music medicine practice"** whereby patients are made to listen to music either by using headphones or by a free field. To make the best possible out of the treatment, music therapy needs to be given right before the beginning of the treatment.

A happy hormone inducer

The secretion of certain happy hormones and Music Therapy are strongly co-related. Serotonin, Endorphins, Oxytocin and Dopamine are said to be the four happy hormones which can make the patient feel good. Endorphins are widely elicited when the patient is subjected to calm music. Playing soft music around a patient is therefore recommended either before the treatment or during the treatment. This will help them by releasing their day-to-day stress along with anxiety if any. It is found that the patients subjected to this therapy are comparatively less worried, less inquisitive about the treatment and co-operate better in comparison to those normal dental setting without an acaustic environment [10].

Music Therapy fosters positive emotions and immune functioning while dismissing anxiety, frustration, and stress. It's clearly evident from our history that even Hippocrates, who was a Greek physician, played music as an adjunct to soothe his patients. Aristotle has infact described music as an emotion purifier [11].

This therapy has clinically reported in

- Lowering down the cortisol levels and epinephrine levels in patients while giving anaesthesia.
- Activating the Parasympathetic Nervous System and reducing the risks of cerebrovascular diseases.
- Altering the plasma concentrations of Interleukin-6, TNF-α, adrenaline and non-adrenaline.
- Markedly increasing the salivary IgA and Interleukin-1 concentrations.

The accepted mechanism

Many mechanisms can be listed under different levels.

At a psychophysiological level

Various evidences state that music can decrease anxiety by impacting the autonomic nervous system and its responses. To be more specific, music suppresses the sympathetic nervous system and renders its anxiolytic effects, as a result both the adrenergic activity and neuromuscular response decrease significantly. There is a decrease in cortisol and other neuropeptides after listening to music.

The limbic system gets triggered and starts producing endorphins when one hears music. Release of these neurotransmitters creates a sense of overall well-being. It is evident from the neuro-imaging studies that listening to music which is pleasing tends to stimulate the ventral tegmental area. The Nucleus accumbens or the NAc is the "emotional center of the brain". When this center gets activated, some happy hormones such as dopamine are released, which are known to regulate mood and emotions. Dopamine is also responsible for central analgesia and acts by interacting with the endogenous opioids.

Amygdala is a key structure in the brain which is responsible for the development of conditioned fear and therefore its suppression is important. Therefore, when the dopaminergic system gets activated amygdala gets suppressed, dental anxiety and dental pain tends to minimize while performing a dental treatment.

At a neurocognitive level

Music is said to deviate a patient's mind from certain factors that evoke anxiety. However this method of distraction through music might not prove useful in extremely anxious patients. Infact, such patients might require some additional assistance to refocus their attention towards music actively. To bring this into effect, some other type of music and not the sedative music would be appreciated.

Also, such subjects might require some other music-based support to encourage even better indulgence into the music. Listening to the music reinforces visual imagery. This provides a relief from a regular and monotonous, boring and stressful reality on a temporary basis and helps manage anxiety.

Anyhow, Self-chosen music leaves an individual with a sense or a feeling of control over the conditions. The perception of a sense of control helps in figuring out dental anxiety and nervousness regarding treatment. Also the environment seems less threatening when the music is self-picked.

On a socio-psychological level

An aesthetic experience full of relaxation, comfort and mental peace is experienced through music, while in waiting area and during the procedure [12]. Additionally, when music therapist who is well trained is put in charge of providing music interventions, he understands and tries to analyse on what does a patient require right at that time [13].

How a patient responds to the music depends upon the given factors

- Age group of the patient
- Gender of the patient
- Cognitive functioning
- How severe is the fear or anxiety
- Whether the patient is familiar with the music provided
- What is the patient's personal preference for the music
- Culture to which the patient belongs
- Patient's taste in music
- Comfort of the patient

However, the patient's response is not totally limited to the above mentioned factors.

Furthermore, some other factors shall also be considered

- Patient's interest in the music
- Whether the patient is paying attention
- The present emotional state of the patient
- How the patient interprets the music at the cognitive level
- How the patient interprets the music at the emotional level
- Imagery stimulated by the music

In case of very much scared patients who are extremely anxious and also those who are specially abled, dental practices are always suggested to hire or call for a music therapist who is well trained and has an expertise in his profession [14].

There are certain clinical guidelines which dental practitioners need to know to inculcate music intervention in their practice. They are as follows

1. Patient-preferred music

While scheduling a dental appointment, patients must be advised to make a choice of music or get their own music along with them which they prefer before hand by the practitioner. Patients are not only suggested to select from a list of music that is available in the dental office but of their interest or preference.

Patients are meant to be conveyed beforehand that the music may belong to any other genre too, and not just necessarily needs to be a typical slow classical soothing music. Infact, patients are appreciated to bring the kind of music that would boost up their mood and catches and sustains their interest and attention even if its pop or rock music. Broadcast music like FM radio stations is not recommended. There may be a chance that patients may not like that music and may get disturbed or irritated despite of feeling relaxed [15].

It is an important guideline and is applicable for all age groups, specially children. Playing the child's chosen music makes dental procedures and management of apprehensive children less difficult.

2. Relaxing music

Music doesn't need to be classical to be sedative, it can be of any style instead. That is why, let the patients select the kind of music as per their own liking.

A music with sedative effects needs the following:

- It needs to be structurally simple
- Harmonious repetitions are encouraged
- It is more soothing if it is an instrumental melody and doesn't contain lyrics
- It needs to have low tempo
- There shouldn't be any tension in the sound or melody
- Musical instruments involving string instruments, harps, and pianos are encouraged rather than percussion instruments
- Sounds of nature, like those of waves, chirping of the birds are appreciated

3. Volume control

Patients must have a control over the loudness of the music so as to avoid any inconvenience or to foster perceived control.

4. Musical aids like earphones, headphones or free field

Patients must be made to use earphones, headphones or use free field. Headphones are successful at masking unwanted sounds in a dental office to some extent, at the same time they may incorporate dental fear in some subjects by hindering the patient-dentist conversation preventing them to convey valuable information at times. So to avoid this, the loudness of the music could be modulated and could be lowered down to enable communication while using headphones.

Noise-cancelling headphones are commonly used, provided that the loudness has to be enough for masking or covering the unwanted sounds and also using a microphoning for conveying information by the dental practitioner was suggested by Aitken *et al*., 2002.

5. Accuracy in timing

It is very necessary to start playing the music right before the beginning of any dental procedure, whenever possible. It helps in avoiding and managing stress at that time when the patient rests in the waiting area before the treatment gets started.

6. Active engagement

The patients are meant to be instructed to clearly pay complete attention to the music instead of just listening to it. Also, a tiny instruction manual can be given to the patient to use while listening to the chosen track.

Music therapy in analgesia and anaesthesia

Music Therapy has a critical role Analgesia and Anaesthesia. Every person has a different threshold in pain tolerance and to manage it is again an art which a dentist needs to master. Music aids in sedation and hypnosis while both peri-operative and intra-operative procedures.

"Trypanophobia" or the "fear of needles" is very often encountered in many patients that visit a dentist. Use of music therapy can aid in subsiding this fear too. Music interventions are very useful in peri-anaesthetic patient care as it fosters the release of endogenous endorphins, which lowers the need of sedatives and analgesics, making the management of pain much easier, whether it is acute or chronic [16, 17].

Needle phobia and its effects in the community is the topic that still remains unsung. The rising fear of needles and the perception of dental treatments being painful might impact the future dental treatments in fearful patients. Maximum of patients are said to have trypanophobia because of the experiences shared by other which can be their parents, some friends, or some relatives in their past. Needle injection while local anaesthesia is procedure routinely performed in clinics and hospitals. Therefore, for a better practice management it becomes very necessary to eradicate this fear and learn to manage it [18, 19].

Rewards of this intervention

This therapy is a largely rewarding therapy. Undoubtedly, music does wonders in emotional improvisation. In context of the patients, it helps them to cope up with their dental fear and in context to the staff employed in a dental office, it benefits them by releasing their stress and work pressure and allows them to work with a happy and a fresh mindset.

This therapy is an exogenous cue and thus it:

- Quickly draws the attention of the subjects
- Modifies social behaviour
- Increases focus and attention
- Helps in stress management
- Improves coping boosts self-esteem
- Improves patient-dentist communication
- Nullifies solitude or isolation

Music Therapy is truly a boon for dental society as it helps in maintaining the arterial pressure, heart rate and respiratory rate, which are important parameters to be considered prior to carrying forward any dental procedure. It even helps in eradicating the white-collar hypertension among the patients. It is the safest non-pharmacological intervention with no side effects at all! [20].

Who all are benefitted from music therapy?

This therapy may be helpful to the patients with extreme age groups i.e., Geriatric patients and Pediatric patients. Drilling sounds or other occupational sounds be it from micromotors, air rotors, suction devices, ultrasonic instruments, compressors, etc. might result in acaustic trauma more in the above age groups, which can however be overcome by music to some extent.

The patients with certain disorders like the following are benefitted from this therapy:

- Cardiac conditions
- Alzheimer's disease
- Autism
- Dementia
- Epilepsy
- Patients suffering with chronic pain
- Patients facing difficulty in communication with dentists
- Nervous patients
- Patients with cancer, etc.

It is even beneficial in those with PTSD i.e., Post Traumatic Stress Disorder.

Music Therapy is the best psychotherapy that can resolve major distress in anxious subjects and prevent the condition from worsening. It definitely helps those people who are apprehensive and the reluctant ones who are the first-time visitors and are entirely new to a dental experience. Not only this but playing music in the waiting area can also protect the patient's privacy as the communication between the patient and the dentist remains confidential and cannot be heard outside in the waiting room [21]. Similarly, the conversations being carried out outside in the waiting room remain outside the operating area avoiding any disturbance.

Methods, sources and the choice of music

There are different methods and sources for providing Music Therapy. Today, this therapy in itself has become a profession. But we dentists are no less a therapist! Even we can make use of this concept in our workspaces and make an excellent outcome out of it.

We can play recorded soft music. Use of recorded harp music has evidence in lowering down the blood pressure in hypertensive patients. White noise music and meditation sounds may too be played in a dental clinic. We can even provide the patients with noise cancelling headphones.

Choosing the right music is also of a major concern as what might be pleasant to one's ears might be unpleasant to another's. So, we need to modulate it as per preference and interest of the patient. We can even ask the patient for their preference; this will only enhance patient communication.

However, the music must be soft and pleasant. Only then it shall prove to be of some psychotherapeutic use. We need to understand that if soft music can control the blood pressure, loud or rash music can shoot it too. So, we must keep in our consideration all these things while using this intervention [22].

On the contrary, when music therapy is used to reinforce active refocusing, calm or sedative melodies are not always apt. In contrast, kind of music which is successful at sustaining a patient's attention is required at that time. For an instance, if the songs are selected by patients themselves, it would permit them to pay attention and focus on it better.

These professionals are multi-trained and have their expertise in a variety of techniques for behavioral management and patient relaxation. These are needed for emergencies where some common techniques do not prove useful for certain patients. Therefore, they are specially trained. It is crucial for these experts to make an assessment of the techniques based upon the particular patient's preference before the treatment commences.

The need to encourage music therapy in dental offices

In our country, there are still many dentists who neglect the perks of incorporating such interventions in dental offices [23]. They don't consider these of dire necessity and are thus not prioritized in many practices in India. They really need to realize and appreciate the wonders this therapy does in patient management. They need to know the remarkable difference that it has made in terms of improvising the patient care in this field so far.

As a rising trend is seen in inquisitiveness and apprehensiveness of patients regarding dental procedures, this intervention can produce tranquillizing and calming effect and can numb the pain by diverting the attention and can ease the handling of such subjects on a dental chair. It can reduce some part of the psychological pain and can render the treatment free from yearning.

In a study conducted in Nagpur, India; a total of 100 participants were categorised into two groups randomly, a control group of 50 participants and a case group of remaining 50 participants. The case group was exposed to low tempo music during various dental treatments while those in control were treated without any musical intervention. It was drawn out that the patients exposed to music had a decrease in in their anxiety levels while the treatment as when compared to the control group. So for better and effortless handling of patients, music therapy needs to be inculcated in dental management system.

Attitude of patients

With an aim of assessing public attitude towards the dental professionals in Bangalore city, India; another study was done in which 39.5% of respondents accepted the notion that fear of pain and their perception that dentistry is painful is the reason which refrains them from utilizing dental services. This negative attitude arises because of the false notion that "dental treatment is always painful."

Where most of the dentists are genuinely interested in rendering quality care, making dental visit a stress-free experience full of patient comfort, public attitude may not always coincide with what dentist thinks. It totally depends upon the public attitude towards dentistry and dental professionals on whether they seek dental care or not and if yes, whether they seek preventive or curative dental care. It determines how much willing is the patient to accept treatment and also that how anxious would he/she be during the treatment. The negligent attitude towards dental treatment depicts that many subjects had never visited the dental clinics and those who did, they only visited the dentist when it was badly needed [24].

Poor oral health due to stress and music therapy

Psychological stress largely contributes to poor oral health status in relation with other systemic diseases. It is suggested that those who perceive greater stress report degraded oral health status and that stress and periodontium are inter-related [25]. Patients who have a stressful lifestyle may require a keen observation and better maintenance of health and hygiene of the oral cavity so as to achieve a better overall health as seen in the individuals with less stress.

Special role in managing pediatric patients

Management of Pediatric patient is an integral segment of community oral health care delivery system. This intervention is the best tool which serves the motive of distraction. It works by diverting the child's attention and also helps in increasing their tolerance for pain and decreasing their anxiety and discomfort levels. As far as the management of stubborn pediatric patients is concerned, Audio Analgesia or White Noise comes to rescue [26].

Various techniques have been employed in dentistry to reduce white coat anxiety/hypertension among young patients, like the Tell Show Do technique. It diverts the child's attention primarily by nullifying the drilling and other sounds of different dental instruments like air-rotor, suctions, ultrasonic scalers, etc.

Music therapy does not only stimulate a young child's mind but has been proven to stimulate a neonate's brain development too by relatively increasing oxygen saturation, by creating a stable and sound musical environment. A little rise in oxygen saturation improves the signs of hypoxia in newborn if encountered any, such as in retinopathy, reactive oxygen species derived conditions and blood dyscrasias [27].

Dentist: A psychologist in disguise

Dentist is somewhere a psychologist in disguise. We, as dentists, need to master an expertise in patient dealing with different mental attitudes and should try to leave no stone unturned and thrive for the best when it comes to providing patient care. Fear regarding dental procedures is still persistent and in order to resolve this dentophobia, a dentist has to manage the patient with words of comfort which indeed makes a dentist a psychologist in disguise.

We must try to serve the best possible patient care from our end. We need to remain well versed with different methodologies and newer interventions that are being introduced every now and then that can help us with better management of patients. Our approach should not only be restricted up-till the clinical procedures but also in providing the patients with a healthy and a happy dental experience. Above all satisfying the patient is our duty.

Conclusion

This intervention is one such way that is helping the dentists to manage patients with different attitudes. We can ourselves imagine how chaotic and undesirable a dental office would become with all those occupational sounds, murmurs and whisperings and the regular humdrum in and around the office. Music Therapy somewhere neutralizes all the noise and makes it go unnoticed. On the top of it, it purifies the ambience and makes the surroundings pleasant to work in or to be treated in. This helps dentists on professional grounds in increasing their patient footfall and will encourage them more to thrive hard in maintaining their standards in providing services to the patients. Also the countless psychotherapeutic benefits that a patient will enjoy are clearly discernible.

"Music can heal the wounds which medicine cannot touch!"

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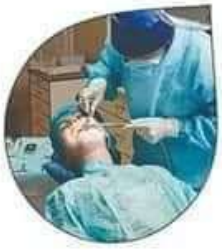

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Chapter - 5
Artificial Intelligence-Driven Imaging Diagnosis in Dentistry

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Chapter - 5

Artificial Intelligence-Driven Imaging Diagnosis in Dentistry

Dr. Veena Benakatti

Abstract

Artificial intelligence (AI) an emerging technology is revolutionizing healthcare and has proven to be the future of medical practice. AI is a promising tool in dental diagnosis, assisting clinicians and saving time, and improving their efficiency. AI has been experimented in imaging diagnosis with various dental imaging techniques. Information in the dental images can be processed by an AI algorithm to provide diagnoses, predictions and analyse treatment outcomes. Each dental specialty has unique AI applications and this chapter summarizes AI-based imaging diagnosis in dentistry specialty-wise.

Keywords: Artificial intelligence, dentistry, imaging diagnosis, radiology

1. Introduction

Diagnosis is the principal element of medical practice and successful treatment starts with the correct diagnosis. Over the years, technology has played a substantiating role in medical diagnosis. Radiography, a major diagnostic tool in medicine and dentistry, has evolved from films, cassettes, and processing solutions to digital radiography. Intraoral radiographs, panoramic radiographs, cephalograms, CT and CBCT are routine investigation procedures in dental practice for diagnosis and treatment planning and are a rich resource of information. Clinicians interpret these radiographic images based on features and arrive at a diagnosis. This process of diagnosis is subjective, time-consuming and prone to human errors [1]. AI one of the leading technologies in the current times is being researched for its applicability in processing this data and providing clinicians with diagnoses. Trained AI algorithms can analyse medical images and recognize patterns that the human eye could miss, improving diagnostic accuracy and saving time. AI can ease the doctor from workload, visual and mental fatigue [2], hence AI has proven to be a promising tool in medical diagnosis and prompting it to be the future of the medical practice.

Machine learning works with a dataset of training and testing datasets, wherein the training dataset trains the AI algorithm for a specific task and the test data analyses the performance of the algorithm. The quality and quantity of medical data determine the performance of the algorithm. Deep learning a subset of machine learning works by convolutional neural networks (CNN) that mimic the human brain and can recognize patterns in a database and extract meanings [3], which may not be possible for a clinician to process such huge data. Generating medical AI is a collaborative work of medical professionals and an AI engineer. Annotation of the data is a crucial component, of the process of labeling medical data done by a medical expert. The performance of AI is a product of useful data and the right annotation.

AI-driven imaging diagnosis in dentistry has unique applications in each specialty, rendering solutions to many health problems. This chapter summarizes the applications of AI for imaging diagnosis in each specialty of dentistry.

The application of artificial intelligence in oral radiology has been diverse as in landmark detection in cephalogram, detections, and classification of teeth, detection of maxillary sinusitis, and diagnosis of osteoporosis in panoramic radiographs [4]. Ariji *et al*. [5] tested a deep-learning model for segmenting the cervical lymph nodes in oral cancer patients and diagnosing metastatic or non-metastatic lymph nodes from computed tomography (CT) images. The accuracy of performance in identifying the metastasis with an area under the curve (AUC) of 0.950, was significantly higher than that of radiologists (0.896). Ameloblastoma and odontogenic keratocyst need to be diagnosed accurately before planning the surgery, this differential diagnosis may not be possible alone by imaging. Liu Z *et al*. [6] aimed to propose an algorithm based on convolutional neural networks (CNN) to improve the classification accuracy of these two tumors. A pre-trained model (CNN) was formulated with transfer learning and new layers, a 19-layer Visual Geometry Group Network (VGG-19) and 50-layer Deep Residual Network (ResNet-50) were applied on top of this pre-trained model. This proposed CNN achieved an accuracy of over 90%, significantly improving the differential diagnosis accuracy of both tumors. Kwon O *et al*. [4] proposed a deep learning framework for automatically detecting and classifying odontogenic cysts, tumors and multiple diseases of jaws using panoramic radiographs. A deep CNN modified from yolov3 was trained for this and the results showed good accuracy with an AUC of 0.86 and an AUC of 0.94 with an augmented dataset.

In conservative and endodontics, several atypical variations occur in root canal morphology leading to endodontic failures, although CBCT is being

used to address this, its cost and availability are a concern. AI algorithms can be trained to identify extra canals and configurations [7]. Dental caries is undoubtedly the most prevalent dental disease and radiography is the commonly used diagnostic tool for the detection of caries. Detecting caries and their extent with a radiograph is very subjective and may lead to invasive treatment decisions. A lack of consistency among examiners in caries diagnosis is an issue, especially with initial caries [8]. AI-driven caries diagnosis has shown to be promising in solving the issue by improving the accuracy of diagnosis and eliminating inconsistency. Research in AI-based caries detection has shown the accuracy of diagnosis to be over a range of 82-99%. AI is beneficial in the early detection of incipient caries, and enamel caries thus playing a vital role in preventing further caries progression. Several commercially available caries detection software has been tried with randomized controlled trials and has demonstrated outstanding performance that can assist clinicians in implementing preventive measures, treatment planning, and improved patient outcomes. This can immensely benefit schools and rural health centers in preventive programs and oral health education [9]. AI can be of benefit when combined with clinical assessment and should be used as a second opinion and treatment decisions should be based on these outcomes [10]. Paniagua *et al*. [11] studied AI algorithms in detecting cracks and fractures in a tooth and found the accuracy of detection was promising to use AI as a tool in diagnosing these conditions which would help in preventing further deterioration of the tooth.

In orthodontics, AI has a range of applications from predicting the need for extraction to treatment planning as in cephalometric and invisible aligners. The decision for tooth extraction in treatment planning is crucial as it is irreversible and the right decision contributes to the success of treatment. Jung S K *et al*. [12] formulated an AI algorithm and found 93% accuracy for the diagnosis of extraction vs non-extraction. The input data were cephalometric tracing and 6 indexes-maxillary and mandibular arch length discrepancy index, molar key index, protrusion index large overjet index, and chief complaint index for protrusion. These expert systems can be a new approach in orthodontics.

Maintenance of periodontium is integral to the tooth's survival. AI models were developed to assist dentists in accurately detecting and interpreting alveolar bone level and radiographic bone loss. These AI models can be a useful adjunct to periodontal diagnosis and treatment planning [13]. Lee JH [14] *et al*. developed an algorithm to diagnose and predict periodontally compromised teeth with input data from annotated periapical radiographs. The

accuracy of diagnosis was 81% and the accuracy of predicting extraction was 82.8%. These systems can bring a significant improvement in diagnostic and prediction methods for periodontal diseases replacing conventional tools with higher accuracy and speed.

In oral surgery, early detection and diagnosis of cysts and tumors of the oral cavity are critical to avoid invasive surgeries and achieve acceptable treatment outcomes. Several studies have shown the role of AI in early screening, prompt diagnosis, treatment, and prevention of morbidity in patients with cysts and tumors. AI has achieved good accuracy in virtual surgical planning in the reconstruction of facial defects. AI is a useful tool in orthognathic surgery to establish a precise diagnosis, analyze the need for surgery and predict treatment outcomes [15].

In prosthodontics, AI models have shown great potential in dental implantology, implant planning, assessing implant performance, and identifying dental implant systems. Lee JH [16] evaluated the efficacy of three deep CNN algorithms in the identification of dental implant systems. A total of 3000 cropped panoramic and periapical radiographs were used to train CNN architectures VGG-19, google net Inception-v3 and resnet-50. They demonstrated that the three CNN architectures showed good performance, VGG-19 with AUC = 0.891, Inception-v3 with AUC = 0.922, and resnet-50 with AUC = 0.907. Kurt Bayrakdar *et al*. [17] evaluated artificial intelligence system for implant planning with three-dimensional cone-beam computed tomography (CBCT) images. They concluded that AI systems will facilitate implant planning assist clinicians and will be a support mechanism in implantology practice.

2. Conclusion

Research in AI applications for dental diagnosis is in its initial stage and further research is still required to be able to implement in clinical scenarios. AI can ease clinicians by assisting in diagnosis, saving time and improving their efficiency. Algorithms in imaging diagnosis show good accuracy yet their real-life implication is guarded by cost, ease of use, and approval by the regulatory agencies. However, AI-powered medical imaging looks to be the future in this information age.

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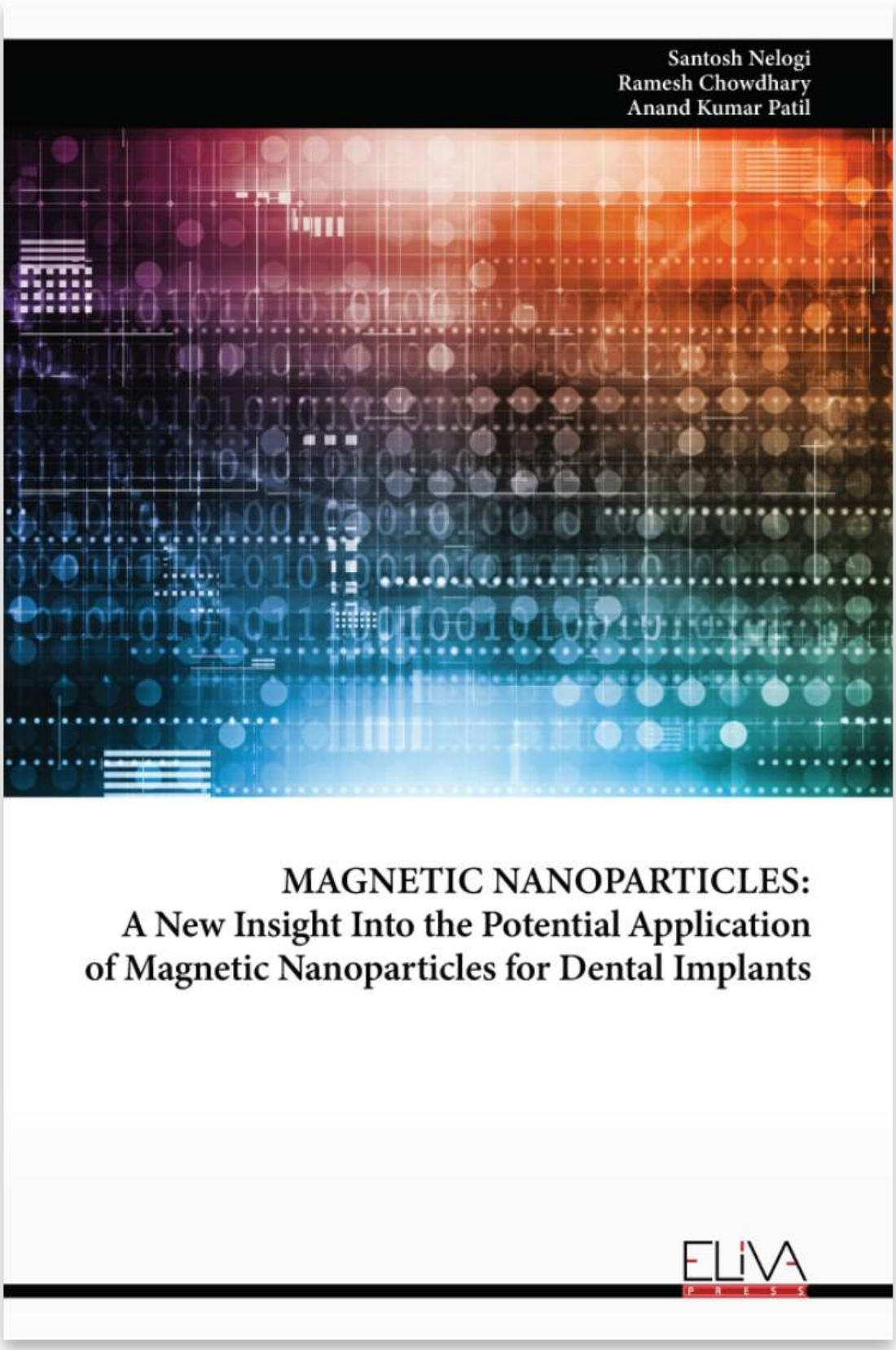

Santosh Nelogi

MAGNETIC NANOPARTICLES: A NEW INSIGHT INTO THE POTENTIAL APPLICATION OF MAGNETIC NANOPARTICLES FOR DENTAL IMPLANTS

Women's Health

Dr. Usharani Shyamasundar Sanu
Dr. Sunil Surendra Vernekar

CHAUKHAMBHA ORIENTALIA

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Published by
Academic Decipher Press, Mumbai
Website:https://academicdecipher.in/
WhatsApp No.:7400253569
Email: admin@academicdecipher.in,
academicdecipher.in@gmail.com

Edition:

Price: Rs.1050/-

ISBN: 978-81-958127-8-3

Exclusively marketed & distributed by Academic Decipher Press, Mumbai.
For sale in India and abroad.

CONTENT

PREFACE

This book is a result of extensive literature survey and research done by students of pharmacy, and other science fraternity from different colleges all over India. It covers the medicine related research done by students under the guidance of faculties.

Students/academicians/industry persons should go through it in order to get research ideas which can be transformed into the product. Thus this book will serve as a guide for people wishing to do research.

We are thankful to all the contributors as without their help publishing this book would have not been possible. We are also thankful to the editors of this book for timely completing the work and helping us to publish this book on time. We wish all our readers knowledgeable and research oriented reading.

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He received 'ISP Eminence Award-2018' by the Indian Society of Pharmacognosy. He received Sri SubbarayaSetty Teachers and Research Students Award 2017 for Teachers for "Excellence in Academic Research" by American Association of Government College of Pharmacy (Bengaluru) Alumini, New York, USA. He received Best Young Scientist Award 2011-12, Best Teacher Award – 2011 from KLE University, Belagavi and National Level Young Pharmacy Teacher Award 2012 by Association of Pharmaceutical Teachers of India. He has received financial support from various funding agencies like UGC, AICTE, DST and ICMR for research projects and for organizing conferences/workshops. He is member of several pharmacy professional societies and has chaired several scientific sessions at national and international conferences.

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ISBN 978-93-5451-860-5

N2403

COMPUTER AIDED DRUG DESIGN OF PHYTOCHEMICALS Prof. (Dr.) SUNIL S. JALALPURE • SHAILENDRA S. SURYAWANSHI

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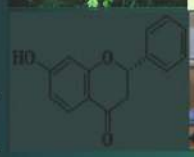
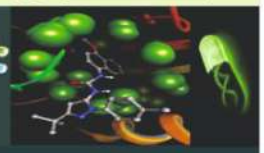
ADVANCEMENT OF KNOWLEDGE





GREEN NANOARCHITECTONICS

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JENNY STANFORD
PUBLISHING

Published by

Jenny Stanford Publishing Pte. Ltd.
101 Thomson Road
#06-01, United Square
Singapore 307591

Email: editorial@jennystanford.com
Web: www.jennystanford.com

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Green Nanoarchitectonics

ISBN 978-981-4968-50-8 (Hardcover)
ISBN 978-1-003-31860-6 (eBook)

Contents

Preface

This book explores the recent breakthroughs and current research trends in the design and synthesis of greener nanomaterials and their eco-friendly utilization at the industrial scale. It is multidisciplinary in nature and discusses micro- and nanofabrication, green chemistry approaches, engineered nanomaterials, spectroscopic characterization, promising possibilities for eco-friendly products, and sustainable industrial-scale applications. Comprising 12 chapters that cover diverse fields of studies, the book defines key material descriptors required for their successful employment in different applications and discusses their cost-effective synthesis from natural extracts. Such materials are desirable to synthesize integrated and adaptive materials and systems development of renewable energy technologies. The overall structure of the book is well-defined to improve its accessibility. Chapter 1 explores phytomedicines that can be improved with the help of a nanoformulation-based drug delivery system, which has great potential future for improving the therapeutic action of phytomedicines. Chapter 2 discusses the simple and cost-effective preparation of novel bionanocomposite materials, which play a significant role in nanomaterial synthesis and also act as surfactants. Chapter 3 gives an overview of the drawbacks and challenges for the photocatalytic remediation of organic pollutants such as dye molecules, emerging contaminants, and heavy metals. Chapter 4 focuses on superior therapeutic systems, including the application of green nanomaterials in targeted and sophisticated drug delivery, theranostics, regenerative medicine, implantable devices, and tissue reconstruction, and these systems are compared with conventional therapeutic system. Chapter 5 presents a systematic outline of the problem beginning with the mechanism of photocatalysis followed by the factors that affect the efficiency of a photocatalyst and various green nanomaterials used for photocatalytic activities. Chapter 6 centers around the emerging nanosorbents for water and wastewater treatment that use diverse sources of plants, microorganisms, and biocompatible green reagents for the production of green nanomaterials (GNMs),

which are utilized for the decontamination and recovery of heavy metals from industrial effluents. Chapter 7 thoroughly investigates how the wood-based product industry might make use of a variety of widely available nanomaterials to improve the performance of existing products or develop new forest-based value-added products. Chapter 8 is an in-depth study of plants' hidden tendency to remodel the inorganic metal ions into nanoparticles through their gifted organic resources, which has opened up new doors to study biochemical analysis. Chapter 9 demonstrates that effective biosynthesis substantially eliminates the use of toxic reagents and employs natural resources to create nanomaterials with potential applications, implying a cost-effective and environmentally friendly solution. This chapter further highlights the improvements in this field and points out the factors that limit efficiency optimization. Chapter 10 proposes how the detailed understanding of nano/bio-interfaces would give a boost to the research on their optimal use in various disease diagnostic and therapeutic techniques. Chapter 11 depicts a comprehensive analysis focusing on the advantages, drawbacks, and prospects of organo-metallic hybrid nanomaterials synthesized especially for green and sustainable nanotechnology applications. Chapter 12 discusses the use of cosmetics with reduced impact on the environment and switching to green approach in cosmetics while not compromising with performance, retention, striking appearance, and, more important, safety. Thus, it may clear to the readers that nanotechnology-enabled green nanoarchitechtonics are starting to scale up dramatically. As they become mature and cost effective in the decades to come, nano/biomaterials could eventually replace traditional, environmentally unfriendly technologies and fossil fuels and also improve the performance of the biomedical industry through the utilization of nanocatalysts, manufacturing materials with high durability.

The book is based on the evidence from academicians, scientists, scholars, and engineers and illustrates the wide-ranging interest in the aforementioned areas. The contributions also address the novel synthesis of high-yield nanomaterials and their biomaterials, graphene, polymeric nanomaterials, green nanomaterials, green polyester, nanobiotechnology, interesting response characteristics of exclusive spectroscopic investigation as well as extensive electron

microscopic study, health care, environmental and plant biology, and social, ethical, and regulatory implications of the industrial utilization of green nanotechnology–based leading functional nanomaterials. With appropriate regulation along with the topics indicated, commercial green production of manufactured nanocomposite materials can be realized.

Lastly, I would like to express my gratitude to the authors and the coauthors for their excellent research contributions.

Kaushik Pal, PhD, DSc (Malaysia)
Editor

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Chapter 1

Fundamental Research Trends of Green Nanoscience and Nanotechnology

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Nanotechnology has received an exceptional deal of public interest because of the desire and utilization of nanomaterials in various fields of human attempts including industry, business, agriculture, public health, and medicine. Because of their unique optical, thermal, and catalytic properties, nanoparticles are employed in biomedical research, rendering it one of nanotechnology's most valuable applications. Nanomaterials are rapidly being used in biomedicine, which opens up intriguing possibilities for the creation of novel equipment and technologies across a wide range of medical fields. Despite huge commercial and public investment, concerns

Green Nanoarchitectonics
Edited by Kaushik Pal

ISBN 978-981-4968-50-8 (Hardcover), 978-1-003-31860-6 (eBook)
www.jennystanford.com

have been expressed about risks posed by nanomaterials. Therefore, in this chapter we present an overview of nanotechnology and its toxicity on human and ecosystem health along with different risk assessment methods. The advanced research on nanoparticle toxicity with respect to various nanomaterials have been exemplified with specific findings, responsible mechanisms and possible toxicities on human health in this chapter. Green nanotechnology is based on green chemistry (GC), or the framework of GC principles has been instrumental in the creation of innovative nanotechnologies for reciprocal economic, social, and health/environmental benefit. Thus, in addition GC and its application in green nanoscience, application of phytocompounds along with their challenges, and applications in green nanotechnology were further explored. Overall, we can conclude that the application of green nanoscience aims to minimize or eliminate risks to environment and health of society by utilizing nature's capacity to eradicate or reduce health and environmental threats associated with nanomaterials. Further, many issues with phytomedicines can be improved with the help of nanoformulation-based drug delivery system that has great potential future for improving the therapeutic action of phytomedicines.

1.1 An Overview of Nanotechnology and Its Toxicology

Richard P. Feynman, a Nobel Laureate in physics, first presented the notion of nanotechnology in his renowned speech "There's Plenty of Room at the Bottom" given at the American Physical Society's December 1959 conference [1]. Nanotechnology's goal is to control the forms and sizes of structures, devices, and systems at the nanoscale in order to offer intentional design, characterization, manufacturing, and application. Nanomaterials are distinguished by their size-dependent characteristics and attributes, which arise as a result of extraordinary electrical, surface activity, optical, and magnetic capabilities along with geometries of nanoscale particles [2, 3]. Electronics, water purification, food industries, information and communication technologies, agriculture, medicine, chemicals, coatings, cosmetics, and energy, all have been affected by

nanotechnology [4, 5]. Companies may create new technologies that are more sustainable by integrating nanoparticles into their goods. Nanotechnology not only influences the efficiency and design of these items, but it also generates significant income [6]. Because of their small size (1–100 nm), nanoparticles are extremely helpful, as their tiny size allows them to reach a wide range of biological settings and equips them with useful size-dependent characteristics that may be used in applications. Though synthetic nanomaterials offer a wide range of uses and advantages today, their development and implementation have traditionally been costly, and in certain circumstances have resulted in the generation of ecologically harmful by-products [7].

Given the huge rates of nanomaterial synthesis, the danger of their release to the atmosphere, as well as the consequences for ecosystem health, seems to be an increasingly serious issue that must be addressed [8]. Nanostructures will get in to the environment because of both deliberate and accidental releases, including the air emissions and liquid or solid industrial waste from manufacturing plants. Nanomaterials in personal and health care, paints and textiles are also released into the environment in proportion to their usage. Nanomaterials emitted will eventually settle on earth and water surfaces. Nanomaterials that reach the earth can pollute soil and move into surface and ground waterways. Wind or rainstorm runoff can transport particles from water discharges, solid waste, direct discharges, or accidental leakages into aquatic systems.

Besides the advantages that nanostructures would enhance human lives, the technology's possible consequences are yet unknown. Do nanoparticles that have been developed represent a threat to the environment? Small particles smaller than 10 μm are respirable and can enter the alveolar areas of lungs, which is a matter of concern. Although academics seek to fill in the gaps in the information to aid risk evaluators, experts all over the world urge the need of regulating and overseeing manufacturers to reduce the hazards of nanomaterial exposure to employees, customers, and animals. To do this, it is important to comprehend the fates and functioning of produced nanosystems in the atmosphere.

Nanomaterials have the potential to affect the environment in three ways: (1) direct action on microorganisms, invertebrates,

fish, and other species; (2) interactions with pollutants, which may alter toxic compound and nutrient bioavailability; and (3) changes to nonliving environmental structures [9]. Nanotoxicity is difficult to assess because of its small size and varied interactions with the environment and biological milieu. The following are some of the current nanotoxicity risk assessment approaches in use:

- Evaluation of the materials' physicochemical qualities, which allow them to interact with and potentially harm biological systems.
- Mammalian toxicity (acute and chronic tests, oral toxicity, cutaneous toxicity, skin irritation tests), mutagenicity tests, and eco-toxicity tests to allow some assessment of environmental danger.
- A set of tests for in vitro cellular assays that indicate the response of a variety of cell types after nanomaterial uptake and distribution, which can be targeted at the portal of entry or systemic sites. In general, in vitro data at the cellular level are more relevant for interpreting the mechanism of nanomaterial biokinetics. The results obtained in vitro can be gathered to predict in vivo Absorption, Distribution, Metabolism and Excretion (ADME)/toxicity of the nanomaterials through systematic information on (a) the effective cellular uptake and bioavailability at target sites, (b) cellular metabolism and organ toxicity, and (c) cellular excretion and tissue accumulation and long-term risks.
- Exposure assessment involves both qualitative and quantitative information on the duration, concentration, frequency, and material of exposure of humans or the environment.
- Hazard identification, to understand what are the adverse health and environmental effects associated with particular nanoparticles [10].

The solutions to these and many other issues will drive the development of regulatory standards that will safeguard the environment while also allowing nanotechnology's benefits to be fully realized.

1.2 Various Nanomaterials and Toxicities

Due to advancements in nanotechnology, industrial nanomaterials have numerous remarkable chemical and physical characteristics; their usage in many sectors is being studied throughout the world. Nanosystems produce a huge range of environmental toxicity in various ways. Few nanomaterials, such as carbon nanotubes (CNTs), quantum dots (QDs), metal nanoparticles, magnetic nanomaterials, and others, have substantial toxicities. CNTs are utilized in a variety of sectors, including optical instruments, solar cell mobiles, semiconductors, capacitors, and space elevator cables with unique properties [11, 12]. A quantum dot is a type of nanoparticle that has been widely studied. QDs exhibit unique optical, semiconductor, photochemical, and catalytic characteristics due to quantum confinement phenomena. Conventional QDs are promising for biological applications due to surface changes to heavy metal QDs and the use of heavy metal-free QDs [13]. Silica nanoparticles possess wide range of characteristics and thus exhibit a huge variety of applications. They are abrasive, tough compounds that effectively reduce friction and are thus used to paint waxed floors and even train tracks. Because of their absorptive characteristics, they can be used as a drainage aid in papermaking. Rubber, polymers, and concrete can all benefit from their use as a binding agent. Most importantly, they are nontoxic and stable materials with a huge range of applications in biomedical, medication delivery, and optical imaging agents [14]. Also, anticancer, medication delivery, radiotherapy enhancement, thermal ablation, diagnostic tests, antibacterial, antifungal, gene delivery, and many other biomedical applications have proven that metal- and metal oxide–supported nanomaterials have a substantial therapeutic impact [15, 16]. Apart from the above-mentioned advantages of nanotechnology, there are indeed several risks connected with this innovative technology. Because nanoparticles are easily absorbed by biological systems, there are worries regarding nanotechnology's impact on humans. Table 1.1 summarizes the reported mechanisms and potential risks associated with nanoparticles.

Table 1.1 Various nanomaterials, mechanisms, and their possible risk factors

Nanomaterials	Mechanisms responsible	Possible risk factors	References
Carbon nanotubes	When respirable particles are breathed into the lungs and phagocytized by alveolar macrophages, inflammatory cytokines as well as chemokines are formed, and recurring exposure to respirable particles in the lungs causes chronic inflammatory damage. Due to excess or improper healing mechanisms, chronic inflammatory damage eventually leads to fibrosis of lungs and respiratory cancer.	Pulmonary inflammation and injury, tumors in the respiratory system are common, genotoxicity.	17–20
Quantum dots	The toxicity of QDs mainly depends on individual QDs' diameter, charge, content, exterior functional groups; photolytic, oxidative, and mechanical stability of QDs, as well as their physicochemical characteristics and environmental circumstances.	Toxic effects due to skin penetration	21

Nanomaterials	Mechanisms responsible	Possible risk factors	References
Silica nanoparticles	The cytotoxicity of SiNPs is determined by the particle's physicochemical characteristics. They alter macrophage/ monocyte activity and ability, increase antigen-specific cellular immune responses, and alter cell functioning. Dysfunction of autophagy.	Induced immunotoxicity	22
Iron oxide magnetic nanoparticles	The chemical composition, size, and dose of the substance, as well as its accumulation in the body, specific toxicity to organs, immunogenicity, metabolism, and elimination from the body.	Inflammation, and reductions in growth rate, ulceration, survival, and neurobehavioral changes in plants and cell lines, as well as animal models.	23–25
Silver and gold nanoparticles	Redistribution and accumulation in vital organs, the emission of silver ions that cause biochemical changes. Toxicities also depend on special characters of nanomaterials, namely, size, surface engineering, and dose.	Neurotoxicity, genotoxicity, inflammation, oxidative stress and interference with intracellular signaling	26–29

(*Continued*)

Table 1.1 (*Continued*)

Nanomaterials	Mechanisms responsible	Possible risk factors	References
MnO_2 nanomaterials	Dissolution of MnO_2 inside the lysosomal compartment, suppression of respiration (basal and maximum), and the supplementary respiratory ability of gill cells are all possible processes along with different biochemical and biodistribution profiles of diverse tissues.	Dysfunctioning of mitochondria and declined cellular respiratory function, genotoxicity	30, 31
TiO_2 nanoparticles	Production of reactive oxygen species (ROS), and skin penetration	Oxidative stress, genotoxicity, metabolic variations, inflammation, as well as carcinogenesis.	11, 32
Al_2O_3, carbon black, Co, and Ni nanoparticles	Physicochemical characteristics of particles, namely, nanosize and surface area are responsible.	High pulmonary toxicity compared to micron-sized particles	33, 34

Nanotechnology's use in several sectors is restricted because of its toxicological consequences on human health and the environment. To avoid such negative effects, scientists are currently attempting to manufacture nanomaterials using green methods. Green nanoscience, as GC, aims to minimize or eliminate risks to environment and health of society by utilizing nature's capacity to eradicate or reduce health and environmental threats associated with nanomaterials.

1.3 GC and Its Principles

Green chemistry is the branch of chemistry that mainly deals with the "the utilization of a set of principles that minimizes or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products." We have total 12 principles in GC, given by Warnerand Anastas [35]. The principles of GC nowadays are mainly applied to develop, design, and manufacture different products including medicines and electronic devices. The objectives of these principles are to reduce the waste, prevent pollutions, and decrease the hazards caused by reagents and chemicals. It also helps to use less amount of chemicals, reagents, and solvents during production of different kinds of materials [36]. Application of these principles has reduced the use of hazardous reagents and solvents. They also help in the improvement of material efficiency and its quality for safer use [37].

The principles of 12 GC are very important and essential for fundamental and sustainable development of society with the advancement in scientific areas. The GC principles are described in Table 1.2.

- The main areas that adopt the principles of GC include [38]:
- New chemical synthesis, processes, and methodologiesDrug and product development

Table 1.2 Green chemistry principles

S. no.	Principles	Description
1	"Better to prevent than to cure"	It is recommended to avoid the formation of waste material before starting any work instead of cleaning up and treating waste later.
2	"Atom economy"	To achieve atom economy, suitable synthetic pathways should be planned to use maximum amount of raw materials and precursor compounds to form desired product.

(*Continued*)

Table 1.2 (*Continued*)

S. no.	Principles	Description
3	"Less precarious chemical syntheses"	During the synthesis or production of any product or chemical entity, we need to plan and follow suitable methods and synthetic routes that may yield maximum product quantity and decrease the quantity hazardous waste.
4	"Designing safer chemicals"	Products or chemical agents with required quality, functionality should be prepared by considering the toxicity of product or chemicals.
5	"Safer solvents and safer auxiliaries"	The cost of auxiliary agents like reagents, separating liquids, solvents, chemicals should be avoided in maximum possible cases. It is recommended to utilize auxiliaries and agents that are harmless.
6	"Design for energy efficiency"	The efficiency of energy is very much important during production of material that affects economic and environmental factors. The chemical synthesis and methodologies should be analyzed and optimized using required energy inputs. The chemical processes are recommended to perform using ambient temperature, pressure, and mild conditions.
7	"Renewable feedstocks"	Whenever feasible in technological and economic terms, the synthetic methods should adopt the use of raw materials and chemicals and feedstocks, which are not limited and renewable.
8	"Derivative reduction"	In the synthesis and production of chemicals, it is recommended not to utilize additional steps and chemicals that are responsible to generate extra chemical waste. The steps like derivatization of functional groups, protection, de-protection and blocking agents should be avoided or minimally used.

S. no.	Principles	Description
9	"Catalysis"	The uses of catalytic reagents are recommended in the chemical reactions. The use of stoichiometric and selective reagents is acceptable.
10	"Degradation"	The chemical entities should be planned and designed in such a way that after the life span and use, the synthesized chemicals should not resist in the biosphere and they should be easily degraded into nonhazardous waste.
11	"Real-time analysis for pollution prevention"	To prevent the pollution, there is need of developing advanced instrumentation techniques for the real-time analysis, monitoring of in-line methods, and control of such steps before the formation of hazardous waste.
12	"Accident prevention by inherently safer chemistry"	To reduce the risk and accidents, fire formation in the laboratory, it is recommended to use the suitable compounds and chemical methodologies.

1.3.1 Utility of Principles of GC

- The principles of GC are approached to develop nanomaterials, nanomedicines, and nanodevices that can be added into high-performance products that are less hazardous to society and environment [39].
- It helps in discovering the synthetic procedures that use the reagents that are less harmful and also increase the efficiency of existing methodologies [37].
- The utilization of GC principles toward nanoscience help to facilitate the formation of safer nanodevices and materials.
- Many applications of green nanoscience and nanotechnology make use of principles of GC in order to prepare the nanoscale materials [40].
- The principles of GC are helpful to give proactive design which assures that the production of nanomaterials is done in safer way and also it is done by considering the biological and ecological hazards [41].

- It plays a very important role in the field of nanoscience that helps in the maximum benefits to the society and reduces the impact on ecosystem [37].
- GC guides for the production of materials, development of new method, and design of application throughout the life cycle [42, 43].

1.3.2 Green Nanoscience to Apply Principles of GC

The green nanoscience is a very important branch of science that deals with applications of green principles of chemistry and green engineering. It mainly helps to reduce the utility of fuel and energy by employing the minimum use of materials and renewable inputs wherever needed. The well-being of society and health of population is the final and very important goal of any type of development in scientific areas. To achieve this goal, implementation of new strategies is needed. Well-being of population can be achieved by providing effective therapeutic medicines and treatments; hence, safe delivery of medicines is important [44]. The clean and green technology development is a rapidly growing field nowadays. The green nanoscience, in phytochemical-based preparations or phytomedicines, significantly play a very essential role in maintaining environmental sustainability with respect to nanoformulation by avoiding any type of harm to environment, society, and health of the human [45].

The utilization of plant materials and related phytomedicines in the preparation of nanoparticles and nanoformulation is essential, rational, and recommended due to its easy accessibility and availability. The usefulness of phytomedicines is accepted in the nanopreparations due to the large variety of primary and secondary metabolites. Diverse number of biological activity shown by the phytochemicals include antioxidant, antibacterial, antiviral, anticancer, antidiabetic activities, and hence, they are greatly involved in the nanopreparations for effective therapeutic management of diseases and disorders. In the green nanoscience and green nanotechnology, the word “green” refers to the utilization of phytomaterials or phytomedicines. The green nanoscience mainly uses the principles of GC and it helps in the energy minimization and

fuel utilization. Many nanotechnological preparations, processes, and utilizations are found to possess the high energy utilization, large amount of fuel utilization, large utilization of water, reduces the greenhouse gases, and generates the hazardous waste. To overcome the limitations of nanotechnology, the concept of green nanoscience and nanotechnology is evolved. The green nanoscience is the approach to minimize the adverse reactions or effects before production [46, 47].

1.4 A Green Approach in the Development of Nanoparticles

Phytomedicines are large source of drugs and the biological activities of such medicines are due to the combined effect of active components of that plant material. The phytoconstituents present in the herbal material show synergistic activity, which in turn improves their therapeutic effect. Phytomedicines are very important and play essential role in the management of various serious diseases and disorders. But the major limitations or disadvantages of phytomedicines include:

- Solubility issues
- Low bioavailability
- Difficulty in absorption
- Difficulty in systemic clearance
- Frequent administration of drug
- Higher dose utilization
- Difficulty in reaching the site of action.

To overcome above limitation of phytomedicines or preparations based on herbal origin, a new research area has been evolved in the phytoformulation research known as nanoformulation. This new area mainly deals with development and validation of nanotechnology-based dosage formulations of drugs from natural origin. Few of the very important nanotechnology-based herbal formulations include polymeric nanoparticles, nanocapsules, nanospheres, proliposomes, nanoemulsions, solid lipid nanoparticles, and liposomes. These novel formulations are very important in the field of phytopharmacological research and advantages of same are presented in Fig. 1.1.

Hence, many issues with phytomedicines can be improved with the help of "nanoformulation-based drug delivery system" (NDDS). This has great potential future for improving their therapeutic action of phytomedicines. The help of nanocarriers as an "NDDS" in traditional drug delivery systems is needed to manage chronic diseases like cancer, diabetes, asthma, and others with the utilization of phytomedicines [48–50].

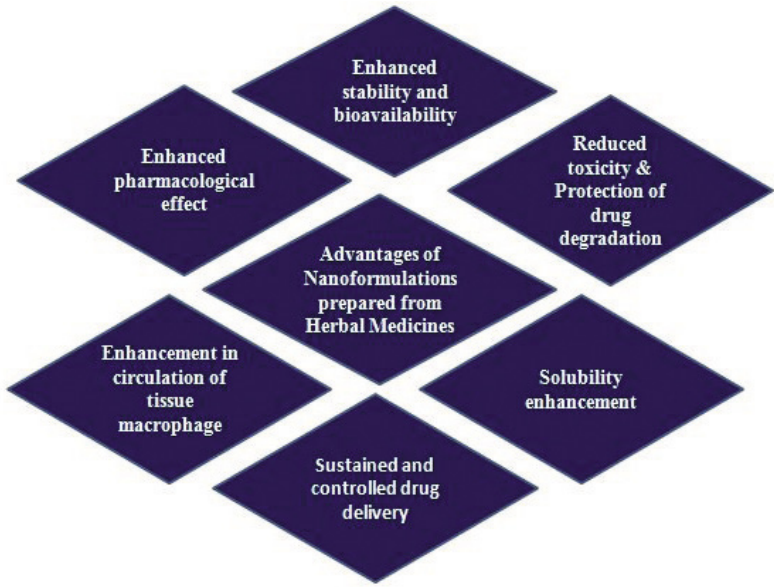

Figure 1.1 Advantages of nanoformulations prepared from herbal medicines.

Many important phytomedicines-loaded nanoparticles have been developed and effectively used in the management of chronic diseases such as cancer, diabetes, and hypertension. Various drugs obtained from plants, which have been loaded into nanoformulation, include curcuminoids, glycyrrhizin, flavonoids, lignans, artemisinin, berberin, camptothecin, and taxel. Table 1.3 summarizes the phytomedicines-loaded nanoformulations [51–57].

Table 1.3 Phytomedicines-loaded nanoformulations along with therapeutic effect and method of preparation

S. no.	Active phytoconstituents	Type of nanoformulation	Therapeutic effect	Preparation method
1	Artemisinin	Nanocapsules	Anticancer activity	Ionic gelation method
2	Berberine	Berberine-loaded nanoparticles	Anticancer activity	Self-assembly procedure
3	Camptothecin	Camptothecin encapsulated nanoparticles	Anticancer activity	Dialysis method
4	Curcuminoids	Curcuminoids solid lipid nanoparticles	Anticancer and antioxidant activity	Microencapsulation method
5	Glycyrrhizin	Glycyrrhizin-loaded nanoparticles	Anti-inflammatory and anti-hypertensive activity	Rotary-evaporated film ultrasonication method
6	Flavonoids and lignans	Nanoparticles of *Cuscuta chinensis*	Anti-oxidant and hepatoprotective activity	Nanosuspension method
7	Taxel	Taxel-loaded nanoparticles	Anticancer activity	Emulsion solvent evaporation method

1.5 Applications or Trends of Green Nanoscience and Nanotechnology

The concept of green nanoscience and nanotechnology is mainly applicable and implemented in huge areas like, bioengineering, nanofabrication, cosmetics, energy, drugs and medicines, nanobiotechnology, and optical engineering [26]. Various research trends of nanotechnology and nanoscience are explained as below and represented in Fig. 1.2.

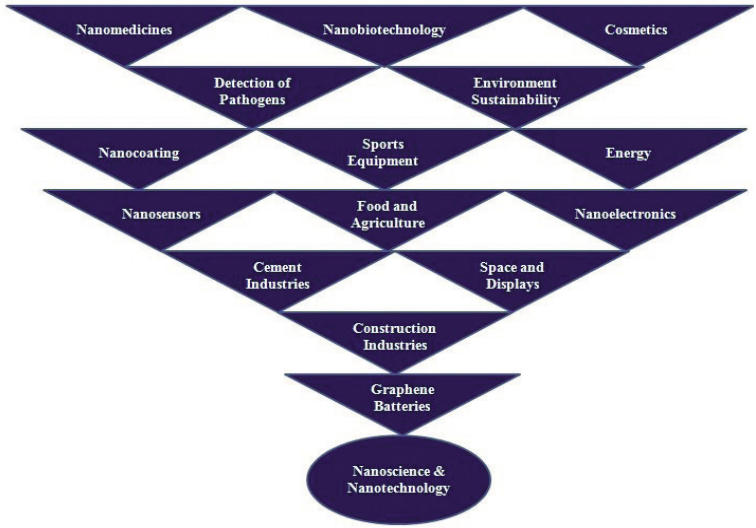

Figure 1.2 Applications and nanoscience and nanotechnology.

1.5.1 Nanomedicine

The utilization of nano-based drug delivery is most potential in the management of various metabolic and other chronic diseases and different types of disorders. The principles of GC and its applications in technology and science for treating, diagnosing, preventing disease and disorders, relieving pain, injury, and improving health of society using molecular tools and knowledge of the human body can be done by using the nanoscience and nanotechnology. The comprehensive control, construction, defense, management, monitoring, and improvement of all human biological systems are useful tools of nanoscience [58].

1.5.2 Nanobiotechnology

Nanobiotechnology is the important technique which utilizes the principles of nanoscience and biotechnology. Nanobiotechnology has vital and great role in the development and application of various tools in the life science studies. Implementation of nanomaterials with that of the biological principles leads to development of different types of analytical tools, treatments, therapy, diagnostic devices, contrast agents, drug delivery vehicles [59].

1.5.3 Nanotechnology in Cosmetics

The applications of nanotechnology, nanoscience, and nanomaterials are very much helpful in the production, cosmetic preparation such as moisturizers, hair care products, sunscreens, and make-up preparations [60].

1.5.4 Detection of Foodborne Illnesses

The principles of "nanoscience and nanotechnology" are helpful in the identification techniques for different types of pathogens. Techniques and materials, such as dye immobilized nanoparticles, fluorescence, luminescence, and metallic nanoparticles, are the useful tools in detecting pathogenic diseases. Nanotechnology helps to detect rapid, sensitive, reliable, and simple isolation and identification method for pathogens [61].

1.5.5 Nanotechnology and the Environment

The climate and environment protection can be very effectively done by utilizing the principles of green nanoscience and nanotechnology. During the production of various nanotechnological equipments, apparatus, devices, products, and methods, principles of GC can be applied, which are definitely helpful in reducing the use of hazardous substances, minimizing the use of raw chemicals, reagents and materials, also energy minimization, and water utilization.

1.5.6 Nanotechnology in Sports Equipment

It has many benefits and strength to improve sports equipments that make athletes comfortable, safer, and more agile. For example, the durability and performance of various sports equipments, such as tennis, baseball bats, hockey sticks, badminton racquets, racing bicycles, golf balls, skis, archery, and arrows, can be improved.

1.5.7 Food and Agriculture

The techniques and principles of nanoscience and nanotechnology are useful in the production of food items and agricultural materials

and devices. It has potential impact and applications in the preparation of functional food, and manufacturing of other biological food products.

1.5.8 Nanocoatings

Nanocoating is very important in the field of aerospace, marine, medical, and oil industries. It is important in the production of multifunctional coatings to different products. The nanocoating is a type of coating that involves the application of nanoscale thin films to surfaces of materials, which helps to improve the function of material, and prevent from corrosion.

1.5.9 Energy

The nanotechnology innovations are very important in different types of energy sectors, energy sources, energy storage, energy distribution, energy conversion, and energy utilization. Nanoscience and nanotechnologies help to increase the efficiency of energy in almost all types of industries.

1.5.10 Nanosensors

The nanosensors are sensing materials with dimensions smaller than 100 nm and they are mainly used for collecting data from different sources. They are developed for the identification of gases from chemical, physical, and biochemical variables, and also for the detection radiations of electromagnetic waves.

1.5.11 Nanoelectronics

It is a very important branch of electronics dealing with the use and implications of nanotechnology in electronic devices. These electronic components are having very small size, may be ranging from few nanometers. Nanoelectronics mainly cover the materials and devices with very small size with physical effects that alter the properties of materials on nanoscale quantum mechanical and inter atomic interactions.

1.5.12 Nanotechnology in Furniture

The principles of nanoscience and technology are helpful in the production of furniture, which helps to decrease the need for functional textiles and adhesives. Nanoscience is helpful in producing good quality of furniture with different properties and applications.

1.5.13 Graphene Batteries

The nanoscience and technology are very much helpful in the production of graphene batteries. The graphene is chemically processed and used for manufacturing of different types of graphene batteries with ultrahigh energy. It is helpful in the production of various types of batteries such as redox flow, lithium, sulfur, metal, and air.

1.5.14 Nanotechnology in Space

Nanoscience and nanotechnology has important role in future space missions. "Nanosensors, dramatically improved high-performance materials, or highly efficient propulsion systems can be produced by using principles of nanoscience."

1.5.15 Nanotechnology in the Automotive Industry

The automotive industry is a largest material-based industry and nanotechnology help to improve the performance of existing technologies. The nanoscience and nanotechnology has useful impact in the generation of lighter but stronger materials, fuel cells, production of good paint quality, batteries, ultra-thin anti-glare layers for windows and mirrors to the futuristic energy harvesting bodywork, switchable colors, fully self-repairing paint, and shape shifting skin.

1.5.16 Nanotechnology in the Construction Industry

Nanotechnology has a great role and impact in the construction industries. It helps in improving the performance and durability of various components used in construction. This also helps in the safety and energy efficiency of the buildings.

1.5.17 Nanotechnology in the Cement Industry

In cement industry, it has a potential role to address issues such as poor crack resistance, carbon dioxide emissions along with low tensile strength, curing time, absorption of high water, and many other mechanical properties. The nanoengineering of cement-based preparations are much helpful and they are outstanding in their performance and also has smart properties.

1.6 Conclusions

Normally, during the period of advancement of new nanotechnology area, experts concentrate essentially around recognizing new properties and applications. Subsequently, the assessment of any accidental properties of the material (e.g., environmental or health hazards) or concerns about risks or efficiencies of the production cycle is regularly conceded. Assessment of the potential toxicological and ecological impacts of nanoscale materials before they are acknowledged as full-grown advancements presents a chance to limit putative unfortunate results from the beginning and eventually lead to the plan of better materials. The phytoconstituents present in the natural material give synergistic action which helps in the improvement of restorative impact of medication, however, they have restricted clinical applications. Blend of green science and nanoscience can be possibly applied to defeat the restrictions of phytoformulations and also proved to be beneficial in developing production-level commercial scale materials. Further many issues with phytomedicines can be improved with the help of nanoformulation-based drug delivery systems that has great potential future for improving the therapeutic action of phytomedicines. Commercialization will rely heavily on the development of high-precision, low-waste nanomanufacturing techniques. GC, in addition to improving research and development methods, has the potential to improve public opinion of nanoscience since, it is very simple to explain and may be utilized to express a proactive approach towards the development of this new technology. For these factors, GC can play a significant role in directing the development of nanotechnology to ensure that these products benefit society and the environment to the greatest extent possible. Further development and application

of green nanoscience to the design and production of various nanomaterials will provide research opportunities and challenges for the foreseeable future.

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Green Nanomaterials Revolution in Cosmetic Products and Skin Treatment

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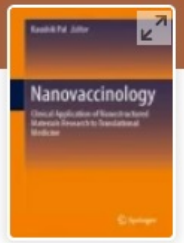

Nanovaccinology pp 161–179 | Cite as

Flexibility in the Design of Nanomedicine Using Biomimetic Immunomodulatory

Archana S. Patil, Rajashree S. Masareddy & Priyanka P. Patil

Chapter | First Online: 23 August 2023

Abstract

Significant increase in immunological diseases has globally attracted attention of researchers to develop molecules able to modulate the immune response. Nanoparticle-based drug delivery systems synthesised from wide array of material based on biomimetic engineering is

Text Book of Pharmaceutical Chemistry for Diploma in Pharmacy

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IMPORTANCE OF ARTIFICIAL INTELLIGENCE IN THE FIELD OF PHARMACY

Abstract

Artificial Intelligence is becoming more widely used, notably in the pharmaceutical business. Long and expensive medicine development cycles, as well as consumer and legislator price expectations, dominate the existing pharmaceutical infrastructure. Artificial Intelligence is being employed in the pharmaceutical sector for therapeutic research and development, immunotherapies, pharmaceutical productivity improvement and clinical trials. Artificial Intelligence is also used in drug development. Learn how to compute the QM/MM of an enzyme's active site. Locate some lead-like library chemicals. Only a few companies have agreed to participate in an AI-related study that could be employed in medicine discovery and creation. The goal of this article is to look at recent advancements in Artificial Intelligence in medicine, as well as provide insight into the challenges and risks that health practitioners and institutions face when integrating augmented medicine into medical treatment and future medical leader education, as well as the most common use-cases where AI-powered therapeutic technologies are already being used in medical care.

Keywords: Artificial Intelligence, Pharmaceutical Business, Pharmaceutical Infrastructure, Immunotherapies and Health Practitioners.

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I. INTRODUCTION

Artificial intelligence (AI) is the computerization of human intelligence (AI). It includes data gathering, usage guidelines, tentative or conclusive results, and self-correction. Many individuals worry that AI will threaten their jobs, although every progress in AI is seen as crucial for society advancement.[1]. Disease diagnosis, monitoring, comprehension, driving autos, trading currencies, and other medicinal chemistry operations could all benefit from Artificial Intelligence. In silico analysis can help with almost any subject that requires the detection of patterns and the discovery of relationships in large datasets [2]. Artificial Intelligence (AI) is widely being used, notably in the pharmaceutical business [3]. Long and expensive medicine development cycles, as well as consumer and legislator price expectations, dominate the existing pharmaceutical infrastructure [2,3]. Artificial Intelligence is being employed in the pharmaceutical sector for therapeutic research and development, immunotherapies, pharmaceutical productivity improvement and clinical trials [1,3]. Artificial Intelligence is also used in drug development [4]. Learn how to compute the QM/MM of an enzyme's active site [5]. Locate some lead-like library chemicals [6]. Only a few companies have agreed to participate in an AI-related study that could be employed in medicine discovery and creation. Euretos is employing massive omics-like datasets to investigate links between biological circuits and diseases [7]. Sparrho's goal is to help the technical community by extracting, curating the most relevant scientific research findings from a growing corpus of literature, employing both AI and human editors. [8]. BioXcel is repurposing traditional medications using artificial intelligence [9] [10]. Creativity is used to identify and answer unmet medical needs**.** The goal of this article is to look at recent advancements in Artificial Intelligence in medicine, as well as provide insight into the challenges and risks that health practitioners and institutions face when integrating augmented medicine into medical treatment and future medical leader education, as well as the most common use-cases where AI-powered therapeutic technologies are already being used in medical care.

II. APPROACHES OF ARTIFICIAL INTELLIGENCE

1. Artificial Intelligence (AI).
2. A higher education level.
3. One type of network is Artificial Neural Networks.
4. A well-known example of Artificial Intelligence is machine learning. This method allows computers to reliably adapt and change their functions (e.g., making predictions).
5. AI is being employed in a wide range of disciplines. (Fig 1).

Figure 1 : Artificial Intelligence is being used in a Variety of Fields

III. ADVANCEMENT OF ARTIFICIAL INTELLIGENCE

1. **Machine Learning:** There are two types of machine learning algorithms [11].

   - **Observed Learning:** In supervised learning, the algorithm makes adjustments in order to respond effectively to a set of training cases. As a result, the anticipated output replies are known to be accurate, and feedback statistics are saved in the database for future training. [11]. Regression analysis techniques include random forests, support vector machines and Artificial Neural Networks. [11,12]

   - **Unrestricted Learning:** It is based on non-example-dependent feature extraction methods [11]. Other machine learning approaches, such as the probabilistic reasoning method, are also used in pharmaceutical sciences. To explain the logic and reasoning behind the assertions. [13]. This method has the advantages of requiring no expert knowledge of the system, compensating for data noise, and providing easily interpretable projections [14]. This method can also be used to model nonlinear relationships. GA is frequently used as a feature selection method in quantitative QSAR studies involving pharmaceutical research [15,16]. Transfer learning is included in active machine learning. The technique of leveraging a previously trained model to construct a new, anticipated fit for the desired aim is known as transfer learning [17]. The database size of the initial formulation is a critical determinant of transfer learning performance. [18].

2. **Artificial Neural Network:** Artificial Neural Networks (ANN) can be utilized in a variety of applications. The brain's ability to learn by example is simulated by Artificial Neural Network (ANN). The interconnectedness of these neurons is made up of several synapses connecting one neuron to the next. [19]. In a biological system, a neuron is

made up of three parts: a cell membrane with a nucleus that regulates cellular activity, nerve cells that connect neurons and give signals to the cell, and axons, which look like one long thread carrying data to the next cell. ANNs, like human neurons, are made up by clusters of neurons (PEs) connected by coefficients (weights) [19]. The inputs, hidden, and SoftMax layers are the four fundamental structural systems of a traditional ANN. The system's input is the first layer of an input neuron, which corresponds to the synapses of a true neuron. The layers exist between the source and destination nodes. Each buried layer [20] is densely packed with neurons. To put it another way, they're a network of interconnected advanced computer bits called 'perceptons,' which resemble biological neurons and respond to electrical impulses similarly to the brain. [21]. ANNs are a sort of network that solves problems by converting discrete inputs into outputs using algorithms, either individually or in groups. [22]. To construct supervised learning that can learn to solve an issue rapidly, repeated intake amounts of antecedent with known responses are used (targets). This is referred to as "learning" or "training." Receiving signals (inputs) from the input layer is the initial step in the learning process. In the hidden layer, these inputs are amplified and summed using network parameters. A transfer function is used to send the results to the output nodes. The activation functions accessible include logistic, tanh, identity, and exponential. [23]. The transfer function is most widely used activation function in medicine. Error back-propagation is an extensively used approach in neural network learning. [24]. In addition to assessing complex data based on elongation and pattern recognition, ANNs are particularly good at simulating nonlinear interactions and collecting extremely precise predictions. [25,26]. The disadvantages of utilizing ANNs include local minimum trapping, noise management, and overfitting/underfitting. The Time Invariant Noise Algorithm (TINA) is used to prevent local minima and control noise. Overfitting can be reduced with this method. Furthermore, stopping the technique at the proper time can helps in preventing both overfitting and underfitting [29].

3. **Deep Learning:** DL is both, Deep-Learning and a representational learning approach [30]. Recent breakthroughs in neural networks are included in the state-of-the-art of DL paradigms. The primary difference between ANNs and DLs is that DLs have many more layers (always more than three) and each layer has many more nodes. DL employs a multi-level representation method to learn complex functions. The architecture of Deep Learning often necessitates a large amount of training data, which may limit its application. Deep learning uses CNNs, RNNs, and tightly integrated FFNs (Feed-Forward Networks) as neural network topologies [31]. In a number of pharmaceutical research domains, including as pharmaceutical formulation design [32], drug development [33], and medication retrofitting [34], DL has become vital and of exceptional quality.

- **Machine Learning Drug Prototyping and Revelation:** Widespread use of HTS (High-Throughput Screening), CC (Combinatorial Chemistry), and computer-aided drug design in pharmaceutical sciences, drug discovery accounts for a significant number of algorithms (CAD). [35]. One of the first ANN applications was in the QSAR research investigations [36,37]. The QSAR criterion connects a substance's physical and chemical properties with its biological and chemical activity. [38,39].

In Quantitative Structure Activity Relationship Structure QSAR research, chemical properties such as molecular weight, partition coefficient (logP), and hydrogen

bonding capacity are commonly used. Because empirical QSAR research involves complicated and nonlinear systems, ANNs were one of the most accessible QSAR modelling methods. As seen by the rapid rise of QSAR research based on ANNs [40], the utility of neural networks in drug development has continued to grow as a result of their power grid and success.

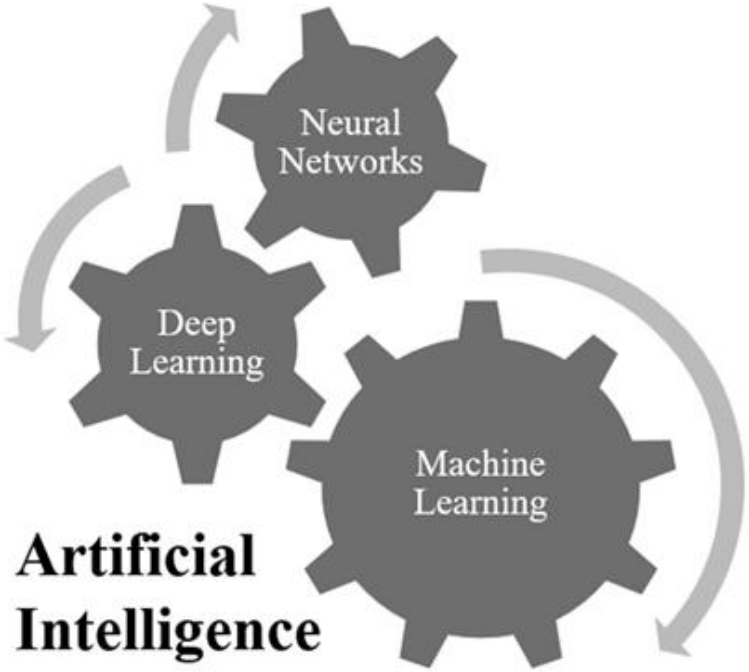

Figure 2 : Advancements of Artificial Intelligence

- **In Pharmacological Sciences, Machine Learning:** Machine learning is widely being used and has vast pharmaceutical applications, from discovery of new drug to the final stages of product development. There are three main areas of pharmaceutics where ANNs and other machine learning technologies have been actively used. Drug design, Preformulation studies, formulation and development research are the three sorts of investigations.

- **Artificial Intelligence and Drug Development (AI):** Developing novel medications that are effective is a difficult task. The situation is clarified by [41]. For drug target definition and validation, drug design, drug repurposing, R&D efficiency, biological data gathering and analysis, and refining the decision-making process to enrol patients in clinical trials, AI technologies have been used at many stages [42,43]. AI applications that reduce inefficiencies, uncertainty, bias, and human participation could help traditional drug development procedures [44]. AI is also used in drug development to predict drug-like chemical synthetic pathways [45], pharmacological properties [46], protein determinants and functions [47], drug synergy and drug–target interactions [48], and medicine repurposing [49].

New pathways and targets found by omics research include therapeutic targets, customised treatment based on omics indicators, and exposing the links between drugs and disorders [50,51]. DL has a history of recognizing novel drug concepts and appropriately appraising their advantages as well as any potential negative effects [52]. New research could use AI to aid in the identification of new therapy targets, rational prescription design, and pharmaceutical repurposing [55,56]. Previous drug development challenges, such as large dataset analysis and time-consuming compound screening while minimizing standard error, necessitated massive amounts of R&D money and effort, totalling around US$2.5 billion and spanning more than a decade [53], are now possible to overcome with AI technologies [54].

- **Artificial Intelligence in Pharmaceutical Manufacturing**

- **Tablets with a Controlled Release:** Hussain and his colleagues at the University of Cincinnati were the first to employ neural networks to simulate pharmaceutical formulations. They patterned the in vitro release properties of a number of medicines implanted in matrices made from various hydrophilic polymers in a series of investigations [57,58]. In every situation, neural networks with a single convolutional layer performed well in forecasting drug release. Overall, the findings corroborated statistical analyses [57]. On the other hand, predictions made outside of the limits of the input data performed badly [58]. Even though evolutionary methods were not utilized to update the formulations, the researchers were inspired to look into neural network-based computer-aided formulation design [58].

- **Immediate-Release Tablets:** Two tests were conducted in this location three years ago. Turkoglu collaborated on a study [59] with colleagues from the University of Marmara in Turkey and the University of Cincinnati to forecast hydrochlorothiazide tablet formulations using neural networks and statistics. To increase tablet strength or find the best lubricant, the networks were utilized to create three-dimensional plots of massing time, compression pressure, and crushing strength, as well as drug release, massing time, and compression pressure. Even though patterns were found, no ideal formulations were given. The patterns were created using statistical methods.

  In a more in-depth research of neural networks in this domain, Kesavan and Peck of Procter & Gamble Pharmaceuticals (Norwich, NY, USA) and Purdue University (West Lafayette, IN, USA) duplicated the manufacture of anhydrous caffeine tablets. Two networks were created from 32 tests, one with five inputs [diluent type, diluent level, binder level, granulation machinery used, and binder addition (wet or dry)] and the other with nine inputs [diluent type, diluent level, binder level, granulation machinery used, and binder addition (wet or dry)]. In forecasting findings, both models were more accurate than hastily generated models with four outputs (tablet strength, friability, thickness, and disintegration time). The AI Ware CAD/Chem application [60] was used to re-analyse the same data.

  Comparable neural network models were created and optimized using genetic algorithms. The optimum formulation was shown to be dependent on both the chemical concentrations used in the formulation and the relative importance of the

output qualities. Only by sacrificing disintegration time can high tablet strength and low friability be achieved. Lactose was utilized as a diluent in all cases, and the granulating analytical technique of choice was fluidized bed granulating [61].

- **Artificial Intelligence Drug Screening:** Research and development of the drug can take nearly a decade and can cost an average of $2.8 billion. Despite this, authorities reject nearly nine out of ten medication candidates that fail Phase II clinical trials. [62,63]. Nearest-neighbour filters (RF), ensemble learning machines (SVMs), and Deep Neural Networks (DNNs) are utilized to predict in vivo activity and toxicity in the case of VS. In areas like immuno-oncology and cardiovascular disease, pharmaceutical corporations like Bayer, Roche, and Pfizer have partnered with IT businesses to construct drug development platforms [62].

- **Creating Drug Molecules using Artificial Intelligence:** The target protein's estimated structure in order to accomplish successful therapy, it is necessary to designate the proper target while generating therapeutic molecules [63]. Several proteins have been uncovered as the illness progresses, some of which have been found to be overexpressed in some patients [64]. As a result, while creating a disease-targeting medicinal chemical, it's crucial to forecast the structure of the target protein. AI can help structure-based regenerative medicine by predicting the impact of a drug on the aim as well as its restrictions prior to its synthesis or manufacture by anticipating the 3D protein structure [65]. AI can aid structure-based regenerative medicine by predicting 3D protein structure as the design is in agreement with the chemical environment of the target protein location [66].

- **For Quality Assurance and Control, Artificial Intelligence (AI) is being Applied:** To obtain the necessary output from raw resources, a variety of attributes must be balanced [67]. For product quality control testing and batch-to-batch consistency, manual intervention is essential. While this isn't always the best solution, it does highlight the urgent need for AI adoption [68]. To better comprehend the critical actions and exact criteria that manage a pharmaceutical product's ultimate quality, the FDA suggested a 'Quality by Design' method [69]. Using a combination of AI and human efforts, early discoveries from production batches were reviewed, and feature selection algorithms were constructed. ANN was used to investigate the solubility and dissolving rate of theophylline pellets [70], with an error rate of less than 8%.

  AI can also be used to control in-line manufacturing activities to obtain the appropriate product grade. An Artificial Neural Network (ANN) that combines auto evolution, multi-objective, and training algorithm methodologies is used to monitor the freeze-drying process. It can be used to determine thickness of desiccated-cake at a later time point and temperature (t + t) for a specific given set of operational parameters, making quality control of the finished version easier [71]. Product reliability can be ensured by combining a complex, intelligent technique with an automated data input platform, like a digital lab notebook[72]. The expert system for total quality management may employ data mining and other knowledge discovery approaches to aid in making challenging judgments and inventing latest technologies for the intelligent management of quality [73].

- **Clinical Trials with AI in the Works:** Clinical trials are used to test a pharmaceutical medication's safety and efficacy in people who have a specific ailment. They necessitate a large financial investment and require 6–7 years to finish. Despite this, just one out of every ten substances tested in these trials gets approved, resulting in huge loss to the industries[74]. Lack of patient selection, lack of technology expectations, or a damaged infrastructure contribute to these failures. AI could be utilized to help resolve these challenges because digital health data is publicly available [75]. A clinical trial spends one-third of its time seeking volunteers. Enrolling competent patients can help a clinical study succeed, despite the fact that it has an 86 percent failure rate [76]. AI can help in the selection of only a particular sick population for the enrolment by utilising patient-specific genome-exposome profile analysis in Phase II and III clinical trials, allowing for the early identification of promising therapeutic targets in the patients chosen [77]. Using other AI components to uncover therapeutic targets ahead to the start of clinical trials, such as predictive ML and other reasoning approaches, aids in the early prediction of lead medications that will pass clinical trials while considering the patient population [78]. Dropouts from clinical trials account for 30% of study failures, requiring further recruiting and losing both time and money. Proper monitoring and encouraging the patients to adhere to the clinical study procedure on a regular basis, can minimize these errors[79].

- **Artificial Intelligence for Market Positioning:** Many business strategies for firms attempting to build their own distinct brand include a positioning plan. It comprises developing a product's brand in the market to attract customers to buy it [80,81]. This method was used to promote Viagra, a game-changing drug used to treat erectile dysfunction in men as well as other quality-of-life issues [82]. Technology and e-commerce can be used as a platform and businesses may now build natural brand awareness in the public realm. According to the Internet Advertising Bureau, organizations use one of the methods for technology platforms to get a competitive advantage in digital marketing and aid in product placement. Companies are constantly attempting to outrank their competitors websites in order to gain visibility for their brand [83]. To improve market knowledge, statistical analysis methodologies and particle swarm optimization algorithms, for example, can be employed in conjunction with NNs (Developed by Eberhart and Kennedy in 1995). They can help build a product marketing plan that is based on realistic client demand projections [84].

IV. CONCLUSION

Artificial Intelligence contributes to a phenomenal growth in the field of pharmacy. AI plays a key role in the drug discovery, Preformulation studies, drug design, formulation of dosage forms and development of business strategies to build a product brand in the market. AI predicts 3D protein structures with proper targets. Deep Neural Networks (DNNs) can predict in vivo activity and toxicity of drug candidates used in cardiovascular disease and immuno-oncology. ANN is widely used in QSAR research investigations which relates the physical and chemical properties of the drug with its biological and chemical activity. AI

based selection of patients for clinical trials helps in the proper selection of therapeutic targets with less errors. Implementation of AI technology in numerous fields of pharmacy will decrease the health hazards and also reduce the cost considerably.AI can play a vital role in the better functioning of pharma industries.

V. ACKNOWLEDGEMENT

Authors express sincere gratitude to the Principal and Department of Pharmaceutics, KLE College of Pharmacy, Belagavi, Karnataka, India.

VI. CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ADVANCEMENT OF KNOWLEDGE

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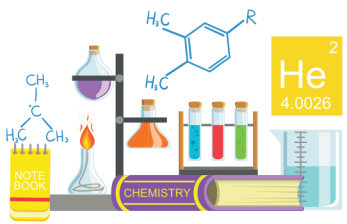

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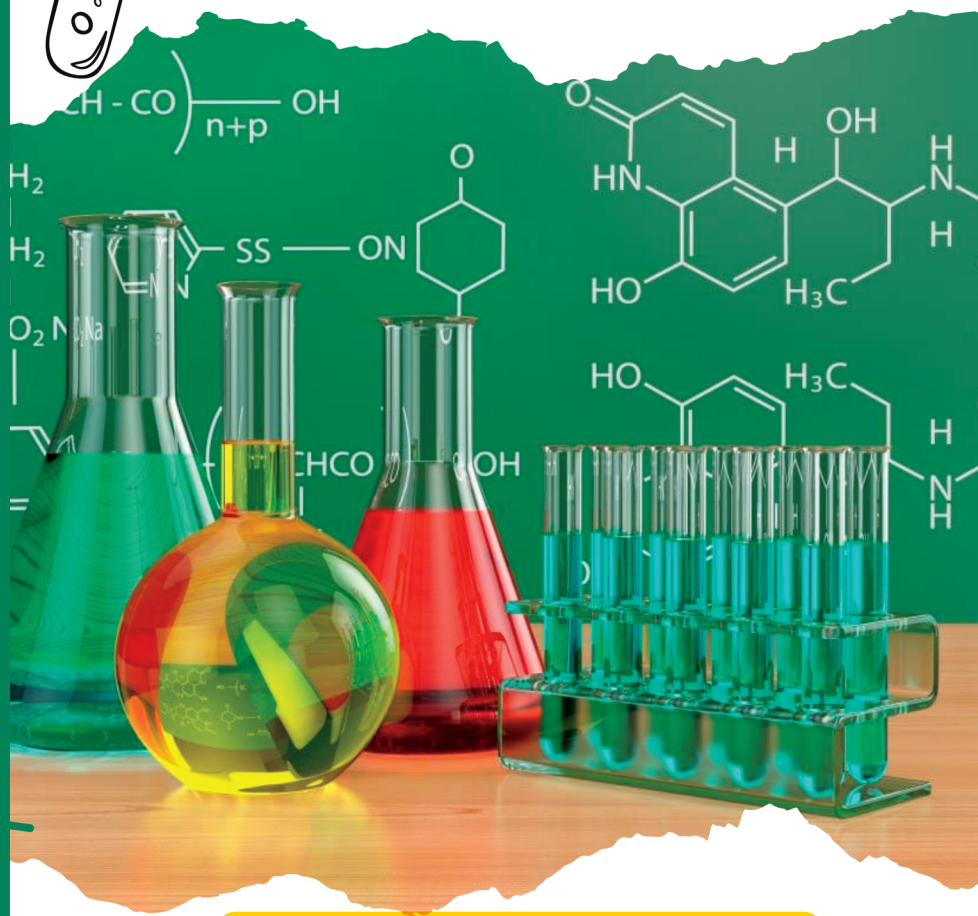
A COMPREHENSIVE TEXT BOOK OF PRACTICAL BIOCHEMISTRY



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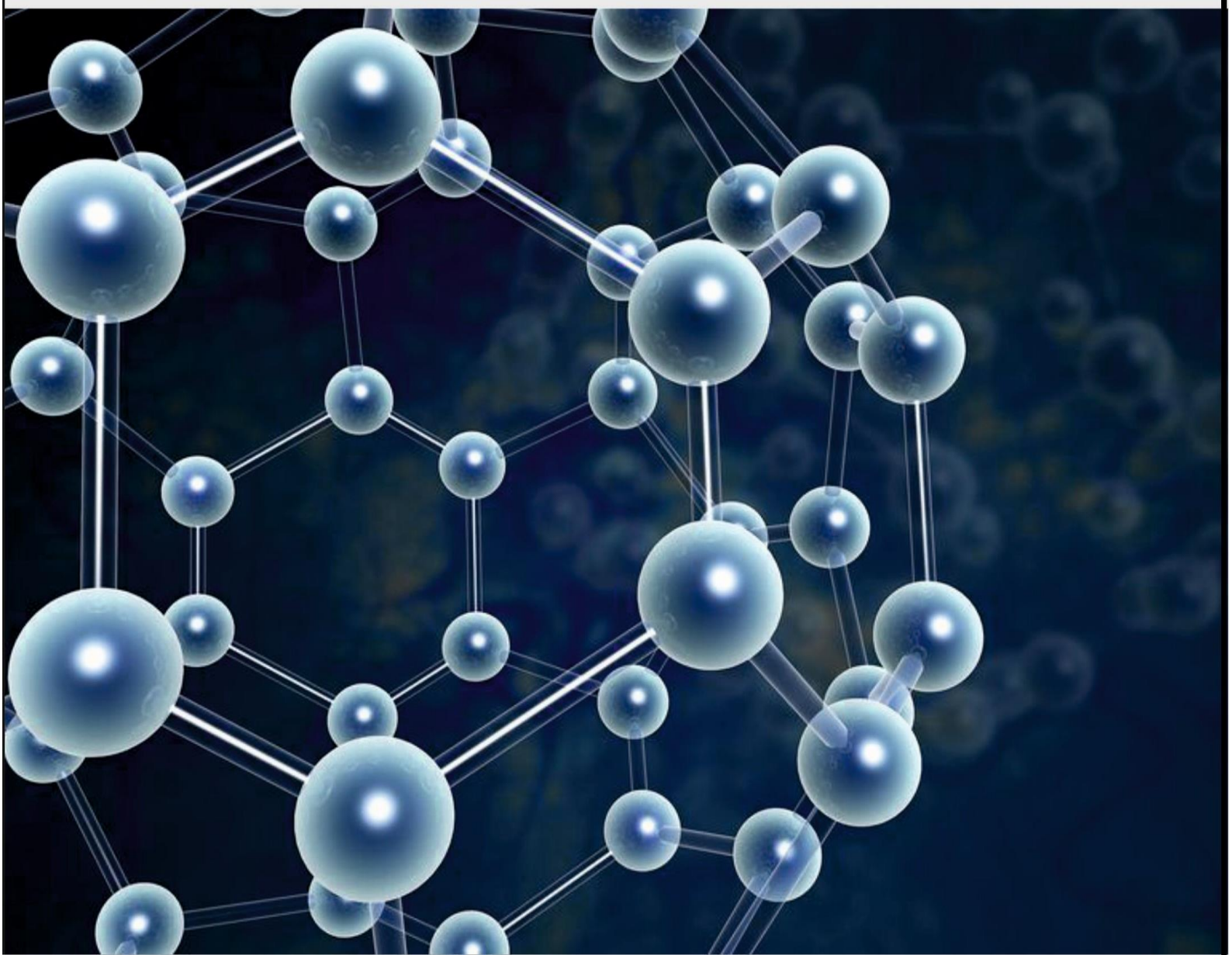
Advanced Organic Chemistry Applications

Editor
Dr. M. R. Jayapal



ADVANCED ORGANIC CHEMISTRY APPLICATIONS

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Book Title: **Advanced Organic Chemistry Applications**

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1st Edition

ISBN: **978-93-94570-79-5**

Published: **Jan 2023**

Publisher:

Kripa-Drishti Publications

A/ 503, Poorva Height, SNO 148/1A/1/1A,
Sus Road, Pashan- 411021, Pune, Maharashtra, India.
Mob: +91-8007068686
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PREFACE

The manner of Organic Chemistry has changed somewhat since my days as a student in the early 2005s. Most notably, organic chemistry books offer more and better descriptions of topics in related fields such as Biochemistry and Materials Science, the internet allows one to search for information about specific topics, and computer software is readily available for modelling chemical structures and reactions. The overall level of sophistication has also risen for the presentation of traditional themes such as stereochemistry, bonding, reaction mechanisms, spectroscopy, and synthesis.

In spite of these changes, however, the mastery of Organic Chemistry as a course of study still requires a sound knowledge of the principles of molecular structure and chemical reactivity, which are topics introduced in most General Chemistry courses. With such a back-ground, a student studying organic chemistry begins to focus on a more limited set of atomic building blocks, particularly of carbon and its elemental neighbours. And while the study of a smaller portion of the periodic table might be expected to be easily manageable, understanding organic chemistry can still seem overwhelming because of the diverse way s that this handful of elements can combine and interact. To learn organic chemistry, one must grasp the recurring patterns that correlate the presented facts.

Toward that end, this textbook organizes and discusses applications of the patterns of chemical reactivity—which constitutes the majority of the subject matter—by combining information about the structures of functional groups (the reactive portions of a molecule) with the reaction mechanisms (pathways of chemical reactions) that these functional groups undergo. This approach differs from the one presented in many other texts, which describe every type of reaction that can occur for a given functional group; each approach has its advantages and disadvantages.

The one I have utilized here evolved from my objective to integrate discussions about biochemical processes with the types of reactions that are carried out in chemistry laboratories. With the use of two points of reference—structures and mechanisms—the similarities that associate biochemical and synthetic reactions can be appreciated more easily.

INDEX

ISBN: 978-93-94570-79-5

1. An Introduction of Polarography

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1.1 Introduction:

On February 10, 1922, Professor Jaroslav Heyrovsky carried out his pioneering experiment with a dropping mercury electrode from which polarography gradually evolved. Since then, polarography became a mature analytical method capable to adjust ever increasing demands on the sensitivity and selectivity and we believe that up to now mercury electrodes are among the best sensors for electroanalytical measurements[1,5]. Limits of determination gradually decreased from 10^{-5} M in the case of classical polarography[2], through 10^{-7} M for differential pulse polarography[3] to 10^{-11} M for adsorptive stripping voltammetry[4].

Development of mercury electrodes which proceeded from classical dropping mercury electrode[6] through mercury streaming electrode[7], hanging mercury drop electrode[8], static mercury drops electrode[9], mercury film electrode[10], mercury amalgam electrodes[11], mercury microelectrodes, chemically modified mercury electrodes[12], controlled growth mercury electrodes[13] and contractible mercury drop electrodes[14]. This process initiated by Professor Heyrovsky resulted in commercially available reliable mercury electrodes suitable for Nano molar and sub Nano molar concentrations. Further progress in this field can be documented by the above mentioned articles of Novotny and Kowalski and by papers of Gutz on versatile automatic mercury drop electrode[15-16].

Development of measuring techniques that proceeded from classical DC polarography[2], Through oscillopolarography[17], Kalousek's switcher[18], AC polarography[19], Tast polarography[20], Normal pulse polarography[21], Differential pulse polarography[22], Voltammetry[23], Cyclic voltammetry[24], Anodic stripping voltammetry[25], Adsorptive stripping voltammetry[26], Convolution techniques[27-28] and Elimination methods[29-30]. Development of preconcentration techniques on the surface of mercury electrodes enabling a substantial increase of sensitivity which proceeded from anodic stripping voltammetry and cathodic stripping voltammetry to adsorptive stripping voltammetry. The role of Professor Heyrovsky in the development of these methods cannot be underestimated. According to Zuman[31] the main contribution of Professor Heyrovsky consists in:

- Recognition of the importance of potential and its control;
- Recognition of analytical opportunities offered by measuring the limiting currents;
- The introduction of dropping mercury electrode as an invaluable tool of modern electroanalytical chemistry.

1.2 Principle of Technique:

Polarography is based on the unique characteristics of the current-voltage curves obtained with dropping mercury electrode, which was first introduced by Kucera[32] for electro capillary studies. In 1934 Ilkovic[33] derived an equation for the resulting constant. It deals with the measurement and interpretation of current-voltage curves when solution of electroactive substances is electrolyzed in a cell in which one electrode is polarisable i.e. mercury falling gravitationally drop wise from fine bore of capillary glass tube, while the other electrode remains non polarisable (saturated calomel electrode). Since the curves are graphical presentation of the dropping mercury electrodes, the apparatus is called 'polarograph' the curves as polarograms and technique is named as polarography. Thus, it is one of the most essential key to chemical analysis. The flow of current in the electrical circuit is observed only when the voltage is applied to electrodes changes at constant rate, raises the potential of a depolarizer present in the solution 10^{-5} moles/liter range. The current increases with the increasing negative potential of the electrode and during this time the concentration of the depolarizer on the surface of electrode decreases. When this concentration decreases to zero, current reaches to a constant value depending on the rate of depolarizer transport to the surface of electrode. In these conditions we have the maximum current which is often called limiting current.

Advantages of Dropping Mercury Electrode:

There are several advantages of the dropping mercury electrode.

- Each drop falling from the electrode exactly duplicates the behavior of the one that preceded it. This is because successive drops are born into solution of identical time, grow at a same rate and reach at the maximum size. Consequently, the currents are accurately reproducible from one drop to next.
- Solid products cannot accumulate on the electrode surface, changing its properties as it is possible with solid electrode.
- It is much less sensitive to mechanical disturbance than stationary electrode.
- High over potential of reduction of hydrogen ion or water on a mercury surface makes it to investigate processes that can occur only under strongly reducing conditions.

1.3 Applications of Polarography:

Polarography can be extensively applied in the field of inorganic analysis[34], organic chemistry[35], pharmacy[36], metallurgy, geology and archaeology[37], polymer chemistry[38], colloids and surface active substances[39], food chemistry[40], petroleum and fuel analysis[41], Trace analysis[42], rare earth analysis complex studies[43], trace determination of drugs[44-48], quantitative and qualitative analysis of organic compounds including drugs[49-54].

1.3.1 Analysis of Organic Compounds by Polarography:

Polarography has contributed significantly to the understanding of processes involved in the electrolysis of organic compounds. In organic chemistry, polarography can be used in the determination of equilibrium and rate constants, in studies of reaction mechanism, in the search of optimal conditions for some preparative reactions, in studies and comparisons of reactivity's of organic compounds and in correlations of structure with polarographic data.

From polarographic curves, identification of electrolysis with other methods may be used for elucidation of organic electrode process. Many organic functional groups undergo reduction or oxidation at dropping electrode and thus led themselves to polarographic determination. In general, the reactions of organic compounds at the dropping electrode are slower and are often more complex than those of inorganic ions; nevertheless, polarographic investigations can be useful for structure determination and for qualitative and quantitative analysis.

Reactions of organic substances at the dropping electrode usually involve hydrogen ions; a typical reaction can be represented by the equation.

$$R + nH^+ + ne^\ominus \rightleftharpoons RH_n$$

Where RH_n is the reduced form of the reducible compound R. As hydrogen ions (supplied from the solution) are involved in the reaction, the supporting electrolyte must be well buffered. Change in the pH of the supporting electrolyte may even lead to the formation of different reaction products. Thus, in slightly alkaline solution, benzaldehyde is reduced at -1.4 volts with formation of benzyl alcohol, but in acid solution (pH < 2), reduction takes place at –1.0 volts with formation of hydrobenzoin:

$$2C_6H_5CHO + 2H^+ + 2e^\ominus \rightleftharpoons C_6H_5CH(OH)CH(OH)C_6H_5$$

Some organic compounds can be investigated in aqueous solution. It is frequently necessary to add an organic solvent to improve the solubility. Suitable water miscible solvents include ethanol, methanol, ethane-1,2-diol, dioxane, acetonitrile and acetic acid. In some cases, a purely organic solvent must be used and anhydrous materials such as acetic acid, formamide and diethylamine have been employed. Suitable supporting electrolytes in these solvents include lithium perchlorate and tetra-alkyl ammonium salts R_4NX (R = ethyl or butyl; X = iodide or perchlorate).

The following functional groups can be expected to react at the dropping electrode.

C=C (When conjugated with another double bond or an aromatic ring), C□C (when conjugated with an aromatic ring), C–X (X = halogen), C=O (aldehydes, ketones, quinones), dicarboxylic acids in which the carboxyl groups are conjugated with each other, Peroxides, epoxides, C=N, Nitro, nitroso, azo groups, heterocycles with two or more nitrogen atoms in the ring, C=S, S–S and S–H (mercaptans give an anodic wave).

1.3.2 Polar Graphic Study of Metal Complexes:

The chemistry of metal complexes is undergoing a period of a rapid development and engaging the attention of many researchers. Its progress has received an added impetus due to its several applications in chemical, industrial, agricultural, biological and technological fields. Metals that are essential for plant growth and animal nutrition have been found to form complexes with materials present in organisms. Metal-chelate formation also plays significant role in the functioning of enzymes and processes like moderate dyeing in the textile industry and the tanning process as in the leather industry. Their applications in inorganic analysis are of many folds and include detection, determination, purification and solvent extraction through complex formation. Complex forming reagents are extensively applied masking agents in various titrimetric, spectrophotometric, polarographic, chromatographic and electrophoresis methods.

Historically, credit to study inorganic complexes by polarography goes to the pioneering work of Stackelberg, Frey-hold[55] and Lingane[56]. The classical method of analysis was thoroughly discussed by Kolthoff and Lingane[57] in the monograph on polarography and related electrochemical techniques which resulted in remarkable progress and is now extensively used in the study of complexes in solutions. Some of the general developments are presented and discussed by Irving[58], Koryta[59], Westwood and Crow[60-62] in their publications. Excellent reviews have also been published by Vlcek[63-64] on relation between electrochemical reactivity and structure of inert complexes. A beautiful review has also been written by Tamamushi and Sato[65]. The contribution of Lingane, Deford and Hume[66], Ringbom and Erikson[67-68], Kacena and Matousek[69] Schwarzenbach[70-71], Buck[72], Butler[73], Macovsch[74] and Crow are there for study of metal complexes. Schapp and MacMasters[75] have extended Deford and Hume's treatment for study of mixed ligand complexes in solution.

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ISBN: 978-93-94570-79-5

2. Organic Reactions

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Abstract:

The chemistry of carbon compounds is now referred to as organic chemistry. When the majority of the substances identified in this discipline of chemistry came from living organisms, the word " organic" was first used to characterize it.

The greatest component of chemistry is organic chemistry, which also ranks among the most popular disciplines in terms of both its factual base and its audience size. There are currently more than a million known organic compounds, and thousands more are constantly being found in nature or created in laboratories.[1]

Chemical processes involving organic molecules are known as organic reactions. Functional groups have a strong relationship with several of these reactions. Analysis of features including bond strength, steric hindrance, and the electron affinities of important atoms are all carefully considered in the general theory of these processes.

Covalent bonds found in organic compounds change most frequently during organic processes. These modifications could include bond cleavage, electric bond displacement, energy modifications associated with covalent bond formation, etc. We must.[2]

Keywords:

Covalent bond, steric hindrance, electron affinities, bond strength, energy modifications.

2.1 Types of Organic reactions:

A. Substitution reactions
B. Addition reactions
C. Elimination reactions
D. Rearrangement reactions

2.1.1 Substitution Reactions:

In a substitution reaction, an atom or group of atoms from a molecule are exchanged out for new ones while maintaining the molecule's original structural integrity. Free radical, nucleophilic, and electrophilic substitution reactions are those in which free radicals, nucleophiles, and electrophiles serve as reactive intermediates.[3]

A. Free Radical Substitution Reactions: For instance, methyl chloride is created when methane combines with chlorine in the presence of sunlight by replacing one hydrogen atom with a chlorine atom in a free radical substitution reaction. This reaction is known as a free radical substitution reaction because it uses free radicals as intermediates.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

This reaction involves the following steps:

- Cl-Cl $\longrightarrow$ Cl +. Cl
- CH_3 – Cl +. Cl $\longrightarrow$ $^{\cdot}CH_3$ + HCl
- $^{\cdot}CH_3$ + Cl- Cl $\longrightarrow$ H_3C – Cl +. Cl

This reaction may proceed further to replace remaining hydrogen atoms by chlorine to form CH_2Cl_2, $CHCl_3$ and CCl_4 by similar mechanisms.

B. Nucleophilic Substitution Reactions: A nucleophilic substitution process is one in which methyl chloride and aqueous potassium hydroxide react to produce methyl alcohol.

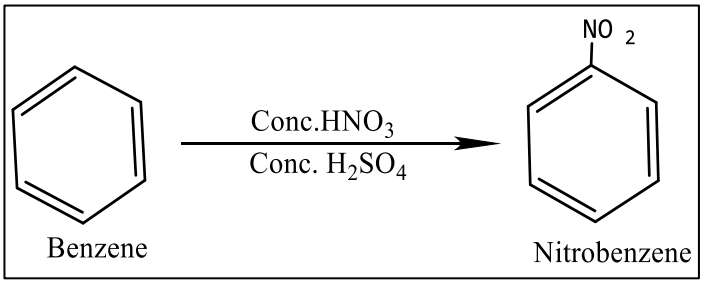
$$CH_3\text{- Cl} + KOH \longrightarrow CH_3OH + KCl$$

In this reaction replacement of Cl by a nucleophile (: OH^-) take place. Substitution reactions of alkyl halide involve nucleophilic substitution reactions.

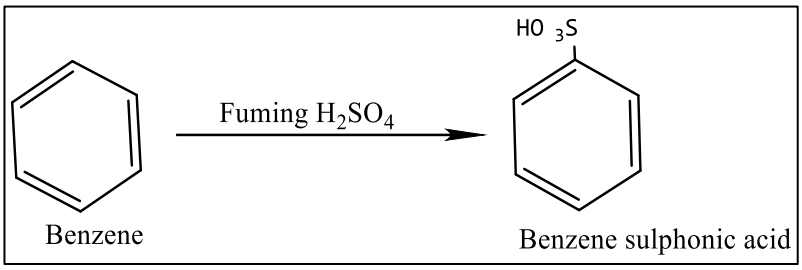
C. Electrophilic Substitution Reactions: Electrophilic substitution reactions include aromatic substitution processes like nitration, sulphonation, Friedel craft reactions, etc. These reactions involve replacement of nuclear hydrogen by an electrophile (Ex- NO_2, R^+ etc)[4]

Example: -

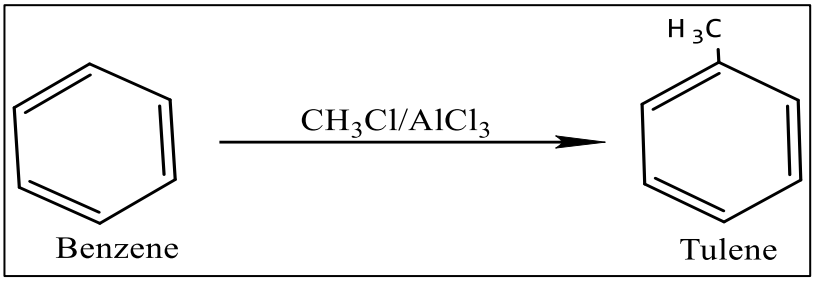
- Nitration



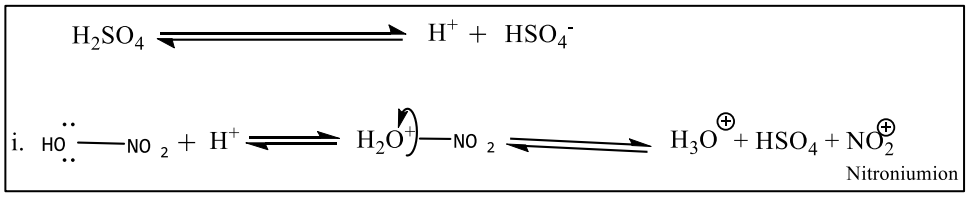
- Sulphonation

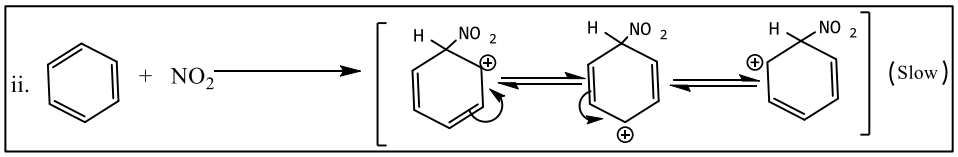


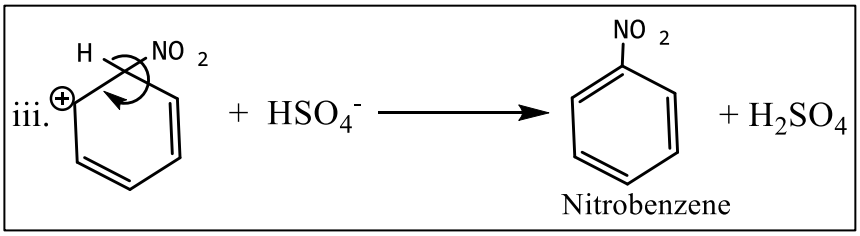
- Friedel craft reaction



- **Mechanism of Nitration:**

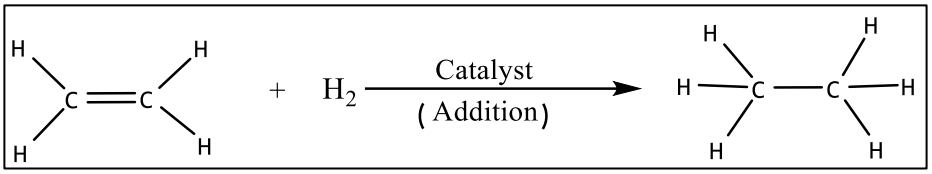






2.1.2 Addition Reactions:

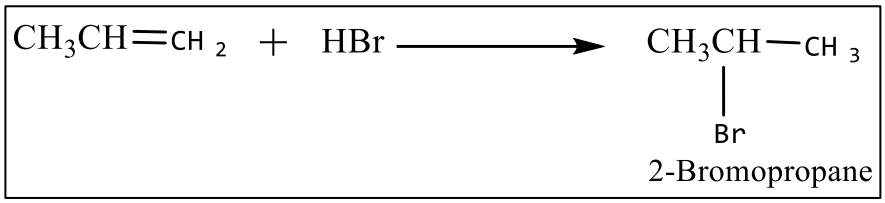
The chemical molecules with double or triple bonds that cause these reactions (unsaturated compounds). These substances easily incorporate hydrogen, haloacids, halogens, etc. into the end product while altering the molecule's shape. For example,



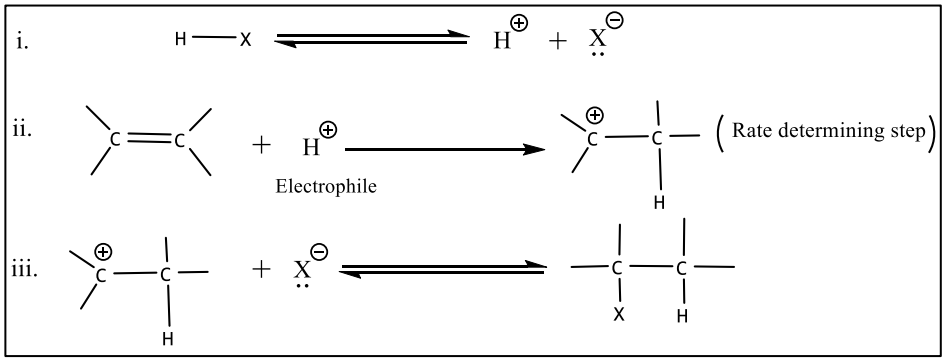
In these reactions, one pi bond, which is weaker than an alpha bond, breaks to produce two new sigma bonds, one on each carbon, which satisfy the valency criteria in the end product.

These reactions are of three types:

A. Electrophilic Additions: These reactions are known as electrophilic addition reactions because they are started by the addition of an electrophile during the rate-determining step. For example,



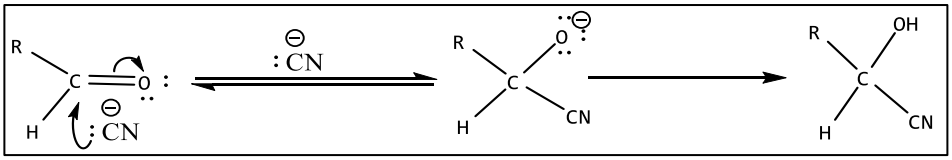
B. Mechanism: It is an electrophilic addition reaction, initiated by the electrophile (H^+) released from the HX. This reaction involves the following steps:



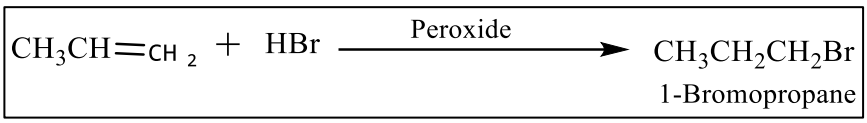
The rate determining step is step (ii) leading to the formation of a **carbocation.**

C. Nucleophilic Additions: Simple aldehydes and ketones' carbon-oxygen double bonds give rise to addition reactions that are typically nucleophilic in nature.

For example, addition of HCN to aldehydes

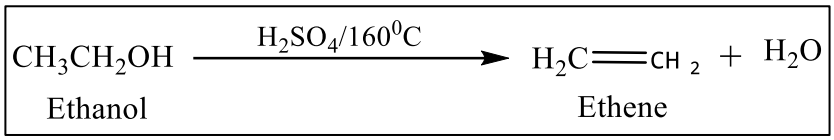


A. Free radical additions: - Free radical mechanism controls the addition reaction of HBr to unsymmetric alkenes (like propene) in the presence of peroxides to produce an anti-Markownikoffs product. Free radical addition reaction is the name given to this process.

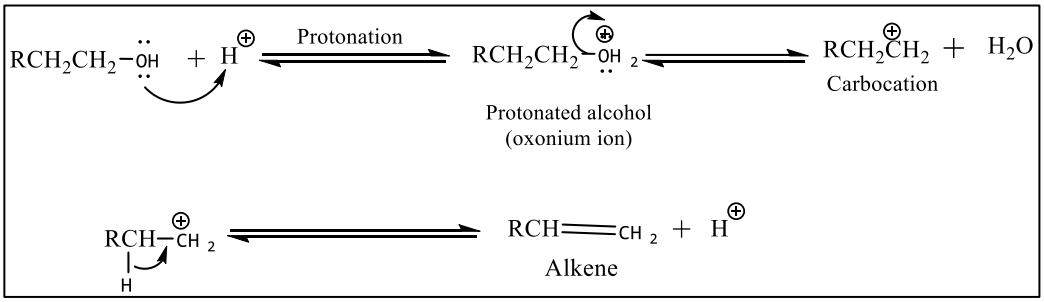


2.1.3 Elimination Reactions:

This reaction is the opposite of the addition reaction. A reactant molecule loses atoms or groups during an elimination process. These reactions result in compounds with many bonds.[5] For example,



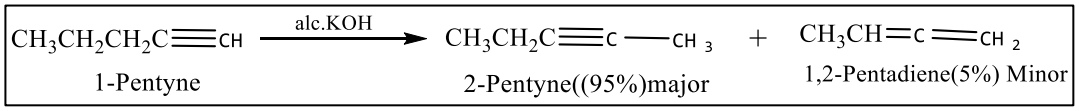
A. Mechanism: It involves protonation of alcoholic group followed by elimination of water and deprotonation.



2.1.4 Rearrangement Reactions:

An atom or a group of atoms may move from one area of a molecule to another area of the same molecule during a rearrangement reaction. Triple bond migration may also be involved.[6]

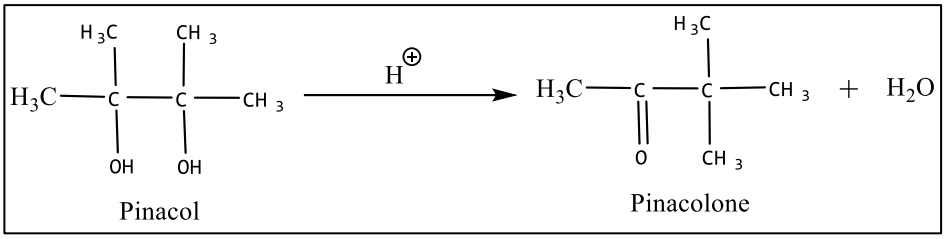
For example, 1-pentylene with alcoholic KOH tend to rearrange with migration or triple bond to form 2-pentylene as major product:



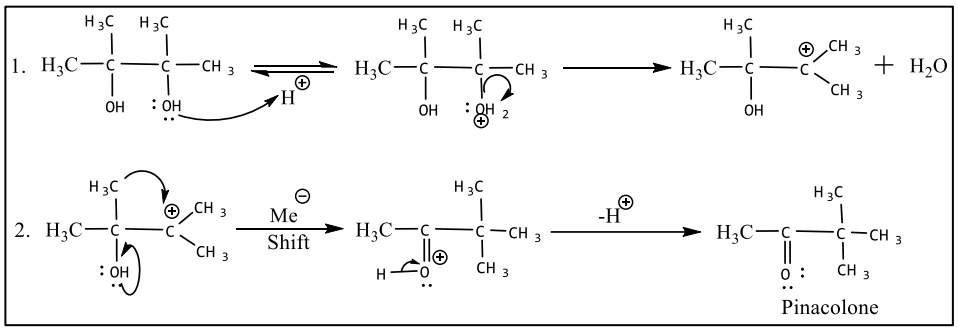
Some of examples of Rearrangement reactions,

A. Pinacol Pinacolone Rearrangement: It involves the dehydration of substituted vicinal diols (pinacols) under acid catalysis, followed by rearranging the carbon skeleton to produce ketones.[7]

For example,



Mechanism:

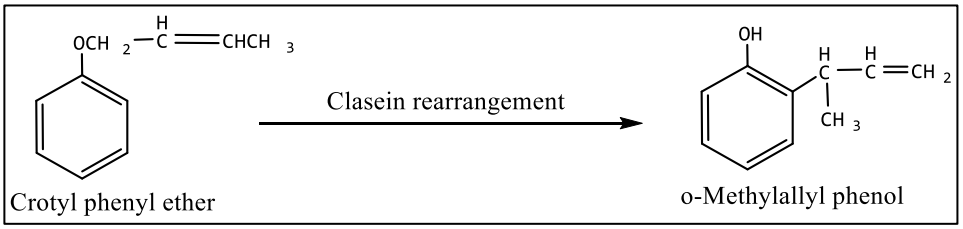


Step 1 involves protonation of that -OH group, which on elimination of water molecule gives most stable carbocation.

Step 2, carbocation undergoes a 1,2-methyl shit to the electron deficient carbon to generate protonated ketone.

B. Claisen Rearrangement: O-allyl ether of phenol undergoes a rearrangement to become o-allylphenol at a temperature of about 200^0C in the absence of any catalyst. The Claisen rearrangement of phenolic allyl ethers is the name of this thermal process.[8]

For Example,



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ISBN: 978-93-94570-79-5

3. Emerging Trends in Microwave Chemistry Assisted Extraction of Phytochemicals

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Learning Outcomes:

At the end of this chapter the reader will be able to understand:

- Introduction
- Microwave Chemistry: Principle, Benefits and Applications
- Microwave Assisted Extraction: Principle, Methodology, Advantages and Applications
- Microwave Aided Extraction Technology in Herbal Drug Research
- Microwave Assisted Extraction of Phytochemicals
- Studies using Microwave Assisted Extraction of Phytochemicals
- Conclusion

Abstract:

Plants are considered as natural factories for construction of wide range of phytochemicals. A large number of secondary metabolites like alkaloids, glycosides, tannins, phenolic compounds, resins and flavonoids are manufactured by plants. Developments in natural chemistry research led investigators to documentation and separation of diverse bioactive chemicals. These phytochemicals are widely used as therapeutic agents in treatment and management of various acute and chronic disorders and diseases. The superiority of active herbal preparation is considerably contributed by extraction techniques. Extraction is crucial and first most important step in the development of phytochemicals. Conventional extraction techniques reported to possess few limitations and disadvantages. The principles of microwave chemistry are useful in order to overcome few of the limitations of conventional extraction techniques. Hence in the Microwave assisted extraction has been introduced. This is an effective and new tool with numerous benefits as compared to the old-style approaches of extraction. The important benefits of microwave assisted extraction

are in terms of reduction in cost, time of extraction, amount of solvent used, and energy consumptions. This chapter give brief overview on basic approach, principle and applications of microwave chemistry. This chapters also emphasizes on the microwave assisted extraction techniques and its applications towards the development of phytochemicals.

3.1 Introduction:

The Microwave region is lie in the electromagnetic range between the radio waves and infrared waves. They have wavelengths between 0.01 and 1 meter, and functions in a frequency array between 0.3 and 30 Ghz. Usually a frequency of 2.45 Ghz is utilized for laboratory activities like to conduct the chemical reactions as this waves proper penetration depth which are suitable for the laboratory reactions. Beyond 30 Ghz wavelength frequency, the microwave frequency overlaps with the radio frequency.

Generally, the microwave electromagnetic range is distributed into two categories namely sub-bands including the lower microwave frequency called as L band and the higher frequency known as W band. L band microwave frequency is mainly used for the purpose of communication and W band frequencies are used for the analytical techniques such as spectroscopic characterization. Microwave chemistry is the branch of chemical science which involves the study and utilization microwave radiation to chemical synthesis.

Microwaves action as high frequency electric fields and mainly causes the heating of any material. It generates the mobile electric charges, such as polar molecules in a solvent or accompanying ions in a solid. Thus the microwaves are widely used in various industries including pharmaceutical, biotechnology, chemicals, petroleum and polymer industries.

The Microwave-assisted reactions are fast, clean, and economic and eco-friendly. The principles and approaches of microwave chemistry have been widely used in the natural products chemistry research as well to extract and isolate diverse chemical entities from natural sources like plants and minerals.

3.2 Microwave Chemistry:

In the year 1946, the technology of Microwave technology was originated and discovered. It was started with research performed by Dr. Percy Le Baron Spencer. He was performing laboratory examinations for a new vacuum tube known as magnetron. Magnetron is a device that produces an electromagnetic radiation.

During this experiment, accidentally he discovered that a candy bar in his pocket liquefied on exposure to radiations of microwave. In the year 1947, Dr. Spencer established the idea and recognized that microwaves might be used as a technique of heating.

Then, he intended the first microwave oven for domestic practice. Subsequently, in future years the expansion of microwave radiation and its applications were studied. Table 3.1 provides the information about development and evolution of Microwave chemistry.

Table 3.1: Development and Evolution of Microwave Chemistry

Sr. No.	EVOLUTION	YEAR
1	Discovery of Microwave radiation as heating method	1946
2	Introduction of first commercial domestic micro oven	1947
3	Development of first laboratory useful micro oven instrument	1978
4	Generation of microwave radiations to dry organic materials	1980-1982
5	Utilization of microwave radiation for analysis of chemicals	1983-1985
6	Publication of research papers related to applications of microwave radiation in synthesis of chemicals	1986
7	Emergence and development of Microwave Chemistry as a field of study due to its useful applications in chemical synthesis	1990
8	Development of first high pressure vessel for conducting full digestion of oxides, oils and pharmaceutical samples.	1990
9	Synthesis of chemicals based on microwave radiations using batch system reactor and single mode cavity system	1992-1996
10	Publication of book titled Microwave Enhanced Chemistry-Fundamentals, Sample Preparations, and Applications	1997
11	Introduction of first commercial microwave synthesizer to carry out the chemical preparation.	2000
12	Conduct of various research using microwave chemistry and its applications, commercialization, industrial utility, publication of research papers.	2022

3.2.1 Principle of Microwave Chemistry:

Microwave chemistry is the branch of chemistry that deals with study and applications of microwave radiations to conduct chemical reactions or chemical synthesis and chemical analysis. The approach of Microwave-assisted synthesis works on the basis of aligning dipoles of the substance in an external field via the excitation fashioned by electromagnetic radiations of microwave and is generally performed in mixture with an identified synthesis scheme.

This technique is moderately beneficial as the synthesis development can be modified to produce product with many advantages. The procedure of alignment or orientation of substance by the external electrical field may result in the creation of internal heat which is accountable for a decrease in processing time and energy requisite. It is particularly due to the heating consistency of microwaves. The reaction time can be fairly condensed by accepting microwave-assisted preparations.

A. Benefits of Microwave Chemistry:

Microwave chemistry has many benefits as mentioned below:

- Microwave radiation are extremely effective and used as heating source in chemical synthesis.
- Microwave chemistry is helpful in emerging the cleaner synthetic routes and procedures.
- Microwave chemistry helps to enhance the rate of chemical reactions and improve the percentage yield of product.
- Microwave chemistry helps to achieve the better reproducibility of reactions.
- It helps to deliver efficient and uniform heating to the chemical reactions.
- It also helps to provide the selective heating in a chemical synthesis schemes.

B. Applications of Microwave Chemistry:

The concept and approaches of microwave chemistry is widely used and applicable in various industries. The wide range of applications of microwave chemistry and related techniques are useful in various fields. Figure 3.1: Shows The Applications of Microwave Chemistry in Various Areas.

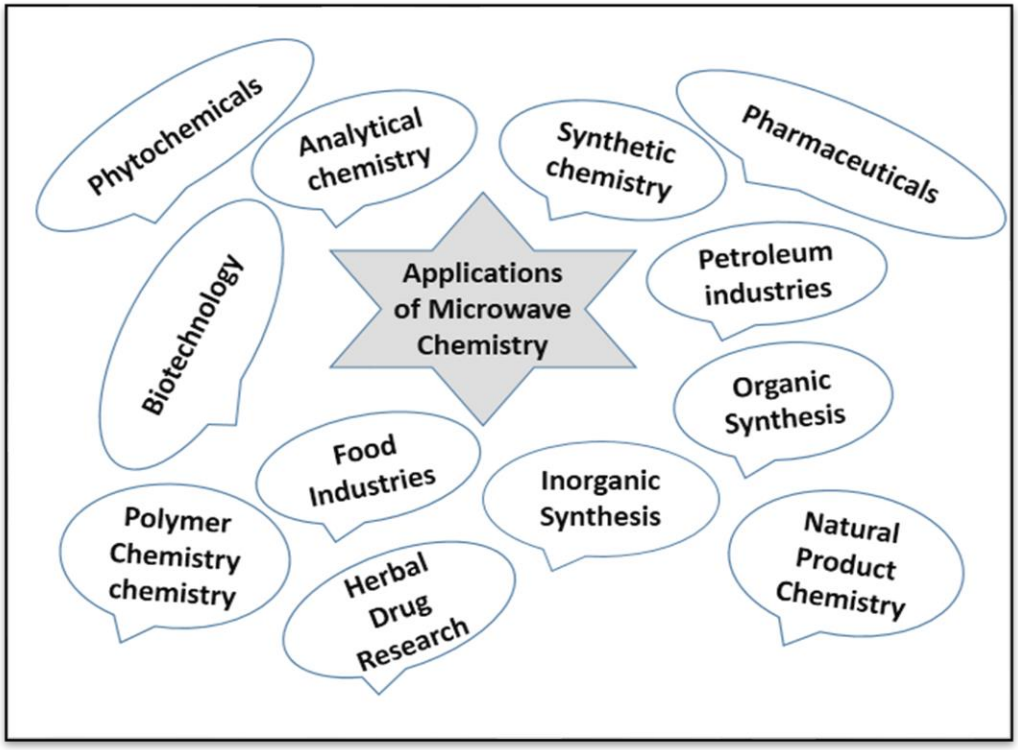


Figure 3.1: Applications of Microwave Chemistry in Various Fields

a. General Applications: The concept of microwave chemistry is widely used in various industries like biotechnology, pharmaceuticals, petroleum, plastics, chemicals and food industries. Various general applications of microwave chemistry are listed as below:

- The microwave chemistry is useful in the field of analytical and synthetic chemistry
- It has wide range of applications in natural products chemistry research.
- Microwave heating is extensively used for ashing in the petroleum and fuels, plastics, pharmaceuticals and food industries.
- Microwave digestion systems are used in analytical laboratories for sample decomposition and preparation.
- Microwave radiation used in trace and ultra-trace metals analysis.
- Microwave extraction is widely used in herbal drug research.
- Microwave assisted extraction systems are used to conduct routine solvent extractions of soils, sediments, sludge, polymers and plastics, pulp and paper, biological tissues, textiles and food samples.
- Microwave assisted moisture analysis has been widely used in the food and beverage, chemical, environmental, organic and pharmaceutical industries.
- Microwave moisture analysis is specifically applied at product development stages such as process and quality control, testing of raw materials, intermediate and finished products.

b. Applications in Chemical Synthesis: The application of microwave radiation are widely useful in the synthesis of large number of chemical moieties. It is widely used in the organic and inorganic synthesis in laboratories. The Microwave-enhanced preparations help the scientist to perform his work faster, get higher yields, and enhance the purity of product. Apart from this due to the advanced instrumentation and innovative research in Microwave chemistry, it has been observed that the yield of product is been scaled up from mg to kg. The techniques of microwave chemistry play valuable role in the organic and inorganic synthesis and few of the important applications are listed as below:

- **Applications in Organic Synthesis:** Organic synthesis can be defined as the synthesis of a preferred organic molecule by using precursors. The Microwave assisted organic preparation is one of the novel research area in the organic preparations as it gives better results with many advantages over the conventional routes and hence Microwave organic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in organic synthesis are highlighted as below:

- The Microwave assisted organic preparations are widely used in the pharmaceuticals companies, mainly in order to develop the molecules in the optimization of lead stage in the drug development.
- Literature reported that the scientist has been successfully used the approach of microwave synthesis in conduct of large number of named chemical reactions. Few of these reactions conducted using microwave techniques are listed below:

    - Condensation reactions
    - Cyclisation reactions

- Cycloaddition reaction
- Dehydration
- Diels Alder reaction
- Epoxidation
- Esterification

- Heck reaction
- Hydrogenation of [beta]-lactams
- Hydrolysis
- Mannich reaction
- Protection and deprotection of functional groups
- Reduction reactions
- Suzuki reaction

- **Applications in Inorganic synthesis:** Inorganic preparations can be defined as the preparation of a preferred inorganic compound from suitable precursors. The Microwave assisted inorganic compound synthesis is one of the innovative research region in the inorganic preparations as it gives better results with many advantages over the conventional routes and hence Microwave inorganic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in the field of inorganic synthesis are highlighted as below:

- The Microwave assisted inorganic preparations are extensively used in the pharmaceuticals companies, mainly in order to develop the inorganic molecules.
- Microwave chemistry is widely used in the preparation of organometallic derivatives.
- Microwave chemistry is also used in the synthesis of coordination compounds.
- It is used in the synthesis of intercalation molecules.
- It is also used in the preparation of ceramic products.

c. Applications in Polymer Chemistry: Polymer chemistry is one of the important field in the chemistry and it is mainly used in the preparation of Polymer products.

- The concept and approaches of microwave chemistry is widely used in the development of polymers and related products.
- The approaches of microwave techniques are also widely used in order to conduct the polymerization reaction.

3.3 Microwave Assisted Extraction:

The microwave assisted extraction is a model and newest green approach to an analytical method in which microwave radiation frequency is used for the extraction of chemical compounds or isolates particularly from plant materials. This technique utilized to extract the samples or chemical compounds from biological matrices for the purpose of its further analysis. Microwave assisted extraction is a procedure of utilizing the microwave energy to heat liquids in connection with a sample in order to distinct the chemical from the matrix into the liquid. Earlier microwave ovens are utilized for the digestion of samples for metal

analysis. All microwave ovens (Home or the laboratory used) are usually operate at 2.45 GHz frequency. The microwave region found to exists at frequencies of wavelengths from 0.3mm to 1m or 100 GHz to 300 MHz.

Principle of Microwave Assisted Extraction: The basic principles of the microwave assisted extraction method are different from traditional methods of extraction like solid-liquid or simple extraction techniques. As we know the electromagnetic radiations are known to cause the cell structure and this leads to the extraction. When the microwave radiation is passed through the matrix or plant materials, it causes the molecular communication with the wave. Thus the microwave radiation is converted into heat energy that supports the mass transfer from plant cell or material into the solvents. By using this principles, the phytochemicals can be extracted from plant materials by using microwave radiation. The traditional solvent extraction techniques from plant materials trust on the appropriate assortment of solvents and the use of thermal energy and agitation to recover the mass transfer and increase the solubility of the anticipated agent. Hence new system of microwave assisted extraction helps to condense the extraction time, less solvent ingesting, decrease the contamination and superior attention for thermolabile chemicals have added consideration.

Methodology: In order to perform the microwave assisted extraction two methods are utilized using different devices mainly:

- Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System
- Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System

a. **Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System:** In case this method the sample is situated in an open vessel to which a suitable organic liquid is placed. The microwave radiation produced from the magnetron is focused by the waveguide onto the sample/liquid, thus producing the liquid to boil. The hot liquid is then arising into interaction with a water cooled reflux condenser. This effects the liquid to condense and reappearance to the vessel. This procedure is recurrent for a little period of time so allowing compounds of interest to be come out from the sample material into the liquid.
b. **Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System:** In this case, the microwave radiations enter into the oven, and are detached by a mode stirrer. The mode stirrer permits an even delivery of microwaves within the oven. In this approach the sample and liquid are situated within the closed container which is typically prepared of microwave transparent resources such as polymers and their derivatives.

3.3.1 Advantages of Microwave Aided Extraction:

A prospective substitute to old-style solid liquid extraction method is the microwave assisted method. Microwave assisted techniques has good number of compensations over the traditional extraction and few of them are listed as below:

- Microwave assisted extraction technique helps to extract multiple samples for at a time.
- Microwave supported extraction method requires small quantity of liquid for extraction.
- Microwave aided extraction technique carries the extraction in very short period of time.
- Microwave assisted extraction gives the Improved yield.
- This technique gives improved accuracy in the results.
- This approach is suitable for the thermolabile chemical extraction.
- It requires remarkably less extraction period and the time of extraction usually extending from few seconds to few minutes.
- It requires very less amount of liquid in extraction and amount is a few milliliters.
- It shows also the better precision due to the automation of the apparatus.
- It is useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the improved mass transfer mechanism due to the agitation of sample vessels.

3.3.2 Applications of Microwave Supported Extraction Techniques:

The wide range applications of microwave aided extraction technology are listed as below:

- The microwave assisted technique is useful in order to extract large number of phytochemicals from the plant materials.
- It is widely used technique in the extraction of sample in herbal drug industries.
- It has showed the utilization in extraction of sample or analyte from the biological matrix in the bioanaytical laboratories in the clinical research.
- In the analytical research and development department of pharmaceutical industries this approach is extensively used.
- This approach is used in order to extract the secondary bioactive chemicals from the plant materials including alkaloids, glycosides, tannins, polyphenols, flavonoids, terpenes, lignans and phenolic derivatives.
- The closed vessel microwave method is used for the extraction of terpenes from plant material.
- The extraction of imidazolinone herbicides and sulphonylurea herbicides has been carried out and reported in the literatures.
- It has been also used in the extraction of fungicides like hexaconzole from weathered soil.
- The extraction of additives polypropylene and polyethylene has been achieved in the polymer chemistry and related research.
- It has been widely used in the food industries in the preparation of vitamins in foodstuffs.
- It can be used for determination of various metals and metallic compounds like Zn, Pb, and Cu from soils.
- Microwave aided extraction is a consistent source of extraction of phytoconstituents.
- It also can be used for the extraction of essential oils from plant sources.
- This technique also used in the analysis of heavy metals and other pollutants present in the different type soils.
- Microwave supported extraction is used in the synthesis and preparation of pharmaceuticals samples in the pharmaceutical industries.

3.4 Microwave Aided Extraction Technology in Herbal Drug Research:

Herbal medicines are also known as phytomedicines and they have been widely used by human culture. The plants are considered as natural factories for manufacture of numerous phytochemicals or plant compounds. A large quantity of secondary metabolites like alkaloids, glycosides, tannins, phenolic derivatives and flavonoids are manufactured by plants.

They act as a great source in the development of modern medicines. The advancements in natural chemistry sciences directed researchers to documentation and isolation of diverse bioactive phytocompounds. The one of the most important step in the development of herbal medicines include the extraction of plant samples. Based on the basis of physical nature and chemical properties of phytochemicals, several approaches are in procedure to gain the crude extract. Few of the conventionally used extraction techniques in herbal drug industries are listed as below:

- Infusion
- Digestion
- Decoction
- Percolation
- Maceration
- Soxhlet Extraction etc.

The above mentioned extraction techniques are used for the extraction of plant chemicals from plant material but at the same time they are also associated with some limitations and disadvantages like:

- Extraction time is more
- Solvent consumption is more
- Soxhlet extraction method is not suitable because in the method the targeted compound may undergoes the decomposition due to usage of high temperature.
- The traditional extraction technique carries the extraction in more time.
- The traditional extraction technique may give the less yield.
- This technique gives less accuracy in the results.
- This approach is not suitable for the thermolabile chemical extraction.
- It requires remarkably more extraction period and the time of extraction usually extending more than hours.
- It requires more amount of liquid in extraction.
- It shows also the less precision due to the non-automation in the extraction apparatus.
- Many time it is not useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the less mass transfer mechanism due to the poor agitation of sample vessels.

In order to overcome one or other limitations of the conventional methods the approach of microwave assisted tool has emerged due to its wide range of advantages as discussed earlier in this chapter.

A. Emerging Trends in Microwave Aided Extraction: A Competent and Modern Approach for Pharmaceuticals and Botanicals:

The microwave aided extraction is attentive and targeted technique of extraction of plant chemicals and can be effortlessly joined with other analytical devices like chromatographic techniques. Its treatment is additional made easier due to the automation of the apparatus. This approach is new and widely used in order to develop the modern medicines and pharmaceuticals from the various botanicals. There are many recent advancements and emerging trends in the development of microwave assisted solid extraction techniques from natural matrices. Some recent trends and applications are discussed in this chapter under below headings:

- Development of marker compounds
- Assessment of plant productivity
- Extraction of plant chemicals for drug development and its commercial applications.

a. Development of Markers: The microwave driven extraction tool is also reported for the development of marker compounds from the plant materials. Literature reported various methods and compound which are extracted and isolated using this approach and successfully used for marker based standardization of phytomedicines and related products**.** Few of the marker compounds extracted using microwave techniques are listed as below:

- Vitexin
- Isovitexin

b. Assessment of Plant Productivity: The microwave driven extraction offers the opportunity for performing the multiple extractions which is suitable for the fast screening of an abundant set of samples to assess the efficiency of organisms. For example, in order to compare amount of coumarin and related compounds like melilotic acid, and o-coumaric acid, the microwave assisted technique can be used also it can be used to analyze the productivity of *Melilotus officinalis* plant.

c. Extraction of plant chemicals for drug development and its commercial applications: The plant compounds isolated from the medicinal plants are widely used in the management and treatment of various diseases and disorders. The plant secondary metabolites include alkaloids, flavonoids, tannins, terpenes, polyphenols and many other functional derivatives. The microwave assisted extraction tool has been reported in the literatures in order to extract these plant secondary chemicals with better extraction and activity reports. Few of the examples of such microwave assisted extracted chemicals are discussed as below:

- **Extraction of Alkaloids:** The alkaloids are a famous class of secondary metabolites characterized by the presence of basic nitrogen. These class of compounds are widely used as therapeutic agent in very small amount. Over the years, many active alkaloids have been extracted microwave irradiation tools. Few important examples of execrated alkaloids by this tool are listed as below:

- Extraction and isolation of ephedrine, cocaine, and ergot alkaloids has been reported by using microwave extraction tool.
- An efficient microwave supported extraction protocol as a drug discovery process has been reported for the extraction and isolation of bioactive alkaloids like neferine, dauricine, liensinine, isoliensinine, nuciferine from *Lotus plumule* plant.
- The simultaneous microwave assisted extraction protocol have been developed for the collection of cocaine, cocaethylene, benzoylecgonine, morphine, 6-monoacethylmorphine, and codeine from human urine, hair, and vitreous humor samples.
- The microwave aided aqueous two phase extraction protocol has been reported for the rapid and simultaneous extraction and separation of alkaloids like oxymatrine, Matrine, 5α-hydroxysophocarpine, sophocarpine, oxysophocarpine, cytisine, N-methylcytisine, sophoranol, and sophoridine etc. from the plant *Radix Sophorae tonkinensis*.
- Recently literatures have reported the microwave supported extraction protocol for multicomponent analysis and the extraction of Berberine and polyphenol chemicals from various plant species of *Berberis*.
- Microwave extraction tool also has been used for the extraction of cocaine and benzoylecgonine from the leaves of *Erythroxylum coca.*

- **Extraction of Stilbene-based Polyphenolic Chemicals:** The Stilbene-based polyphenolic chemicals have been widely used as antibacterial, anti-inflammatory, hypolipidemic, cardiovascular, anti-diabetic, anti-ulcer, hepatoprotective, and anticancer agents. The few examples of useful Stilbene-based Polyphenolic Chemicals extracted by using microwave radiations includes: *trans*-resveratrol (3, 5, 4′-trihydroxystilbene), pterostilbene, viniferin, and other polyphenolic-stilbene derivatives etc.
- **Extraction of Terpenoids:** The Terpenes and isoprenoids, in general, expanded much consideration for their many biological functions like hormones, aliphatic tissue anchors, upholding tissue structure, biotic roles like defense compounds, insect or animal attractants, and wide medicinal uses such as flavors, fragrances, and drugs etc. Few examples of terpenes and related derivatives which are extracted using microwave techniques are listed as below:
    - Artemisinin from *Artemisia annua*
    - Paclitaxel from *Taxus baccata L.*

3.5 Microwave Assisted Extraction of Phytochemicals:

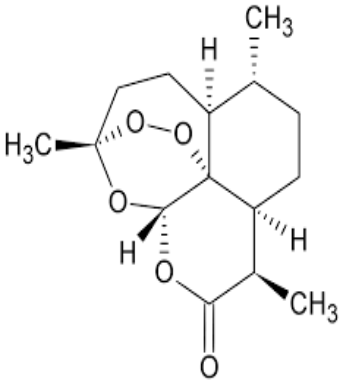
The extraction includes separating dissolvable chemical from non-dissolvable material using suitable liquids. There are two groups of extraction techniques reported for phytochemicals collection namely the traditional and modern extraction techniques. The list of traditional extraction methods includes the Soxhlet, soaking, maceration, digestion, decoction etc. These traditional extraction tools are associated with some limitations. In order to overcome the limitations of older extraction techniques few modern extraction techniques are evolved which includes turbo-fast blending, sonication, ultrasonic aided, subcritical, supercritical, enzyme assisted, pressure assisted, and microwave assisted techniques. Out of all these listed modern methods of extraction, the microwave supported

extraction has established the highest responsiveness due to its condensed consumption of liquid, less operation time, good reproducibility, improved recovery, upright selectivity, and condensed sample manipulation. In recent years, the microwave assisted extraction is usually used in gaining the chemicals of bio origin from plant materials. This has significantly improved the total attention in expansion and growth of research areas in plant chemistry research. It is a green expertise that is operational for taking out the plant compounds from plant sources. The microwave supported extraction has been employed in several ways to extract bioactive compounds from different plant samples. The isolates from these plant materials are being used in nutraceuticals and pharmaceutical uses. The microwave irradiation is mostly used to resolve some of the drawbacks associated with traditional methods. Table 3.2 presents some of the previous studies and the list of phytochemicals extracted from plants using microwave aided technology. The chemical structure of selected phytochemicals extracted using approach of microwave chemistry are given in Karnataka, India.

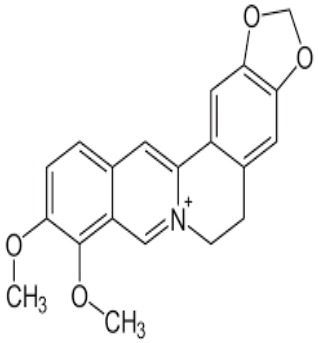
Table 3.2: List of Phytochemicals Extracted by Microwave Chemistry Approach

Sr. No.	Phytochemicals	Source of Plant
1	Artemisinin	*Artemisia annua* L.
2	Berberine	*Berberis aristata*
3	Coumarin	*Melilotus officinalis*
4	Caffeine	Green tea leaves
5	Carvone	*Carum carvi* L.
6	Carvone	*Mentha crispa* L.
7	Curcumin	Turmeric plant
8	Eugenol	*Ocimum basilicum* L.
9	Glycyrrhizic acid	Licorice roots
10	Isorhamnetin-3-O-rutinoside	Sea buckthorn
11	Limonene	*Carum carvi* L.
12	Limonene	*Mentha crispa* L.
13	Linalool	*Ocimum basilicum* L.
14	Monoterpenes	*Lavandula angustifolia* Mill.
15	Oxygenated monoterpenes	*Lavandula angustifolia* Mill.
16	Pectin	Grape fruis

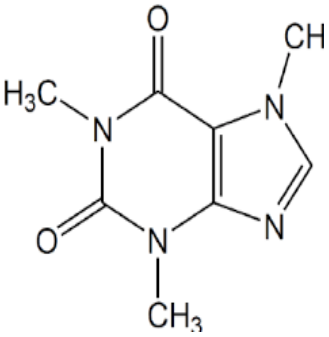
Sr. No.	Phytochemicals	Source of Plant
17	Phenolics chemicals	*Cinnamomum zeylanicum*
18	Polyphenols	Green tea leaves
19	Quercetin	Cranberry
20	Quercetin 3-O-Glucoside	Sea buckthorn
21	Sesquiterpenes	*Lavandula angustifolia* Mill.
22	Silybinin	*Silybum marianum* (L.)
23	Triterpene saponins	*Xanthoceras sorbifolia* Bunge.
24	5,8-Dihydroxycoumarin	Sweet grass leaves
25	5-Hydroxy-8-O-β-D-glucopyranosyl-benzopyranone	Sweet grass leaves



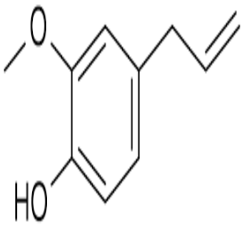
Artemisinin



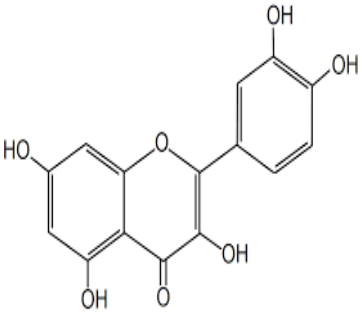
Berberine



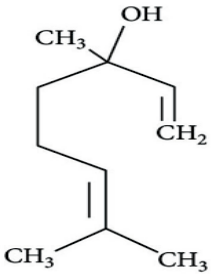
Caffeine



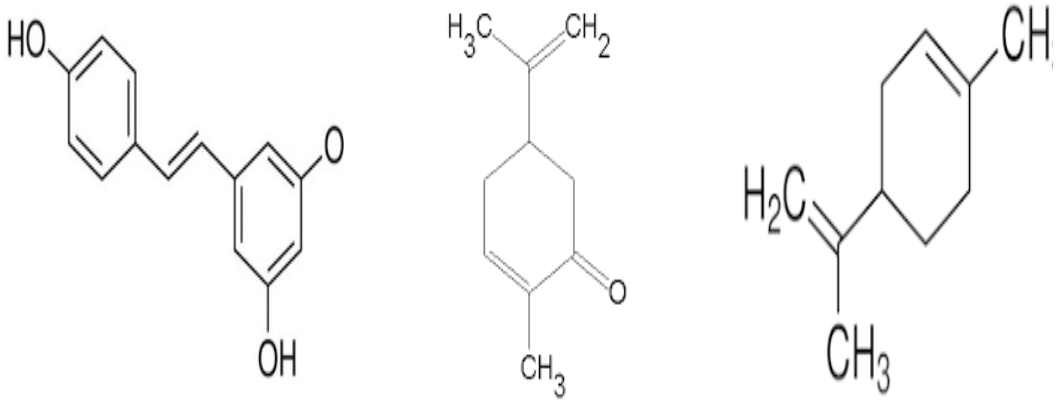
Eugenol



Quercetin



Linalool



Resveratrol **Carvone** **Limonene**

Figure 3.2: Structures of Phytochemicals Extracted by Microwave Chemistry Approach

3.6 Studies Using Microwave Assisted Extraction of Phytochemicals:

a. **Microwave Aided Extraction of Plant Chemicals from Ficus racemosa:** This research was conducted and published in the literature to optimize the microwave aided extraction procedure for the pulling out of plant chemicals from fruits of Ficus racemosa, which is measured as an underutilized and extreme basis of numerous polyphenols. The extreme phytochemical characteristics were found in the optimized conditions using 30 second of time 3.5 of pH, and 360.55 W microwave power using microwave oven. The research work further identified and quantified the presence of ascorbic acid, catechin, gallic acid, tannic acid, and quercetin. The research showed that F. racemosa can be positively applied for the extraction of phytochemicals by microwave supported extraction technique, which can be further used in food and pharmaceutical productions.
b. **Microwave Aided Extraction of Plant Chemicals from *Nonea pulmonarioides:*** In this research investigation the microwave supported extraction tool was selected to isolate the secondary plant chemicals from *Nonea pulmonarioides*. They suggested that the microwave chemistry approach in extraction is an efficient method. In this study of *N. pulmonarioides*, extracted using microwave extraction technique they found that the faster extraction was obtained in 5 minutes of time with an more yield than the maceration extraction technique. The phytochemical screening specified the existence of several classes of plant secondary compounds.

3.7 Conclusion:

The microwave assisted extraction technique has quickly grown during the latest periods as a technique for the extraction of secondary plant compounds which are of pharmaceutical and nutraceuticals attention. This is a model and innovative approach utilized for the extraction of phytochemicals due to several advantages like less extraction time, decrease in the solvent consumption, more precision and accuracy in results, better yield, and

multiple sample extraction etc. This technique has proven to be operative in all features, including inexpensive and practical, compared to old-style extraction practices. Microwave supported technology showed the effective role in the extraction of plant secondary chemicals including alkaloids, flavonoids, terpenes, polyphenols, Coumarin derivatives, and saponins etc. The advanced instrumentation leads to better extraction and it has helped to develop the modern medicines for management of various diseases and disorders. Hence microwave assisted extraction technique is considered to be an emerging trend and one of the model approach in the field of natural products chemistry research especially it has gained more attention and scope in the phyto chemistry and drug development research.

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ISBN: 978-93-94570-79-5

4. Application of Synthesized Ion Exchanger Tin (IV) Vanadomolybdate

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Abstract:

The distribution coefficient of Tin (IV) vanadomolybdateion exchanger for various metal ions revealed that the exchanger is selective for Ni2+ and Cu2+ ions, by the help of KD values. Binary separation of some important metal ion pairs was achieved. The ion exchanger may also be employed in the removal of transition metal ions from their aqueous solution. The effective separation of Ca2+and Mg2+ ions from hard water and the removal of colour metal ions were also achieved.

Keywords:

Distribution coefficient, Binary separation, Water softening, Removal of transition metal ions.

4.1 Introduction:

Ion exchange[1,2] is the process in which ions are exchanged between a solution and an insoluble solid. Ion exchange serves as one of the most important analytical technique for the separation of charged species from a solution that would ordinarily be very difficult and time consuming. Ion exchange process may be done with the help of an ion exchanger, interchange of ions of the same charge by other ions[3]. The earliest systematic studies of ion exchange were described with base exchange in minerals present in the soil[4].Ion exchanger may be natural or synthetic. Most natural ion exchangers like zeolites are crystalline materials having cation exchange properties. First synthetic industrial ion exchanger was reported in 1905[5]. In recent years' various zeolites with completely regular crystal structure have been synthesized and these products are exact counterparts of the natural materials. The examples of such kind of material include zeolite 4A[6] and zeolite A[7]. Now a day's synthetic inorganic ion exchangers have drawn the attention since they are less sensitive to higher temperature and to different chemicals and are also selective to certain ions. Further it was shown that three component ion exchangers show a better IEC than the two component ion exchangers. Tin (IV) based ion exchangers have been studied in detail previously by Varshney et al[8]. Various two component ion exchangers based on tin (IV) were reported in the literature[9-14]. Similarly, some examples of three component ion exchangers reported are stannic (IV)silicomolybdate[15], stannic(IV)arsenosilicate[16], stannic(IV)iodophosphate[17], stannic(IV)molybdophosphate[18], stannic(IV)phospho-tungstate[19] and stannic(IV)arsenophosphate[20]. Trace element can be removed from water by a range of physicochemical method such as membrane filtration, precipitation and ion exchange[21].

The present work is concerned with the application of Tin (IV) vanadomolybdate ion exchanger the synthesized ion exchanger finds several applications in analytical chemistry. Ion exchanger process is applied in several cases for separation of Ions that interfere in many analytical procedures may be removed. Some important application of ion exchanger is binary separation of metal ions, water softening and removal of colour metal ions.

4.2 Requirements:

A. Glasswares: Burette converted into column, Funnel, Glasss wool, Burette stand, Chemical balance, Oven, Mangnetic stirrer, Pipette, Beaker, Glass rod, Test tube with Test tube stand. All glass ware that is used throughout the experimental work was Borosil mark.

B. Reagents and Chemicals: Sodium hydroxide, Lead nitrate, Bismuth nitrate and EDTA were Qualigens product. All the acid that is Perchloric acid Hydrochloric acid, Nitric acid were also Qualigens product. Chemicals such as Zinc acetate, Cobalt acetate, Copper acetate, Nickel acetate, Ammonium chloride were also used in the experimental work.

4.3 Experimental:

A. Distribution Behavior:

In order to examine the affinity of tin (IV) vanadomolybdate towards various metal ions, distribution coefficient (k_d) values for ten metal ions were determined by batch process[22-28]. In this process ten equal portions 0.50g each of the exchanger were treated separately with 25ml of 0.1M aqueous metal salt solutions. The mixtures were then kept for twenty-four hours at room temperature and subsequently determination of metal ions was done by titrating the solutions against the standard solution of EDTA (Complexometric Titration)[23] with the help of appropriate indicators. The k_d values as given in Table 4.1 were calculated according to the formula-

$$K_d = \frac{I - F}{F} \times \frac{V}{W}$$

Where, I – Initial volume of the EDTA solution used

F – Final volume of the EDTA solution used

V – Volume of the metal ion solution taken

W – Weight of the exchanger

Table 4.1: Distribution Coefficient for Different Metal Ions with TVM

Sr. No.	Metal ions	Form	K_d(ml/g)
1	Ca^{2+}	Carbonate	2.54
2	Mg^{2+}	Acetate	6.11
3	Zn^{2+}	Acetate	5.33
4	Cu^{2+}	Acetate	12.25
5	Mn^{2+}	Acetate	0.40
6	Co^{2+}	Acetate	0.20
7	Ni^{2+}	Ammonium sulphate	23.67
8	Pb^{2+}	Nitrate	5.09
9	Bi^{3+}	Nitrate	10.73
10	Cd^{2+}	Chloride	6.36

4.4 Separations Achieved:

The values of separation factor for different metal ion pairs obtained for the exchanger were greater than three and the values are obtained by using following formula.

$$\alpha_B^A = \frac{K_d\ Value\ of\ A}{K_d\ Value\ of\ B}$$

Where

α_B^A is separation factor

A. Binary Separation:

The ion exchanger Tin (IV) vanadomolybdatewas also employed for binary separations of Ni-Pb, Zn-Co, Ni-Co, Ni-Mn, Ni-Mg, Cu-Co Combination as indicated by the value of separation factors for these metalions pairs. In binary separations. 0.50g of the exchanger in H^+ form was packed in glass columns. The column was washed with demineralized water and then metal ion mixtures were poured in column separately. The absorbed metal ions were eluted with appropriate eluents one by one. The flow rate of the effluent was maintained at 1ml/min through the elution process. The effluents were collected separately in different conical flasks and metal ions concentration were determined (Complexometric Titration) against disodium EDTA salt solution using suitable indicators[24-28]. The results are summarized in Table 4.2.

Table 4.2: Binary Separation Achieved with The Help of Tin(IV)Vanadomolybdate

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ni^{2+}	8217	8158	99.21	- 0.79	50ml	0.1M $HClO_4$
	Pb^{2+}	2279	2279	100	0.00	40ml	0.1M HNO_3
2	Zn^{2+}	1831	1766	96.45	- 3.55	40ml	0.2M $HClO_4$
	Co^{2+}	707.16	650.23	91.94	- 8.05	60ml	1.0M NH_4NO_3
3	Ni^{2+}	8217	8334	101.42	+1.42	40ml	0.001M HNO_3
	Co^{2+}	707.16	707.16	100	0.00	60ml	0.1M HNO_3 +0.5M NH_4OH
4	Ni^{2+}	8217	8275	100.71	+ 0.71	50ml	1.0M NH_4Cl + 0.1MHCl
	Mn^{2+}	1540	1428	92.72	- 7.27	30ml	

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
							0.1M HCl
5	Ni^{2+}	8217	8099	98.56	- 1.44	80ml	1.0M HNO_3
	Mg^{2+}	1944	1871	96.24	- 3.76	70ml	0.4M NH_4NO_3
6	Cu^{2+}	2923	2796	95.65	- 4.35	50ml	0.2M HNO_3
	Co^{2+}	707.16	707	99.84	- 0.27	60ml	0.2M $HClO_4$

B. Water Softening:

Hardness causing $Ca^{2+}$and Mg^{2+}were also removed with help of Tin (IV) vanadomolybdate. Column operation was used for the removal of metal ions. The hardness of the water sample was determined by complex metric titration method, in which Eriochrome Black-T was used as an indicator. In water softening, definite volume of hard water sample was passed at rate of 10 drops per minutes through the column maintained the bed of ion exchanger in column. This process is repeated for three times. Hardness causing calcium and magnesium loaded in the column were eluents using 1M HNO_3 and 0.01M $HClO_4$ as eluents respectively. The elution rate was maintained at 5 drops per minute. The eluted Ca^{2+} and Mg^{2+} amount was determined by quantitatively with appropriate indicators. The results are shown in Table 4.3.

Table 4.3. Removal of Ca^{2+} and Mg^{2+} With the Help of TVM

Sr. No.	Metal ions	Amount loaded(μg)	Amount found (μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ca^{2+}	240.5	218	90.65	-9.35	50ml	1.0M HNO_3
2	Mg^{2+}	1775	1750	98.59	-1.41	50ml	0.01M $HClO_4$

C. Removel of Transition Metal Ions:

Application of the exchanger in removing the metal ions from different water samples was done using by Column method. The determination of Co^{2+}, $Ni^{2+}$and $Cu^{2+}$was done ascertain the amount of these ions in their aqueous solutions. The method of determination was done on the basis of two types. In qualitative determination, different definite volumes of the three solutions were loaded on the ion exchanger packed in three different columns.

The flow rate of ten drops per minutes was maintained the solution were passed three times through the exchanger. The effluents of the three columns were collected in three different containers. The presence of the metal ions in all the containers was confirmed by performing qualitative analysis as given in Table 4.4. All the qualitative test was found to be negative.

Table 4.4: Qualitative Tests for Transition Metal Ions for TVM

Sr. No	Metal ion	Colour of the salt solution before passing through exchanger	Colour of the salt solution after passing through exchanger	Detection of metal ion in the effluent
1	Ni(II)	Green	Colorless	a) Effluent NaOH Solution- No Precipitate Ni(II) absent b) Effluent Ammonia- No Precipitate Ni(II) absent
2	Co(II)	Pink	Colorless	Effluent + Sodium hydroxide Solution-No Precipitate Co(II) absent
3	Cu(II)	Blue	Colorless	a) Effluent NaOH Solution- No Precipitate Cu(II) absent b) Effluent Ammonia- No Precipitate Cu(II) absent

For quantitative determination of metal ions, suitable eluents were passed through all the columns containing loaded exchanger.

After elution process the amount of metal ions was determined by complex metric titration using suitable indicators. The results are shown in Table 4.5.

Table 4.5. Removal of Transition Metal Ions with The Help of TVM

Sr. No.	Metal ion	Amount loaded (μg)	Amount found (μg)	% of Metal ion eluted	% Error
1	Co^{2+}	707.16	665.45	94.10	-5.89
2	Ni^{2+}	8217	8092	98.48	-1.52

Sr. No.	Metal ion	Amount loaded (µg)	Amount found (µg)	% of Metal ion eluted	% Error
3	Cu^{2+}	2923	2798	95.72	-4.27

4.5 Result and Discussion:

The study of the values obtained for distribution coefficient revealed that the material shows high selectivity for Ni^{2+} and Cu^{2+} for which the k_d values were 23.67ml/g and 12.25ml/g respectively. The distribution coefficient for the metal ions (Table 1) follows the sequence-

$Ni^{2+} > Cu^{2+} > Bi^{3+} > Cd^{2+} > Mg^{2+} > Zn^{2+} > Pb^{2+} > Ca^{2+} > Mn^{2+} > Co^{2+}$

In binary Separation of different combinations were quite successful through ion exchanger. The exchanger removed different metal ions to different extent such as 650.23µg Co^{2+} was removed out of 707.16µg Co^{2+} while 8334µg Ni^{2+} was removed out of 8217µg Ni^{2+}. The removal is seen from 91.94% to 101.42%. In Ni –Pb separation, the difference between loaded amount and amount found show that lead is 100% eluted with 0% error and nickel is eluted to 99.21% with -0.79% error. The recovery ranges of nickel is present in all combination from 95-100% and the results are summarized in Table 2.

The synthesized ion exchanger Tin(IV)vanadomolybdate can removed Ca^{2+} and Mg^{2+} from hard water and it may helpful in water softening. The results for these ion exchanger implies that Mg^{2+} can be removed from hard water up to 98.59% and removed of Ca^{2+} is 90.65% and the results are shown in Table 3.

The role of the ion exchanger is found to be useful in decontamination of the chemicals. Detection of the metal ions are (qualitative analysis) made it possible decide the determination process. The results are shown in Table 4. Quantitative determination of metal ions in a sample helped in knowing the amount of metal ion present which in turn was helpful to decide the exchange process. The observation table clearly indicates that Tin (IV) vanadomolybdate was found to be able to decontaminate cobalt 94.10%, Nickel 98.48% and 95.72% Copper respectively. The results are shown in Table 5.

4.6 Conclusion:

In the present work the analytical applications are performed for Tin (IV) vanadomolybdate. The ion exchanger possesses selectivity for trace metals such as, Ni^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+}. The ion exchanger is also employed for the binary separation of heavy metals present in aqueous media and also used as in water softening.

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ISBN: 978-93-94570-79-5

5. Biomaterials: Review and Applications

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Abstract:

Since it has been around for almost 50 years, the science of developing biomaterials is not a recent one. The study of biomaterials is known as biomaterial science. It is a contentious field of study that has expanded consistently and dramatically throughout the duration of its existence, with various companies investing sizeable sums of money in the development of new products. Biomaterial science encompasses tissue engineering as well as biology, chemistry, and materials science.

Keywords:

Biomaterials, Review

5.1 Introduction:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. When applied to a more interactive application, such as hydroxyapatite-coated hip implants (such as the Furlong Hip, manufactured by Joint Replacement Instrumentation Ltd. in Sheffield), biomaterials can be either benign or bioactive. One such instance is Sheffield, where such implants can endure up to twenty years. Additionally, biomaterials are regularly utilized in medical procedures, dentistry, and drug delivery.

Although it has been challenging to define the term "biomaterial," more commonly " working definitions that are recognized include: A biomaterial is any material, natural or man-made, that comprises whole or part of a living structure or biomedical device that performs, augments, or replaces a natural function."

A. Applications:

- Joint replacements
- Blood vessel prostheses
- Bone cement
- Bone plates
- Bone cement
- Artificial ligaments and tendons
- Dental implants for tooth fixation
- Contact lenses
- Cochlear implants

Here are the 2 examples.

first intraocular lens

Basic components: Silicone and PMMA (acrylic).


Combining long-term biocompatibility with optical performance is difficult.

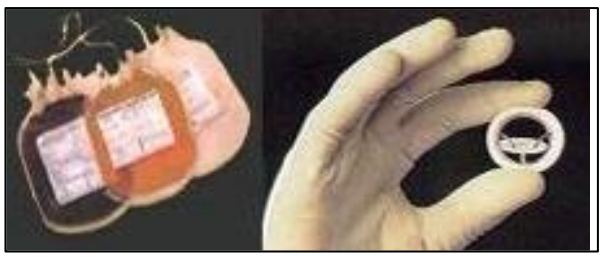



B. Artificial Hip Joints:

Stainless steel, titanium and its alloys, and UHMWPE are the basic materials. Prevention of wear and loosening over long durations (10–15 years) is a challenge.

C. Substitute Heart Valves:

D. Indian Chitra Heart Valve:



E. Vascular Grafts:

Dacron, Teflon, and polyurethane are the basic materials.

Maintenance of mechanical integrity and long-term blood compatibility are obstacles (avoidance of blood clotting).

The proximal load transfers for the human complete hip system shown below is provided by a titanium, dual tapered stem design, significantly lowering possibility of the calcar resorption and proximal hypertrophy Not a fool! System offers a straight stem design and an anatomic fit. Polyethylene serves the function of cartilage in this application. Biomet Corporation is the cited to learn more about hip replacement and the situations under which it is performed, visit the Medline Plus website (many great illustrations).

5.2 Some Commonly Used Biomaterials 2:

a. Silicone rubber
b. Dacron
c. Cellulose
d. Poly (methyl methacrylate)
e. Polyurethanes
f. Hydrogels

g. Stainless steel
h. titanium
i. Alumina
j. Hydroxyapatite
k. Collagen (reprocessed)

Applications:

- Catheters, tubing
- Vascular grafts
- Dialysis membrane
- Intraocular lenses, bone cement
- catheters, Pacemaker leads
- Opthalmological devices, Drug delivery
- Orthopedic devices, stents
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Ophthalmologic applications, wound dressings

A. Protein-Surface Interactions in Biomaterials:

The underlying cause of medical device biocompatibility—or lack thereof—is protein–surface interactions. Proteins quickly adsorb onto the surface of a solid substance that comes into contact with a fluid containing soluble proteins, like a catheter, stent, hip joint replacement, or tissue engineering substrate (such as blood, interstitial fluid, cell culture media). Within seconds to minutes, this saturation happens. Because of this, living cells actually make touch with the molecular structure of a biomaterial when they approach its surface. Living cells are larger than proteins and move more slowly adsorbed protein layer rather than the surface of the material itself. Of course, cells cannot "see" the layer of adsorbed proteins; instead, they probe their environment using membrane-bound receptors that can bind to specific bioactive features that the adsorbed proteins provide.

Following their binding, these receptor-protein interactions are then conveyed through the cell membrane via a number of carefully regulated molecular mechanisms in such a way as to excite particular intracellular activities that ultimately define the response of a cell. As a result, how bioactive locations differ offered by the protein layer that is absorbed is the most essential factor in determining cellular response.

The number, kind, and packing arrangement of proteins that are adsorbed as well as it is possible to control their packing, conformation, and direction on the biomaterial's surface. The emphasis will be on showcasing a few among the most fascinating relatively recent techniques that have been developed and applied to increase our comprehension of the sub molecular principles underpinning how surface chemistry impacts the orientation, conformation, and organisation of adsorbed proteins.

If we want to move past moving from the mostly trial-and-error-based surface design of the present to a future where surfaces are purposefully created to directly regulate adsorbed protein bioactivity, and hence govern cellular response, we must continue to develop our understanding of these processes. Though conceptually straightforward, the vast variety has been made possible—and continues to be made possible—by the complex structural features of soluble proteins found in physiological fluids. —a very difficult subject.

B. Computer Simulation of Protein Adsorption to a Material Surface in Aqueous Solution: Biomaterials Modeling of a Ternary System.

Because biomaterials frequently come into touch with the body or body fluids, crucial aspects like biocompatibility and bio reactivity are controlled by interfacial processes, particularly protein adsorption. A mechanistic understanding of the interactions the development of biotechnology tools like DNA/protein micro arrays and micro fluidic systems will also require the improvement of the interface between biological macromolecules and material surfaces. As a result, the atomistic characterization of structure function correlations at the interface between biological macromolecules and materials surfaces will be crucial for the development of a wide range of bioengineering and biotechnology applications in the future.

They used typical computer modelling software to simulate protein adsorption to a material surface in water. Bovine pancreatic trypsin inhibitor was used to model a multi-component system in which a hydrated protein was present (BPTI), comes into contact with a MgO surface in pure water, molecular dynamics and local minimization were used. In water and in living things, soluble proteins are known to bind to charged substance surfaces. In three distinct initial protein orientations, the simulations demonstrate the binding of BPTI with binding energies of 242, 350, and 241 kcal/mol to MgO in water. Our research shows that in this watery environment, there is hardly any interaction between the atoms of the protein and those of the surface. The solvation layer facilitates important surface binding mechanisms in the interphase (double-layer) area. Although this fact is often not explicitly taken into consideration in the protein adsorption literature, it is anticipated on the basis of traditional electrochemical theory.

C. Carbohydrate derived protein resistant biomaterial:

The Side-chain polyethers obtained from carbohydrates can be made using monomers made from naturally occurring carbohydrates to condensation polymerize. These substances are biodegradable, resistant to proteins, and allow for functionalization in places other than the chain ends. To accomplish desired protein resistance, biodegradability, and/or functionalization, the compounds of the present invention may be formed, at least in part, into various devices, apparatus, and manufactured goods.

D. Hard Tissue: Biomaterial Interactions:

Because bone and cartilage are prone to damage, biomaterials—artificial and modified natural materials—have been effectively employed for many years to replace and/or regenerate these tissues. Science has lately developed the idea of tissue engineering, which

combines the use of biomaterial-based scaffolding, cultured cells, systemic and/or local hormones/mediators, and, more recently, genetic modulators, to try to restore damaged tissues. Since many years ago, musculoskeletal illnesses and disorders have been treated extensively with tissue engineering products, which are essentially biomaterials of various shapes and forms. Currently, materials for replacing bone, cartilage, and joints include ceramics made of hydroxyapatite (HA), calcium phosphate, and polymers like polymethyl methacrylate, as well as metals like titanium, cobalt-chrome, and steel in pure and/or alloy form.

E. Modeling and Simulation of Biomaterials:

Simulation and modelling are being used more and more in materials research. The authors of this paper cover modelling and simulation applications in the emerging subject of biomaterials. The authors don't cover biochemical or biological applications in order to somewhat condense the subject; instead, they concentrate on the structure and characteristics of biomaterials. an explanation of how molecules and groupings of molecules can be studied using atomistic level simulation. After that, we concentrate on simulations of structure and behaviour at the mesoscale, followed by a brief discussion of continuum scale methods.

F. Nano Biomaterials:

Enzymes have been included in detergent recipes for a very long time to help combat particularly difficult filth. Chemical engineer Jonathan Dordick of Troy, New York's Rensselaer Polytechnic Institute is advancing the fight against dirt by employing nanotechnology to create a self-cleaning plastic in which the enzyme molecules are a fundamental component of the substance. The enzymes in the plastic attack bacteria and other pathogens when they come into touch with it, preventing them from adhering to its surface.

G. Bioengineering of Improved Biomaterials Coatings for Extracorporeal Circulation Requires Extended Observation of Blood Biomaterial Interaction under Flow.

Cardiopulmonary bypass systems are frequently hindered by the thrombus development and also infection after prolonged use. The CPB circuitry's insufficient hem compatibility is one cause of several of these issues. In biomaterials science, creating true long-term hem compatibility of biomaterial surfaces is largely unexplored territory. For instance, the bulk of studies evaluating the interactions between blood and biomaterials under flow using the well-known Chandler loop model have only been described for a maximum of two hours.

Two commercial CPB tubings with hem compatible coatings were thoroughly compared in this study with one uncoated control. Examining human whole blood from four separate donors while it was flowing for five hours, analyzing luminal surfaces with scanning electron microscopy, and timing the formation of thrombin were all part of the study. The research showed that the tubing's hem compatibility varied. Furthermore, it seemed that one could only tell one biomaterial covering from another after several hours of blood contact.

Platelet counting, myeloperoxidase quantification, and scanning electron microscopy were the most efficient methods. It is believed that these findings are relevant to the bioengineering of extracorporeal devices that are intended to work for lengthy periods of time in contact with blood.

H. Protein-Based Vascular Tissue Engineering Advances:

Vascular tissue engineering is driven by improved blood artery replacements are clinically necessary, especially for small-diameter applications. Although the blood vessel's form and function are well known, because it is a complicated tissue, it has been difficult to create engineered tissues that are suitable for widespread clinical application. This article discusses vascular tissue engineering techniques that use proteins as the primary matrix or "scaffold" material to create fully biological blood vessel substitutes.

This review specifically discusses the following four vascular tissue engineering methods: Protein hydrogels with cells, crosslinked decellularized natural tissues, self-assembled scaffolds, and protein scaffolds are the first four types of materials. These approaches' benefits and limitations are highlighted together with recent developments in each of these field.

I. Biomaterials: where we have been and where we are going:

The field of biomaterials has had sustained expansion with the steady introduction of fresh concepts and fruitful branches since its founding just over 50 years ago. This assessment outlines our progress to date, the current state of the art, and potential future developments. Here, they highlighted some of the most recent developments in biomaterials with the goal of regulating biological reactions and ultimately promoting healing. Biologically inspired materials that mimic natural processes, the creation of sophisticated three-dimensional (3D) architectures to provide clearly defined patterns for diagnostics, the synthesis of synthetic materials with regulated qualities for medication and cell carriers, and precision immobilization of signalling groups on surfaces are all included in this new generation of biomaterials.

J. Biomaterials for Blood Contacting Applications:

Biomaterials should be taken into account for applications involving blood contact while also considering blood-biomaterial interactions, blood response parameters, and evaluation techniques.

When analyzing blood-biomaterial interactions, factors such protein adsorption, platelet responses, intrinsic coagulation, fibrinolytic activity, erythrocytes, leukocytes, and complement activation can be taken into consideration. Blood response to a biomaterial in a therapeutic environment is influenced by the biomaterial's structure, the presence of an antithrombotic agent, the patient's condition as indicated by the disease and pharmacological therapy, and the particulars of the application. Ex vivo and in vitro procedures are important for biomaterial development, and there are choices for clinical, in vivo, ex vivo, and in vitro evaluation of biomaterials.

K. Biomaterials in Canada: The first four decades:

The 1960s saw the start of Canadian biomaterials research. Significant advancements in a wide range of fields, over the past 40 years, a variety of biomaterials have been developed, including dental, orthopedic, cardiovascular, neurological, and ophthalmic materials. Canadians have also been involved in the tissue engineering derivative industry. The federal and provincial governments provide the majority of the funding for the biomaterials laboratories that are now present at universities and other research institutions from coast to coast. Initiated in 1971, the Canadian Biomaterials Society has contributed significantly to the growth of the industry. In 1996, the Society hosted the Fifth World Biomaterials Congress in Toronto. An overview of Canadian researchers' work during the previous four decades is provided. The scientific field of biomaterials and tissue engineering is deemed to be mature and robust in Canada and is predicted to remain so in the future.

L. Future directions in biomaterials:

The field of medicine has greatly benefited from biomaterials. However, there are still several difficulties. This essay examines three pertinent topics with significant medical issues. First, drug delivery systems; important factors to take into account are interactions between pharmaceuticals and polymers, drug transformation, drug diffusion characteristics, and, if polymer degradation occurs, the products of polymer degradation through polymer matrices. New tailored polymers are also being developed for specialized applications including vaccination and pulsatile release. Second, how cells interact with polymers, including what happens to inert polymers, how to use polymers as templates for tissue regeneration, and how to investigate polymers that make cell transplantation easier. The third category is orthopedic biomaterials, which includes fundamental research on the behaviour of chondrocytes, osteocytes, and connective tissue-free interfaces as well as applied research using computer-aided design of biomaterials and the production of orthopedic biomaterial.

M. Smart Biomaterials Design for Tissue Engineering and Regenerative Medicine:

Tissue engineering (TE), a significant approach in regenerative medicine, has been an active area of scientific research for almost three decades. However, due in part to the small number of biomaterials that have been given human use approval, the clinical application of TE technology has been somewhat constrained.

Even though a lot of great biomaterials have been created recently, their implementation into clinical practice has been delayed. Since biodegradable polymers were initially licensed for use in humans over 30 years ago, many researchers still utilize them today.

N. Systematic Effects of Biomaterials:

The tissue reaction at the implant site is typically the main focus of analyzing the host's reaction to implanted biomaterials. Similar to how looking at battles out of their historical context can lead to incorrect judgements, this can also.

A larger perspective reveals a number of potential and actual systemic consequences of a bacteriological, immunological, metabolic, and carcinogenic character. The absence of epidemiological data makes it difficult to identify these impacts in patients.

O. Biomaterials and Biomedical Devices:

The variables crucial to the integration of biomaterials and technology into tissue are covered in this review. Surface modification approaches and surface-sensitive analytical techniques are mentioned. The effectiveness or biocompatibility of specific biomaterials and devices are assessed using in vitro procedures. There is discussion of current and future directions in dialysis, artificial organs, plasma and cytapheresis, artificial blood or bone substitutes, orthopaedic prostheses, dental materials, neural prostheses, and cardiovascular materials.

P. Biomaterials for Healthcare:

Animal-derived islets were encased in a device with a membrane composed of polycarbonate and a support. The encapsulation chamber was given an extracellular matrix to prevent the islets from congregating. By interconnecting 20 devices, it was possible to implant up to 20 000 pancreatic islets, as needed for testing on a mini-pig in a plate-type support. After up to 92 days following implantation, the biocompatibility of sterile macro devices was examined in normal mini-pigs. Despite the generation of fibrosis, the peripheral immune system did not significantly change or show any signs of an inflammatory response.

Q. Optimization Studies on the Features of an Activated Charcoal supported Unease System:

The enzymatic hydrolysis of urea has been made possible by the successful adsorption of urease onto activated charcoal derived from petroleum. The enzyme support system has been plasma polymerized to coat hexamethyl disiloxane, resulting in a biocompatible surface. Electronic Chemical analysis using spectroscopy and scanning electron microscopy methods were used to evaluate the effectiveness of the resultant coat. Studies on the urease's adsorption, activity, and stability on the support have been made in an effort to improve the properties of the urease supported by charcoal and increase its accessibility for usage in clinical applications.

R. Bioactive Specific Biomaterials: Present and Future:

In order to interact specifically with living systems, bioactive biomaterials are replaced with specific chemical functional groups carried by the macromolecular chain and made of synthetic or artificial polymers.

These polymers, which can be soluble or insoluble, are made from dextran and polystyrene. When these modified polymers come into contact with circulating blood, they have low thrombogenicity because they may be endowed with anticoagulant heparin-like characteristics. It has been specifically designed for other functional polymers to interact with immune system elements.

Other polymers can influence cell development and biological activity or only biological activity when in contact with cells, without necessarily changing all of the features of the cells. From the aforementioned ideas, it is conceivable to show that the biological features of these polymers correlate with a statistically random chemical group distribution along the macromolecular backbone.

S. Macromolecular Engineering of Fluorinated Polymers and Hybrid Composites for Dental Resoration Application:

Investigated were novel polymeric materials that shrink less during polymerization and have low surface energy. New fluorinated ring-opening monomers were synthesised in order to produce the requisite polymers and composite resins. Different polymeric and co-polymeric systems' properties, including reactivity, chemical composition, thermal behaviour, and surface features, were thoroughly investigated. Even at comparatively low fluorinated chain side group concentrations, the ordering of the fluorinated groups caused the polymers to form liquid crystalline mesophases. Surface studies showed the existence of uniform, well-ordered surfaces with low surface tension due to the fluorine enrichment of the air-polymer interface. Fluorinated ring-opening monomers and crosslinkers were used to create dental composite resins. The function of the components in the resin formulations was evaluated in terms of bacterial adhesion, surface topography and composition, and mechanical properties. Without appreciably changing the mechanical properties, the introduction of fluorinated groups resulted in a significant decrease in volume shrinkage. There was a suggested relationship topography, surface energy, and fluorine surface segregation.

T. Toward A Suture Less Vasovasostomy: Use of Biomaterials and Surgical Sealants in A Rodent Vasovasostomy Model:

Vasectomy reversal has become a routine treatment with an annual reversal rate of 3% to 8% and 500,000 to 800,000 vasectomies performed. The gold standard for surgical vas reconstruction is still a two-layer microsurgical vasovasostomy. The process is time-consuming and technically difficult. They discovered how biomaterials and surgical sealants might cut down on the amount of sutures needed, improve the water tightness of anastomoses, and shorten operating times.

5.3 Conclusion:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. Biomaterials may be bioactive or serve a benign purpose, such as in the construction of a heart valve such as hydroxyapatite-coated hip implants, which last up to twenty years and are used for more interactive purposes.

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ISBN: 978-93-94570-79-5

6. Supramolecular Chemistry, Types of Supramolecular Systems and Its Applications

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6.1 Supramolecular Chemistry:

Supramolecular chemistry, also known as "chemistry beyond the molecule", is a fast-expanding discipline concerned with the chemical interactions of molecules. Recent years have seen a substantial increase in interest in this topic as a result of the possibility of developing novel materials and systems with distinct functions. In this chapter, we will discuss the fundamental concepts of supramolecular chemistry, recent trends and advancements in the field, and potential future applications. Supramolecular chemistry is fundamentally concerned with the interactions between molecules that take place via non-covalent interactions [1], such as hydrogen bonding, metal coordination, hydrophobic interactions, etc., [2]. Through their interactions, molecules can create intricate structures known as supramolecular assemblies, which can exhibit their unique properties. And behavior is different from those of the individual molecules.

One of the main goals of supramolecular chemistry is to design and synthesize molecules that can self-assemble into well-defined structures. These structures can have a wide range of functions, such as the ability to store and release energy, conduct electricity, or act as catalysts. [3] Supramolecular chemistry has several important applications in various fields such as medicine, materials science, nanotechnology, etc.

In medicine, supramolecular systems can be used for targeted drug delivery, as the self-assembling nature of these systems allows for specific targeting of diseased cells. In materials science, supramolecular systems can be used to create new materials with improved mechanical and thermal properties. In nanotechnology, supramolecular systems can be used to create nanoscale devices with a range of applications. [4]

In recent days, supramolecular chemistry is focused on the development of new materials and devices with improved properties and also the development of new synthetic methods and characterization of supramolecular systems. In addition, the development of new theories and models can easily understand their behaviour in the application of these systems in real-world problems, due to the numerous applications and the potential for further discovery, supramolecular chemistry remains a rapidly growing and exciting field.

6.2 Mechanically Interlocked Molecules (Mims):

Mechanically interlocked molecules (MIMs) are a class of supramolecular compounds that are held together by non-covalent interactions, such as hydrogen bonding, electrostatic interactions, and van der Waals forces [5]. There are several different types of MIMs, each with its own unique properties and potential applications. Some of the most well-known types of MIMs are discussed in this chapter.

A. Rotaxanes:

Rotaxanes are a class of molecular structures that consist of a macrocycle, or large ring, that surrounds a smaller and linear component called an axle. The axle is able to move within the macrocycle but it is prevented from completely escaping from the macrocycle due to the presence of one or more stoppers, like bulky groups, that are attached to the axle. This unique mechanical bond between the macrocycle and the axle makes rotaxanes an attractive subject for research in the field of supramolecular chemistry. The structure of rotaxanes resembles A dumbbell-shaped molecule with a ring trapped between its two ends.

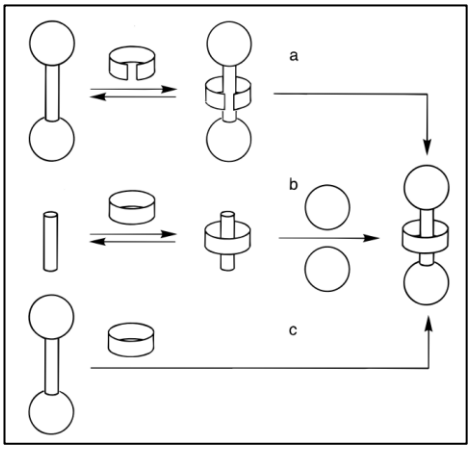

Figure 6.1: Three different approaches to the construction of rotaxanes: (a) “clipping”; (b) “threading”; (c) “slippage” [5].

Rotaxanes have been shown to have potential applications such as drug delivery [6], chemical and biological sensors [7], and data storage [8] due to their ability to undergo dynamic changes in conformation and responsive behavior to external triggers. Furthermore, rotaxanes also have the potential for use in molecular machines and devices as their mechanical bond allows for rotational motion and/or translation of the axle [9].

B. Catenanes:

Catenanes are a class of molecular structures in which two or more interlocked macrocycles are connected in a "chain" formation. They are similar to rotaxanes, but with multiple macrocycles linked together. Catenanes are named based on the number of interlocked rings, e.g. a [2] catenane consists of two interlocked rings (Figure 6.2). The "ane" ending of the term is a reference to alkanes, and catenanes are typically considered to be organic compounds, although they may not always consist of hydrocarbon groups. In situations where the interlocked ring system can act as a ligand for a metal centre, the terms [n] catenand and [n] catenate may also be used, in analogy with the terms cryptand and cryptate. The term "catenand" refers to the free ligand that forms a catenate complex in the presence of metal ions [10].

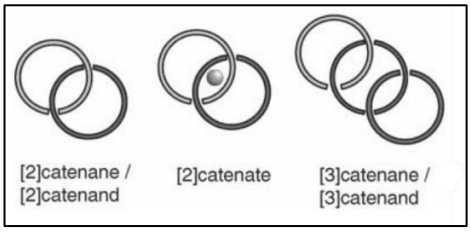

Figure 6.2: Nomenclature and schematic representation of Catenanes [10].

The synthesis of catenanes can be challenging, but various methods have been developed, including template-directed synthesis, mechanically interlocked synthesis, and chemical synthesis [11]. Catenanes have potential applications in fields such as molecular electronics, drug delivery, and as molecular machines. Their unique properties, including their ability to perform mechanical movements in response to external inputs, can be utilized for switching and sensing purposes. They have also been explored as molecular shuttles, molecular switches, and artificial muscles [12].

C. Clathrates:

Clathrates are a class of molecular structures in which a host molecule encapsulates or "traps" a guest molecule inside a cage-like structure. The host molecule forms the walls of the cage, and the guest molecule is held inside by non-covalent interactions such as hydrogen bonding or van der Waals forces.

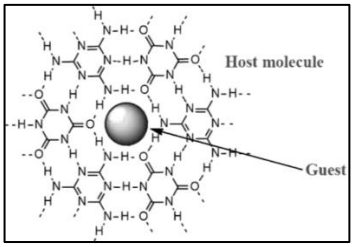

Figure 6.3: Schematic representation of Clathrates

Clathrates have been found in various forms of matter such as gases, liquids, and solids. In the field of chemistry, clathrate hydrates are known for their ability to trap gases such as methane and carbon dioxide, making them of interest for natural gas storage and carbon capture [13]. They also have potential applications in various fields such as drug delivery, catalysis [14], storage of gases like natural gas, hydrogen, and others in solid form, treatment of wastewater and concentration of organic mixtures, as well as separations and storage of gas mixtures. Clathrates are a topic of ongoing research, and the full potential of these structures is yet to be fully understood and harnessed. Further research is needed to develop new synthetic methods and to better understand the properties of these complex structures.

D. Cavitands:

Cavitands are a class of molecular structures that are characterized by a "cavity" or a hollow interior space. These cavities are formed by the arrangement of atoms or chemical groups in a specific way, and they can be either hydrophobic or hydrophilic in nature, which has potential applications in various fields like molecular sensors [15], catalysis, drug delivery, and separation science. In separation and purification, cavitands can be used to sort and isolate specific molecules, such as proteins and enzymes, based on their size and shape. They have also been explored as scaffolds for the formation of supramolecular assemblies, and in the field of host-guest chemistry as receptors for specific molecules [16].

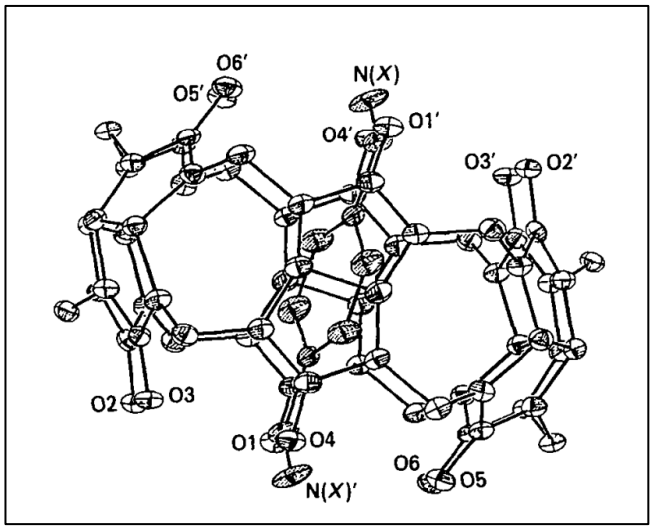

Figure 6.4: A cavitand (cucurbituril) bound with a guest p-xylylenediammonium [16].

F. Cryptands:

Cryptands are a class of molecular structures that have found significant application in the field of supramolecular chemistry. They are characterized by a "crypt" or a hollow cavity that can selectively bind or "capture" specific guest molecules within it. The structure of cryptands is composed of a macrocyclic ring with a number of binding sites that can interact

with specific guest molecules via non-covalent interactions viz., hydrogen bonding or electrostatic interactions. In supramolecular chemistry, cryptands have been used to form various types of assemblies, including host-guest complexes, supramolecular polymers, and supramolecular gels. They have also been explored as receptors for specific molecules, such as small ions or metal ions [17].

Cryptands have numerous applications in a variety of fields such as chemistry, biochemistry, materials science, etc. Their ability to selectively bind specific guest molecules makes them attractive for use in chemical separations, and the formation of supramolecular assemblies can be used to create new materials with specific properties. These molecules are valued for their high selectivity and specificity in recognizing cations, anions, neutral molecules, and even isotopes. They play a crucial role in ion transportation studies and are used as stationary phases in column chromatography for separating cations, anions, and isotopes. In addition, they are utilized in the study of redox systems, photo physical properties, non-linear optics, amphiphiles, sol-gel materials doping, and as structural directing agents in synthesis [18].

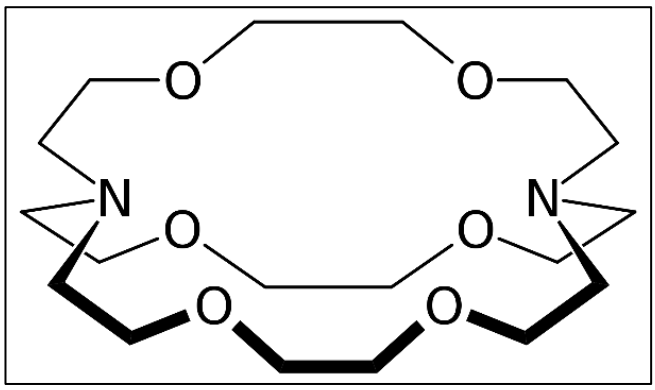

Figure 6.5: Structure of [2.2.2] Cryptand

6.3 Molecular Self-Assembly:

Molecular self-assembly is a fundamental concept in supramolecular chemistry that refers to the process by which individual molecules come together to form ordered structures without any external inputs. This process is driven by non-covalent interactions such as hydrogen bonding, electrostatic interactions, and van der Waals forces. Self-assembly has been used to create a wide range of structures including, but not limited to, vesicles, fibers, gels, and even more complex supramolecular systems [19]. The ability to manipulate and control the self-assembly process is of great interest in supramolecular chemistry, as it allows the creation of new materials with specific properties [20]. Self-assembly can be directed by various strategies such as the use of pre-designed templates or by controlling the chemical composition and stoichiometry of the system. The utilization of self-assembling peptides, small molecules, and lipids is also gaining recognition as a flexible approach to creating new materials with specific characteristics [21]. Molecular self-assembly is an active area of research in supramolecular chemistry and has potential applications in fields such as materials science, nanotechnology, biotechnology, etc.

A. Micelles:

Micelles are a form of supramolecular structures that are composed of a core of hydrophobic units surrounded by a shell of hydrophilic groups. They form spontaneously in water-based solutions and are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Micelles are of great interest in supramolecular chemistry due to their ability to encapsulate hydrophobic molecules and act as a carrier for drugs and other hydrophobic molecules, allowing for targeted drug delivery and improved bioavailability [22].

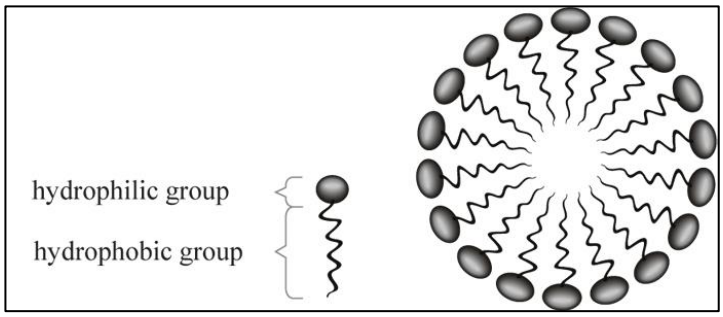

Figure 6.6: Schematic Structure of Micelle

Micelles have a wide range of applications due to their unique properties. Including, drug delivery, biomedical imaging, environmental remediation, cosmetics, etc [23].

B. Lipids:

Lipids are a class of biomolecules that play an important role in supramolecular chemistry. They are composed of a hydrophobic tail and a hydrophilic head, which allows them to spontaneously form structures such as vesicles, bilayers, and micelles in aqueous environments. These structures, known as lipid assemblies, have unique properties that make them of great interest in various fields, including cosmetic and food industries, and in nanotechnology [24]. Lipid assemblies have been used as a model for cell membranes and have been explored as a carrier for drugs and other hydrophobic molecules in targeted drug delivery [25].

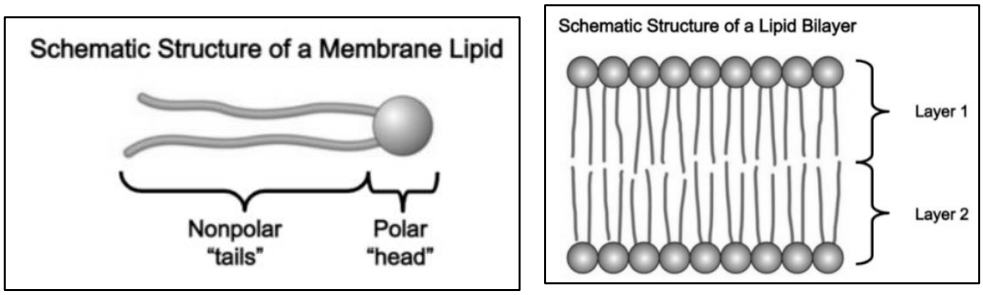

Figure 6.7: Schematic Structure of Lipids

Lipid assemblies have also been explored as a scaffold for the formation of supramolecular assemblies, and as a tool to understand the principles of self-assembly.

C. Liposomes:

Liposomes are a type of supramolecular structure that is composed of a phospholipid bilayer enclosing an aqueous compartment [26]. They are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Liposomes have been used as a carrier for drugs, allowing for targeted drug delivery and improved bioavailability. Additionally, they have been explored as a means of gene therapy and as a tool for delivering drugs to specific cells or tissues [27].

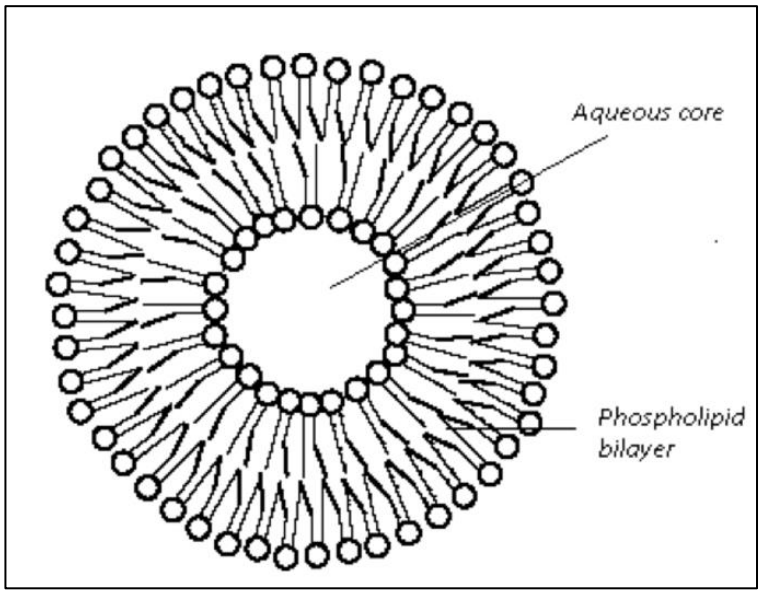

Figure 6.8: Schematic Representation of A Liposome

Liposomes have been used to create new materials with specific properties, such as liposome-based membranes for separation and filtration. Liposomes have also been found to be useful in the field of 'sensing', as they are able to encapsulate and detect specific molecules [28]. In addition, it is also useful in various fields like healthcare, cosmetics, medical imaging techniques, and the agricultural industry.

6.4 Molecular Recognition (Host-Guest Chemistry):

Molecular recognition is the specific interaction between more than two molecules via non-covalent interactions such as hydrogen bonding, metal coordination, hydrophobic forces, Van der Waals forces, pi-pi interactions, electrostatic, and electromagnetic effects. The molecule that receives an incoming entity is referred to as a host molecule, while the incoming entity itself is known as a guest molecule. The main concept of molecular recognition is lock and key. In this model, the host molecule makes interaction with a guest molecule or ion.

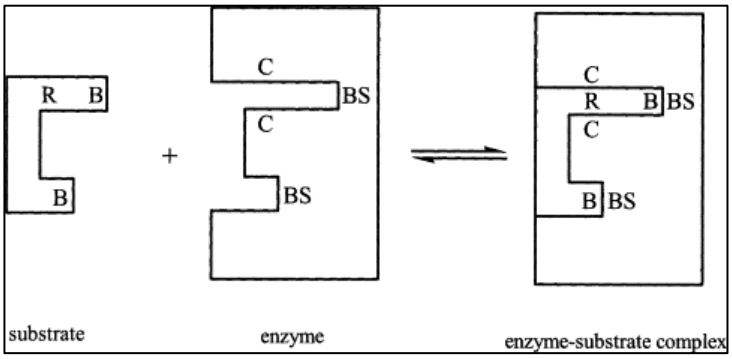

Figure 6.9: Lock and Key Model

Host + Guest= Host Guest Complex; Host = Enzyme; Guest = Substrate

In this complex, the host molecule is bigger in size and also has hollow nature than the guest molecule. Such kinds of interactions are mainly known as the bio-recognition process. Eg., enzyme–inhibitor, antigen-antibody, and DNA- protein interaction.

A. Crown ether:

Crown ethers are the first class of artificial host cyclic compounds which consist of ring groups containing ether (R-O-R). The most common crown ethers are oligomers and ethylene oxide. E.g.; 18-crown-6

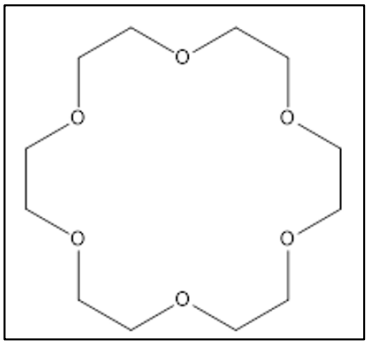

Figure 6.10: Structure Of 18-Crown-6

In the crown ether, the number used in the first is referred to as the number of atoms in the system and the last one says the number of oxygen atoms present in that system. Crown ethers are strongly bound to form complexes with metal ions based on the size of the atom. Crown ethers are soluble in nonpolar solvents because of their hydrophobic character which is mainly useful in phase transfer catalysis [29].

The modification of crown ethers, based on their number of the atom to giving various crown ethers by attaching some functional groups to the edges of the crown ethers, which enrich them with some interesting properties and made them ideal candidates for the fabrication of supramolecular polymers [30].

B. Cyclodextrin:

Cyclodextrin is a naturally occurring cyclic host molecule, which is a family of oligosaccharides of a macrocyclic ring of the glucose subunits joined by 1,4 glycidic bonds constituted by 6-8 glucopyranoside units. Which is prepared by the treatment of starch materials with enzymes. The CD has the molecular recognition capacity, and also enhanced their properties through chemical modification by introducing the –OH groups on the exterior rims. β-CD derivatives are widely used as greener textile auxiliaries for potential applications in the textile industry [31]. E.g.; β cyclodextrin

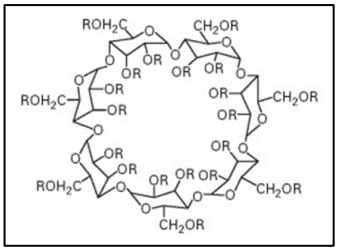

Figure 6.11: Structure Of B Cyclodextrin.

Cyclodextrin sponges are a microporous newly cross-linked 3D network of cyclodextrin that was designed as novel delivery for the lipophilic or hydrophilic active agents. Cyclodextrin's hydrophobic outer cavity and hydrophilic inner cavity enable their ability of novel delivery. Cyclodextrin possesses various applications like they are versatile absorbent for volatile organic compounds abatement [32].

C. Polyamine:

Replacing an oxygen atom in the crown ethers by nitrogen atom-induced cyclic hosts are called macrocyclic polyamines, many synthetic polyamines feature NCH_2CH_2N linkages which contain more than two amino groups most of the alkyl polyamines are natural and some of them are synthesized by the laboratory. Several synthetic polyamines are used in the chemical industry and the research laboratory. They are mainly used as additives to motor oil and as co-reactants (cold hardeners) with epoxy resins. E.g.; Cyclen

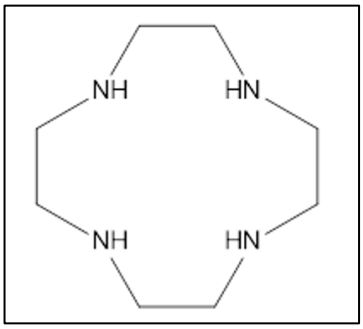

Figure 6.12: Structure Of Cyclen

Polyamines are possible therapeutic agents in biological disorders such as cancer and parasite diseases. They also act as ion–exchange blockers or vectors in gene delivery.

D. Calixarene:

Calixarenes are made from phenol units, which are attached by methylene bridges known as calixarene, and can have different cavity sizes. Each of these has conformation isomers, and the phenolic hydroxyl group is constantly modified. This type of character possesses to made calixarene derivatives with various structural modifications.

This isomeric host has different selectivity in metal ion inclusion in the upper cavity and the lower cavity. The number of phenol inclusion in the calixarene alters the guest molecule size appropriate for effective inclusion.

Calixarenes has attention in the treatment of cancer, it is mainly useful in delivery systems because of its biocompatibility and non-cytotoxicity [33]. And also used in the field of host-guest chemistry and sensing of metal ions.

E. Cyclophane:

Cyclophanes are three-dimensional cyclic hosts made from the linking of aromatic rings between aliphatic units. Cyclophanes are classified as follows, [n] orthocyclophane,[n] metacyclophane,[n] paracyclophane.

The aromatic ring in the cyclophane system is maybe either heterocyclic or carbocyclic. Cyclophane core unit is in many biologically active molecules and is also used in pharmaceutical catalysis [34]. Figure; [6.12**]** paracyclophane

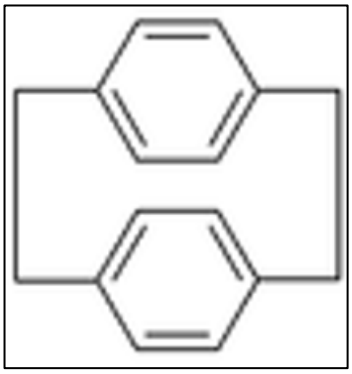

Figure 6.13: Structure of Paracyclophane

The small cyclophanes are the model for the fundamental studies of strain and aromaticity. The short bridges in cyclophanes give free rotations of the ring, and this takes place to thermodynamically disfavoured rotation to each other. This is not in open-chain molecules. This cyclic core was twisted because of the strain on the whole system. This kind of strain only acquires natural cyclophanes, not artificial ones [35].

6.5 Molecular Tree:

A. Dendrimers:

Dendrimers are tree-like macromolecules, which consist of core, branching, and surface units. It is in nanometres to tens of nanometers in size, which is larger than a typically closed molecule (diameter,0.7nm) and smaller than a microsphere(diamatere0.1-10μm). In dendrimers, if we increase the branching units, which will increase the dendrimer generation from zeroth to first, second, and so on.

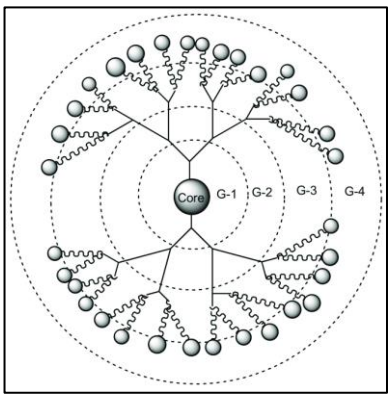

Figure 6.14: Schematic Representation of A Dendrimer Structure [36].

Dendrimers have been widely studied for their potential applications in drug delivery [63], where they can be utilized to transport therapeutic agents directly to diseased cells or tissues. In addition, they have been investigated for their use as imaging agents for diagnosing diseases, as well as in tissue engineering and regenerative medicine, where they can be utilized to deliver growth factors to promote tissue regeneration. Dendrimers have also shown promise as carriers for gene therapy, where they can be used to deliver genes to specific cells, thereby modifying their functions. These and other applications highlight the versatility and potential of dendrimers in the fields of medicine and biology [37].

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ISBN: 978-93-94570-79-5

7. Recent Updates on Methyl Fluorosulfonyl Difluoroacetate Mediated Synthesis of Trifluoromethylated Molecules

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Abstract:

Organofluorine compounds have been widely used in pharmaceutical and agrochemical field. Triflurorомethylated compounds particularly show extensive applications in field of life sciences and material sciences. The trifluoromethyl group is used in biologically important molecules due to its enhanced anti-oxidant ability, improved metabolic stability and increased lipophilicity of the compound. MFSI, which was first reported by Chen and Wu in 1989 is used as an efficient, safe, resistant to moisture absorption and economical reagent for trifluoromethylation in synthesizing variety of trifluoromethyl containing heterocycles having great significance in drugs and many bioactive molecules. Contrary to its widespread applications, this reagent has not been exploited much and thus a comprehensive review of MFSI mediated trifluoromethylations is reported here, which we believe will provide further exposure to the chemists about this underutilized reagent.

Keywords:

7.1 Introduction:

In current years, a huge variety of applications[1-5] have been steadily developed in the sphere of organofluorine chemistry. Amongst the fluorinated compounds, trifluoromethyl-substituted molecules have created significant interest. The trifluoromethyl group is most attractive moiety and mostly used in pharmaceutical[6-8]and agrochemical industries.[9-13]

There are many CF_3 containing drugs available in market [14-21] (Figure 7.1). It is used in biological applications because of its high electron withdrawing ability, increased anti-oxidant ability, enhanced metabolic stability and increased lipophilicity of the target molecule.[22-25] The trifluoromethyl group can promote the drug efficacy by enhancing electrostatic interactions with targets, elevate cellular permeability and amplify the power towards oxidative metabolism of drug.[5,26,27]

Trifluoromethyl group is also widely used in dye industries in which trifluoromethylation of chromophore prevents from fading when exposed to light.[28,29] Trifluoromethylated polymers have upgraded chemical and thermal stability, better solubility and improved mechanical properties.[30] It has applications in developing batteries and cells.[31-33]

Ritter et al[34] proposed that if more complex trifluoromethylated compound is needed it is easier to start with simple molecule containing trifluoromethyl moiety and then build structure around it. Nagib et al[35] proposed the direct trifluoromethylation of arenes and heteroarenes by C-H activation through photo redox catalysis.

There are various reagents, which are used for trifluoromethylation. Rupert−Prakash reagent, CF_3SiMe_3 (trifluoromethyl) trimethylsilane is used for trifluoromethylation of heteroarenes and highly electron deficient arenes.[36] For trifluoromethylation of arenes and heteroarenes, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) is also used[35].

Moreover, $PhSOCF_3$ and $PhSO_2CF_3$ are used as a source of trifluoromethyl anions.[37-39] Alkynyl triflones[40,41], Togni's reagent[42] and many more reagents (Sulfides[43,44], Sulfoximines[45], Sulfonium Salts[46], Sulfinate Salts, Sulfonyl Halides[47-49]) were evolved for the trifluoromethylation in different substrates.[50]

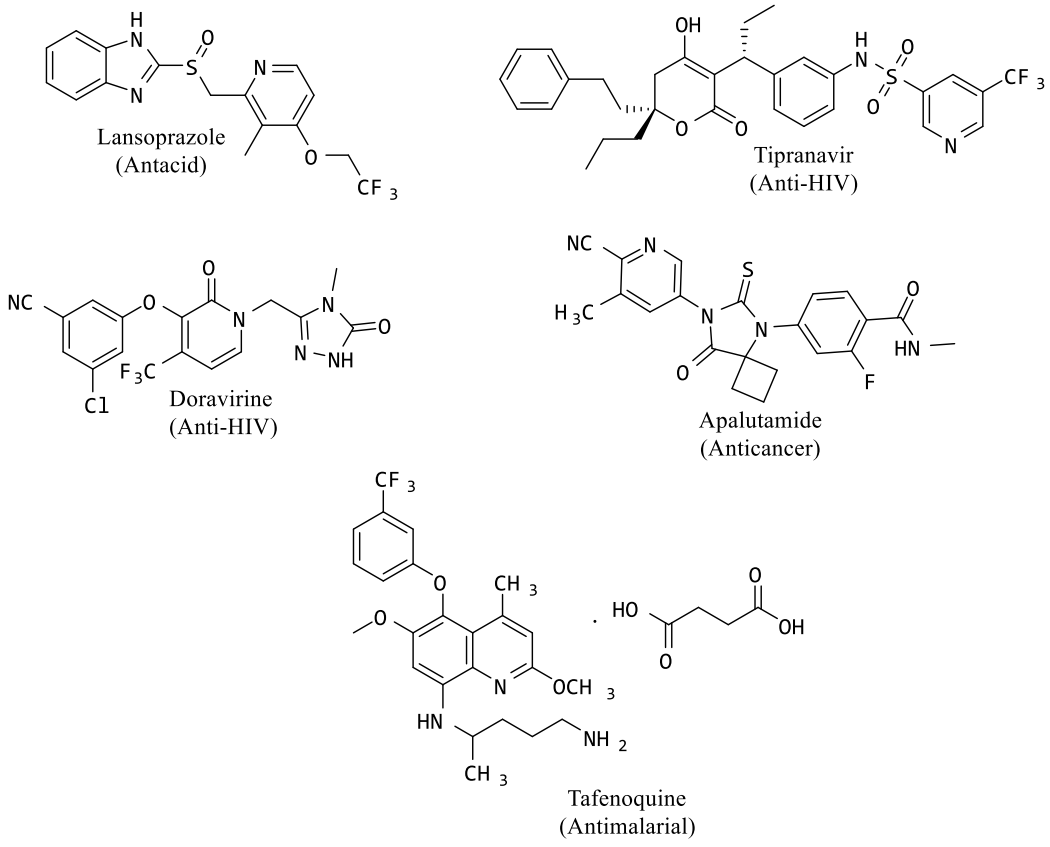


Figure 7.1: CF_3 Containing Drugs

In this chapter, we particularly emphasize on economical and widely used methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSDA or MFSI), reagent. We have focused here on summarizing the literature reports involving the synthetic transformations brought about by MFSI in the last one decade.

7.2 Discovery of trifluoromethylating reagent: Methyl fluorosulfonyldifluoroacetate (MFSI):

Methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSI) reagent also known as Chen's reagent and was first reported by Chen and Wu in 1989[51] as a trifluoromethylating reagent. It has CAS No. 680-15-9 and b.p. 116–118°C.

It is comparatively economical, safe and convenient to use and resistant to moisture absorption.[52] A number of methods have been developed for the trifluoromethylation of different substrates.[53-56] MFSI is used for the synthesis of a wide variety of trifluoromethyl containing heterocycles that is of greater significance in synthesizing drugs and making many bioactive molecules. MFSI is commercially to be held and purchased from the chemical industries but it can also be prepared within the laboratories by using diverse techniques. For example, MFSI can be synthesised *via* reacting 3,3,4,4-tetrafluoro[1,2]oxathiethane-2,2-dioxide with sodium methoxide[57], in two steps from difluoro(fluorosulfonyl)acetic acid[58] or by the addition of methanol to trimethylsilyl fluorosulfonyldifluoroacetate.[59] Finally, the reaction of tetrafluoroethylene with sulfur trioxide gives a useful cyclic compound tetrafluoroethylene β-sulfone.[60,61] Successive reaction with methanol affords MFSI in 85% yield.[62]

MFSI displays the nucleophilic trifluoromethylation reaction and used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides for diverse copper mediated reactions. Chen and Wu showed the order of reactivity of halide to be RI>RBr>RCl where the bromo derivatives being more useful and the chloro derivatives is quite slow. Presence of CuI is crucial for the success of reaction. KI can also be used as an alternative of CuI.[9]

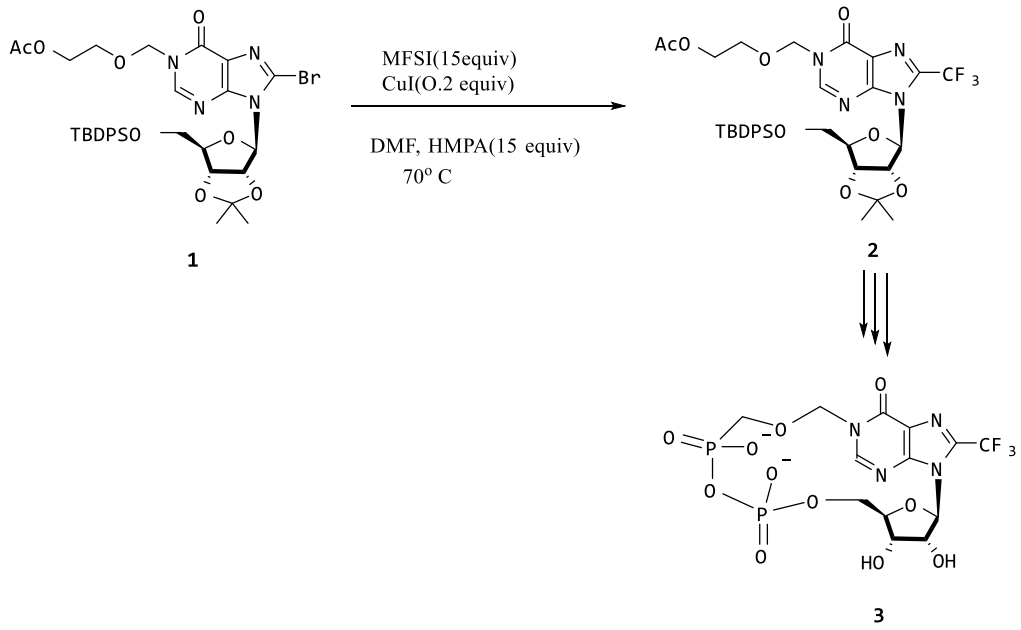
Scope of Methyl Fluorosulfonyldifluoroacetate in Trifluoromethylation reactions

MFSI has been reported in various organic transformations from last so many years and a summary of those reports is being summarised here starting from the year 2010. The triazolylpyridine system are not found in nature in free form but its trifluoromethylated derivatives shows many biological properties like insecticides, antibacterial activity[63], anti-proliferative activity against tumour[64], more cell permeability[65] and many more biological activity[66-70]. Dong et al[71] reported the synthesis of 8- CF_3-cIDPRE **3** (N1 - [(5"-O-Phosphorylethoxy) methyl] -5'-O-phosphoryl -8 - tri-fluoromethylinosine 5", 5"-Cyclic pyrophosphates.

8-CF_3-cIDPRE is agonist and mimics the cADPR (cyclic adenosine 5'-diphosphoribose). 8-CF_3-cIDPRE penetrate the plasma membrane and releases Ca^{2+} which is required in variety of cellular process. Fluorine has strong electron withdrawing property and ability to form hydrogen bonding, it shows metabolic stability and membrane permeability. In this, there is introduction of trifluoromethyl group at 8- position of purine nucleoside, which is important intermediate for synthesis of 8- CF_3-cIDPRE **3**.

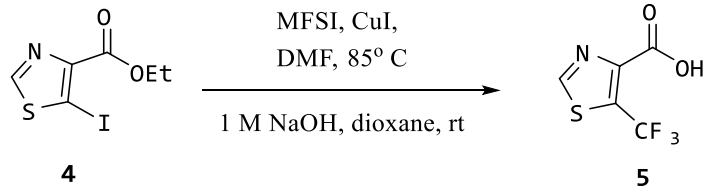
Huang et al[72] also reported the synthesis of trifluoromethylated analogues of cADPR using MFSI. In this, MFSI is used for trifluoromethylation of bromo derivative *viz N*1-[(5``-

Acetoxyethoxy) methyl]-5`- O-TBDPS-2`,3`-O-isopropylidene-8-bromoinosine **1** in the presence of CuI in DMF, HMPA and reaction was stirred for 12hrs at 70° C to form *N*1-[(5``-Acetoxyethoxy) methyl]-5`-O-TBDPS-2`,3`-O-isopropylidene-8-trifluoromethyl inosine **2,** which is an important intermediate and further undergo reaction for synthesis of 8-CF_3-cIDPRE **3** (Scheme 7.1).



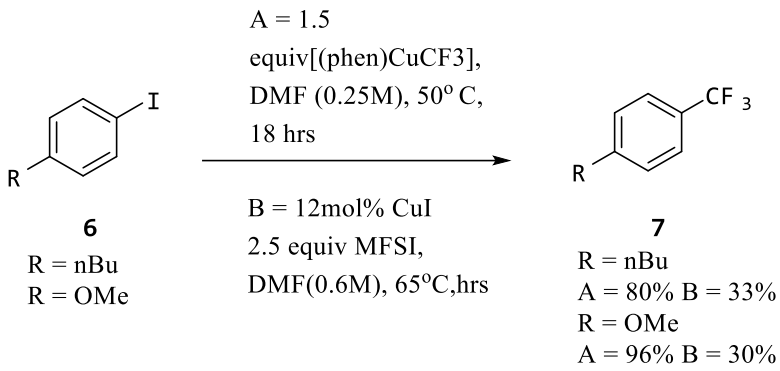
Scheme 7.1: Trifluoromethylation of cyclic adenosine diphosphate ribose.

Hodgetss and his coworker[73] reported that MFSI is used to introduce trifluoromethyl group in thiazole ring **4** to obtain trifluoromethylated product **5**, which is a bioactive molecule. (Scheme 7.2)



Scheme 7.2: Trifluoromethylation of thiazole ring

Boechat et al[74] reported the synthesis of trifluoromethylated derivatives of 1*H*-1,2,4-triazol-3-yl benzenesulfonamide to develop new antimalarial lead compounds with 50%-62% yield. Morimoto et al[75] reported the use of MFSI in copper iodide mediated reactions for the trifluoromethylation of aryl iodides **6** and bromides. The yields of trifluoromethylarene products **7**, which was determined by ^{19}F NMR analysis using 4-$CF_3OC_6H_4OMe$ as internal standard, were much higher (above 80%) under the reaction conditions with 1.5 equiv phen-ligated 1 than with catalytic CuI and 2.5 equiv. $FSO_2CF_2CO_2Me$. (Scheme 7.3).

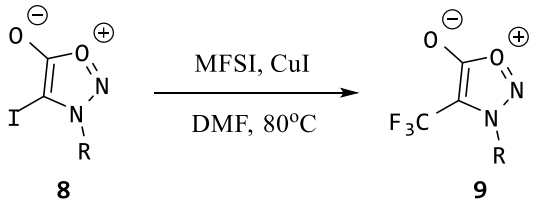


Schemes 7.3: Trifluoromethylation of aryl iodides

Foster et al[76] designed more efficient policy for trifluoromethylation of pyrazoles using MFSI. He reported the trifluoromethylation of 4-iodosyndones **8** to synthesize bioactive 5-trifluoromethylpyrazoles **9** with good yield in the presence of MFSI, CuI and DMF, which was further used as an intermediate to synthesize herbicide fluazolate.

He suggested that when the reaction was accomplished with 4-iodo-*N*-phenylsyndone, the yield of trifluoromethylated product is 79%. When electron-donating substituent like p-methoxyphenyl group is present, the obtained yield is similar (80%).

When the reaction was executed with electron- withdrawing like p-nitro phenyl group, the time taken for trifluoromethylation was increased with comparatively low yield (55%). Non-aromatic group on nitrogen were also accepted under same reaction conditions. (Scheme 7.4).



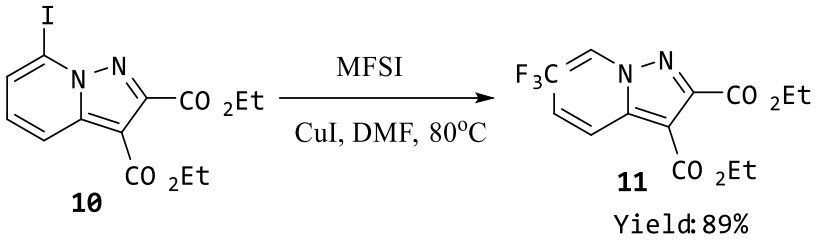
R= Ph

R= Me, Bn, Ph, 4-OMeC_6H_4, 4-$NO_2C_6H_4$

Scheme 7.4: Trifluoromethylation of 4-iodosyndones.

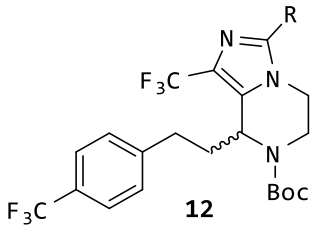
Chong and Bullock[77,79] synthesized 7-Trifluoromethylpyrazolo[1,5-*a*]-pyridinedicarboxylate **11** which is an important intermediate for a potential drug candidate.

MFSI reacted with iodide derivative of pyrazolo[1,5-*a*] pyridine dicarboxylates **10** in the presence of CuI in DMF at 80° C to give trifluoromethylated pyrazolopyridinecarboxylate **11** with 89% yield. (Scheme 7.5)



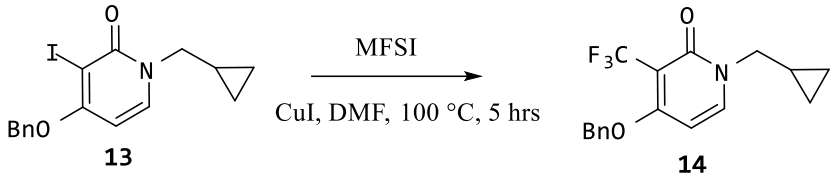
Scheme 7.5: Trifluoromethylation of iodo derivative of pyrazolopyridine dicarboxylates

Sifferlen[79] et al has been reported the incorporation of trifluoromethyl moiety using MFSI in synthesis of bioactive intermediate **12** which was further used in synthesis of 5,6,7,8-tetrahydroimidazo[1,5-*a*] pyrazines which is an orexin receptor antagonist.



Cid et al[80] discovered a novel bioactive derivative of phenylpiperidine substituted pyridones which act as an allosteric modulator of glutamate receptor.

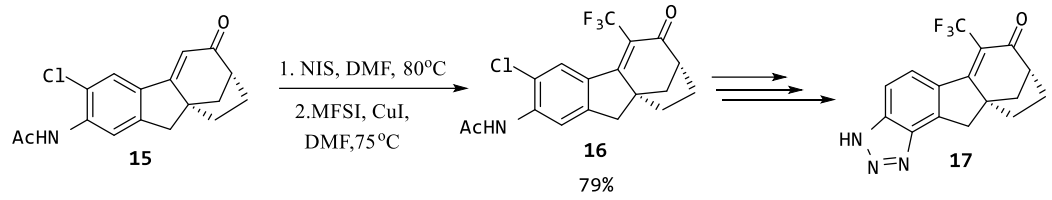
MFSI used for trifluoromethylation of 3-iodopyridones i.e., 4-Benzyloxy-1-cyclopropylmethyl-3-iodo-1*H*-pyridin-2-one **13** to synthesize 3-trifluoromethylpyridone i.e., 4-Benzylox-1-cyclopropylmethyl-3-trifluoromethyl-1*H*-pyridin-2-one **14** which is a key intermediate to form the bioactive molecules. (Scheme 6).



Scheme 6. Trifluoromethylation of 3-iodopyridones

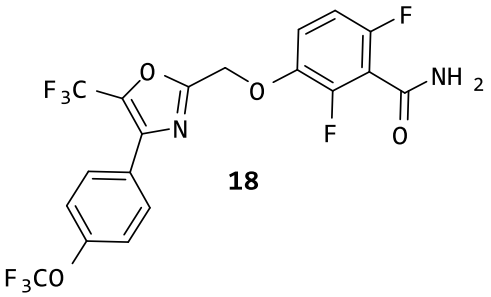
Madess et al[81] discovered derivatives of tetrahydrofluoroene which act as beta agonist for estrogen receptors used in therapy of postmenopausal women for treating the symptoms related with decreased oestrogen level.

Compound **15** undergo iodination followed by trifluoromethylation using MFSI, CuI in DMF to synthesize the compound **16** with high yield which on further transformation give desirable bioactive molecule i.e., tetrahydrofluoroene **17** (Schemes 7.7)

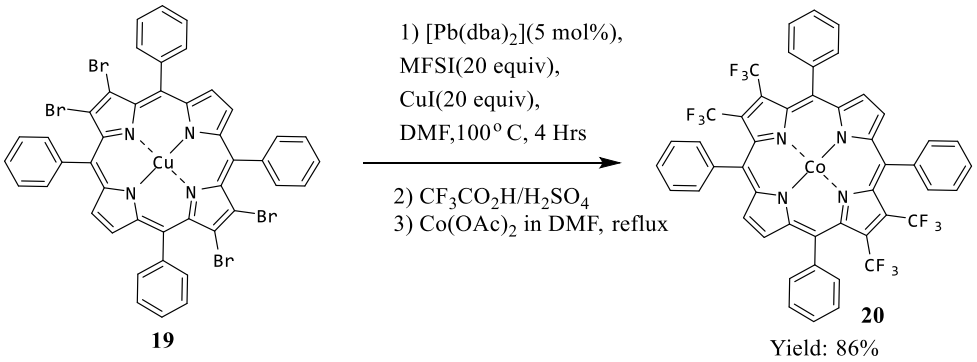


Schemes 7.7: Trifluoromethylation of intermediate in the synthesis of tetrahydrofluoroene

Stokes and coworkers[82] suggested the synthesis of bioactive intermediate **18** by the trifluoromethylation of its oxazolyl iodide intermediate using MFSI.



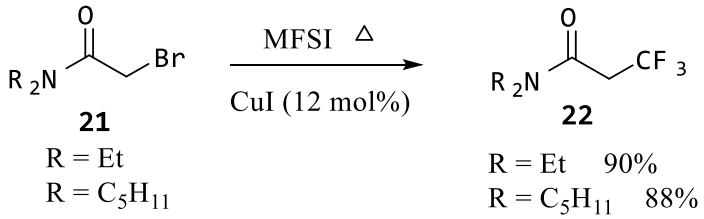
Zhao et al[83] reported that cobalt (II) β-tetrakis- (trifluoromethyl)-meso-tetraphenylporphyrin ($CoTPP(CF_3)_4$) exhibited excellent catalytic selectivity as well as conversion of benzylamines to imines through oxidative coupling with the product yield of 52–89% . He prepared $[Co\{TPP(CF_3)_4\}]$ **19** by the trifluoromethylation of $[Cu(TPPBr_4)]$ **20** in good yield using MFSI and subsequent insertion of Co^{II}. (Schemes 8)



Schemes 7.8: Synthesis of $[Co\{TPP(CF_3)_4\}]$

Zhang et al [84] reported the wide use of MFSI for various copper mediated reactions in a review published in 2014. MFSI was used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides and trifluoromethylthiolation of aryl halides. Alonso et al [85] reported in their review that MFSI was used as trifluoromethylation of various substrate in presence of CuI.

(a) trifluoromethylation of bromomethyl amide **21** to synthesize parallel trifluoromethyl derivatives **22** with excellent yield. (Schemes 7.9)

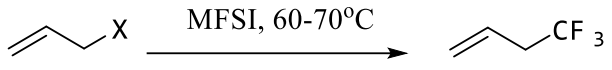


21
R = Et
R = C_5H_{11}

22
R = Et 90%
R = C_5H_{11} 88%

Schemes 7.9: Trifluoromethylation of bromomethyl amide

(b) trifluoromethylation of allyl halide **23** to give trifluoromethylated derivative **24** in high yield. (Schemes 7.10)

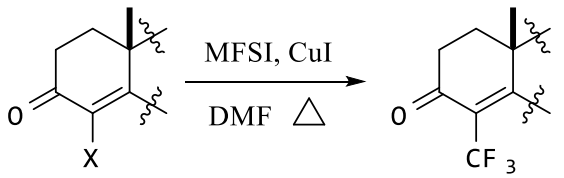


23
X = Br, I

24
Yield :68-70%

Schemes 7.10: Trifluoromethylation of allyl halide

(c) trifluoromethylation of iodo- steroidal molecule **25** to give trifluoromethyl steroids **26** with good yield. Trifluoromethylated flavonoid and antitumor trifluoromethylated flavonoid derivatives were also prepared using this methodology[86] (Schemes 11).



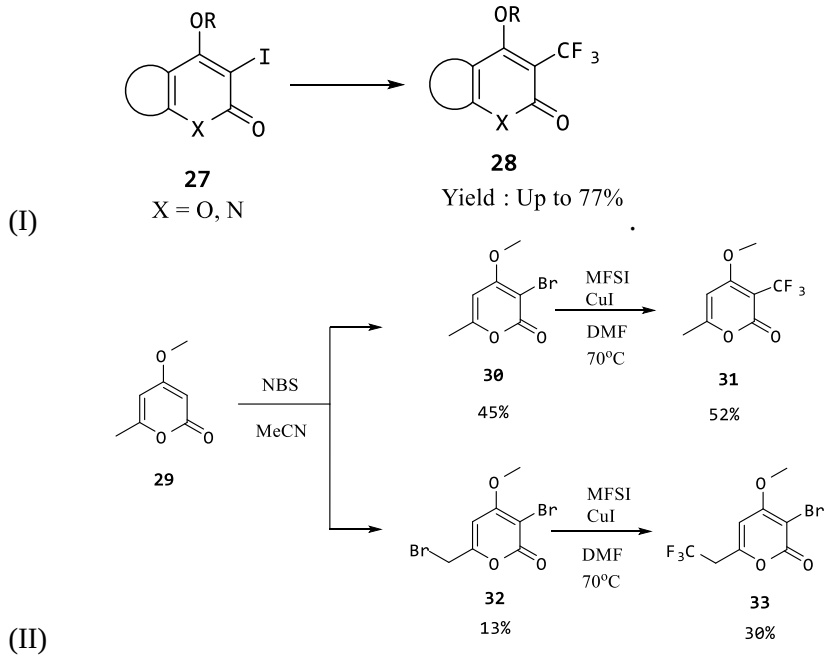
25
X = Br, I

26
Yield : 70-91%

Schemes 7.11: Trifluoromethylation of iodo-steroids

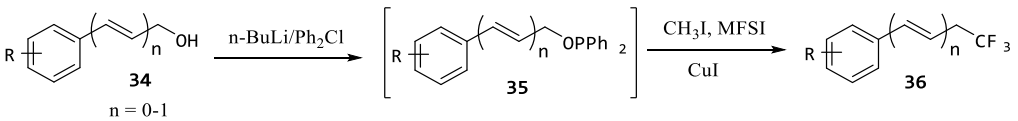
Clarke et al[87] developed the trifuoromethylated series of 4-alkoxy -2-pyrones, pyridones and quinolone using MFSI. These compounds have special biological properties.

They reported that when 1.2 equivalents of MFSI with 1.2 equivalents of copper iodide in DMF were used, good yields were obtained. As shown in scheme 7.12 (I), trifluoromethylation of iodinated starting material **27** gave **28**.



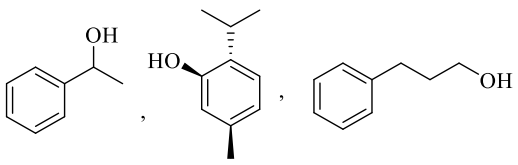
Scheme 7.12: Trifluoromethylation of pyrones, pyridones and quinolones

whereas mono **30** and di brominated **32** products were obtained by the bromination of 4-methoxy -6-methyl -2- pyrones **29**. The bromo derivative further underwent trifluoromethylation to yield product **31** and **33**. [Scheme 7.12(II)]. Li et al[88] suggested an efficient method for the trifluoromethylation of benzyl alcohol or allyl alcohol **34** to obtain various trifluoromethylated compound **36**. Derivatives of **35** were formed by reacting compound **34** (benzyl or allyl alcohol) with *n*-BuLi, Ph_2Cl. Intermediate **35** undergo trifluoromethylation in the presence of methyl iodide and MFSI in the presence of copper iodide when stirred at 80° for 15 hrs to obtain compound **36**. A variety of compounds were prepared from this method. (Scheme 7.13). Electronic density of alcohols affects the yield of reactions. Electron-donating groups such as methoxy and methyl group gave good yield whereas halide-substituted alcohols gave the moderate yield and low yields were observed with secondary alcohols because of steric hindrance.



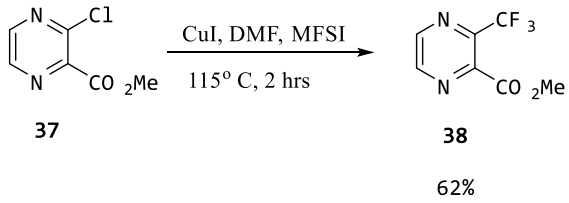
R= p-CF_3, -OMe, p-Me, p-Br, o-Cl, p-Cl,

n= 0,1



Scheme 7.13: Trifluoromethylation of benzyl alcohol or allyl alcohol

Oda et al[89] suggested the application of MFSI for the trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate **37** in the presence of CuI in DMF, toluene and converted into methyl 3-(trifluoromethyl) pyrazine-2-carboxylate **38** which is a key intermediate to synthesize pyraziflumid and many other derivatives. Pyraziflumid shows excellent fungicidal activity partiparticularly against gray mold, Brown rust and powdery mildew. (Scheme 7.14). Sharma et al[90] described the successful nucleophilic trifluoromethylation of differently substituted α-iodinated oxoketene dithioacetals **39** *via* using MFSI in presence of CuI and DMF which provided α-trifuoromethylated oxoketene dithioacetals **40** with good to outstanding yield. Those synthons were further utilized for the synthesis of biologically important diversely substituted trifluoromethylated pyrazoles. (Scheme 7.15).

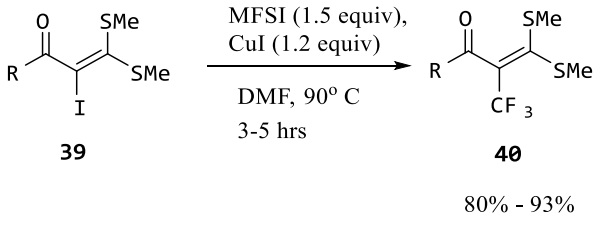


37 **38**

62%

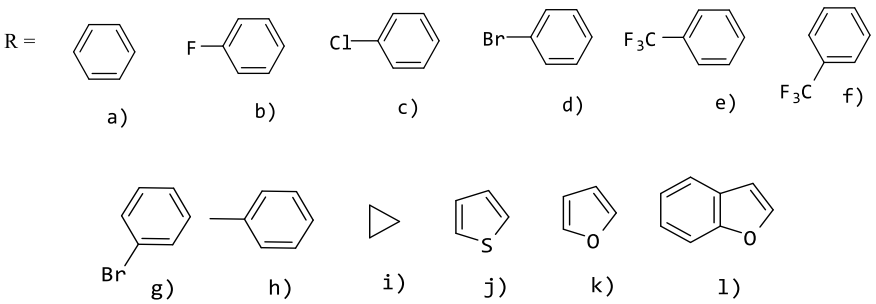
Scheme 7.14. Trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate

Electron withdrawing group present at the *m*- and *p*- position in the α-iodinated oxoketene dithioacetals (b-g) contributed good yield of α-trifuoromethylated oxoketene dithioacetals. Though, electron releasing group in substrarte with *p*-CH_3 gave decent yield. On the other hand, with *o*-CH_3 in α-iodo oxoketene dithioacetals at -*o* or -*p* positions were confirmed unproductive due to incapability towards nucleophilic substitution. High yield was obtained with cyclopropyl substituted substrate. Heteroaromatic substituted α-iodo oxoketene dithioacetals (j – l) produced good to excellent yield.



39 **40**

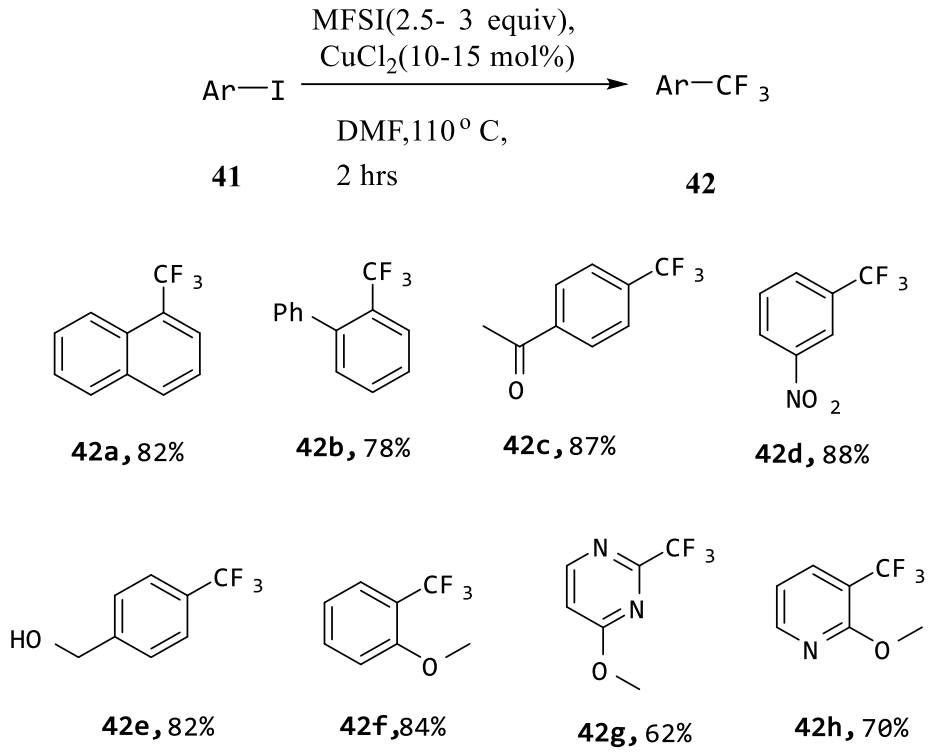
80% - 93%



Scheme 7.15: Trifluoromethylation α - iodinated oxoketene dithioacetals

Zhao and coworkers[91] proposed the nucleophilic trifluoromethylation of various aryl and heteroaryl iodides **4** using MFSI, and carried in the presence of $CuCl_2$ with excellent yield. In their review, they started with the trifluoromethylation of 1- iodonapthalene.

After the successful trifluoromethylation of iodonapthalene, they further synthesized a number of structurally diverse trifluoromethylated (hetero) aryl derivatives **42(a-h)** in the presence of $CuCl_2$ as catalyst at 110°C when stirred for 2 hrs. Effect of others salts of Cu on the yield, were also studied. (Scheme 7.16)

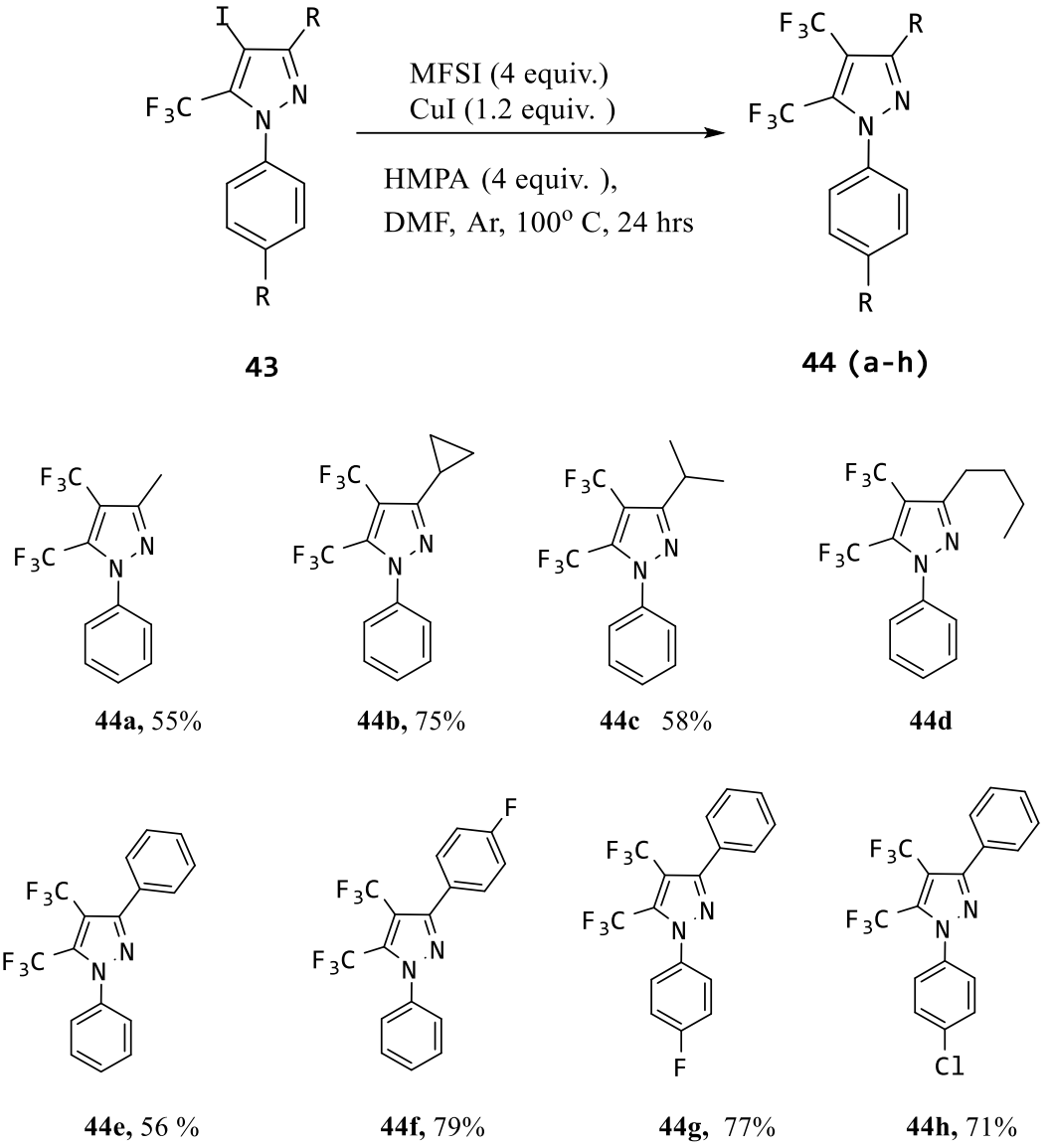


Scheme 7.16: Trifluoromethylation of aryl and heteroaryl iodides

Junges et al[92] reported the trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles **43** in CuI, MFSI and HMPA under anhydrous DMF for 24 hrs at 80°C to obtained a chain of 1-aryl-3-alkyl(aryl)-4,5-bis(trifluoromethyl)-1*H*-pyrazoles **44(a-h)** in good yield which showcased the insecticidal property. (Scheme 7.17).

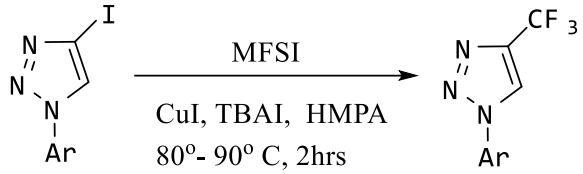
Recently Xie and Hu[93] posted an article on huge application of MFSI in area of organic chemistry wherein they mentioned about the discovery, applications and reactions of Chen's reagent.

MFSI used normally to acquired trifluoro methylated and difluoro alkylated compounds. Over a decade, a substantial amount of research has been performed to use MFSI as a difluorocarbene precursor and radical difluoro alkylating agent in presence of visible light.



Scheme 7.17: Trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles

Panja et al[94-98] reported the common method for trifluoromethylation of 1-aryl-4-iodo-1*H*-1, 2, 3-triazole **45** which were carried out in TBAI (Tetrabutylammonium iodide), CuI and MFSI, stirred at 80-90°C for 2 hrs. to obtain 1-aryl-4-(trifluoromethyl)-1*H*-1, 2, 3- triazole **46** in moderate yield. (Scheme 7.18). The reaction was not dependent on the electron density of substituent in aryl ring and it was chemoselective when carried out with bromo and chloro derivatives. Consequently, this is a useful method for synthesis of many 1-aryl-4-trifluoromethyltriazoles[99-101] from the respective iodo-precursor. TBAI act as useful reagent as it is solubilizing the Cu and make it available for the reaction.



45 **46**

Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_{44}-F-C_6H_4, 4-CH_3-C_6H_4, C_6H_5, 3,5-$(CF_3)_2$-C_6H_3
4-$COCH_3$-C_6H_4, 4-$CO_2CH_2CH_3$-C_6H_4, 4-CN-C_6H_4, 4-OCF_3-C_6H_4

Scheme 7.18: Trifluoromethylation of 1- aryl 4-iodo-1, 2, 3-triazoles

7.3 Conclusion:

Since MFSI was discovered in 1989 as a trifluoromethlating reagent, it has found wide application for the trifluoromethylation of aromatic, herteroaromatic and alkenic compounds. A huge number of CF_3 containing biologically important and structurally diverse molecules have been synthesized by using this excellent reagent. Instead, it shows significant advantages over other trifluoromethlating reagent like CF_3CO_2Na and Ruppert Prakash reagent ($TMSCF_3$). Ruppert Prakash reagent is widely used as a trifluromethlating reagent but it is very expensive. MFSI reagent is commercially available, pretty cheaper and persuadable for trifluoromethylation of halogenated compounds. Scientists are doing more research on this reagent in organic synthesis. However, it has been somewhat underutilised by chemical community. We demand for extra attention to this crucial reagent. This reagent will continue to find more uses in the field of life sciences and material science.

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List of Abbreviations:

CF_3 - Trifluoromethyl

CF_3SiMe_3 - Ruppert-Prakash reagent

CF_3SO_2Cl - Trifluoromethane sulfonyl

$PhSOCF_3$ - Trifluoromethyl sulfoxide

$PhSO_2CF_3$ - Trifluoromethyl sulfone

MFSI - Methyl fluorosulfonyldifluoroacetate

CuI - Copper iodide

KI - Potassium iodide

DMF - Dimethylformamide

HMPA - Hexamethylphosphoramide

NaOH - Sodium Hydroxide

NIS - Nickel sulfide

$[Pb(dba)_2]$ - Bis(dibenzylideneacetone) Palladium

CF_3CO_2H - Trifluoroacetic acid

$Co(OAc)_2$ - Cobalt(II) acetate

NBS - N- Bromosuccinimide

MeCN - Methyl cyanide

n-BuLi - n Butyllithium

CF_3CO_2Na - Sodium trifluoroacetate

ISBN: 978-93-94570-79-5

8. Medicinal Chemistry

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Abstract:

Medicinal chemistry involves designing and developing of pharmaceutical drugs. Medicinal chemistry deals with the identification, synthesis, and development of medicinally active compounds. Quantitative structure –activity relationship (QSAR) and quantitative structure property relationship (QSPR) studies are important in silico methods in rational drug design. The goal of this medicinal chemistry is to produce pharmacologically active drugs. QSAR and QSPR Methods are having the goal to optimize the existing leads in order to improve their medicinal property and physicochemical properties. These methods also gives the information about biological activities of untested and yet unavailable compounds. QSAR study is good prediction tool for investigating drug activity and binding capacity on specific receptors.

Keywords: *QSAR, SAR, Drug discovery strategies, conventional synthesis, combinatorial synthesis. And computer aided drug design.*

8.1 Introduction:

Medicinal or pharmaceutical chemistry is the branch of chemistry involved basically with designing and developing pharmaceutical drugs. It involves the identification, synthesis and development of new chemical entities suitable for therapeutic purpose. It also includes the study of existing drugs, their biological properties and their quantitative structure-activity relationships. It concerns the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at the molecular level. It also includes study, identification, and synthesis of the metabolic product of both synthetic and naturally occurring drugs and related compounds.

Medicinal chemistry is interdisciplinary science which covers the biochemistry, pharmacology, molecular biology, immunology, toxicology, pharmacology on one side. on other side it covers chemistry based disciplines such as physical chemistry, crystallography, spectroscopy, and computer based information technologies.

It is the branch of chemistry concerned with the design, development and synthesis of pharmaceutical drugs. Medicinal chemistry is also involves the designing and developing of pharmaceutical drugs. It also includes the study of existing drugs, their biological properties, and their Quantitative structural activity relationship (QSAR).

Medicinal chemistry involves the isolation, characterization, synthesis, mechanism of action of compounds that can be used as medicines in the treatment of diseases. It is the linkage between structure and biological activity of compounds.

Medicinal chemistry covers three critical steps.

A. Discovery step
B. Optimization step
C. Development step

A. Discovery step:

It deals with the therapeutic target that is enzyme, transport group, receptor etc. and the identification and production of new active substances interacting with the selected target. Such compounds are usually called lead compounds. The sources of Lead compounds are

- From natural products.
- Chemical libraries.
- Computational medicinal chemistry.
- Green chemistry

Importance of lead molecules:

- Lead compounds are having potential to treat particular disease.
- It is chemical compound or natural product which is having biological activity against disease.
- Lead identification and optimization plays an important role in drug discovery process.

B. Optimization step:

It deals with improvement of the lead structure. The optimization process takes primarily into account the increase in potency, selectivity and toxicity. Its characteristics provide analysis of structural activity relationships to produce understanding of the molecular mode of action such as pharmacokinetic parameters that is absorption, distribution, oral bioavailability of lead compounds.

C. Development step:

This step involves the identification of candidates, synthesis, characterization, validation, screening, and assays for therapeutic efficacy. Once compound has shown its significances in these investigations, it will initiate the process of drug development earlier to clinical trials. It involves the improvement of pharmacokinetic properties and fine tuning of

pharmaceutic properties of the active substances in order to render them suitable for clinical use. This chemical formulation process consist in the preparation of better absorbed compounds, of sustained release formulations, of water soluble derivatives or in the elimination properties related to patience compliance (causticity, irritation, painful injections, undesirable organoleptic properties).

Structural activity relationship: The analysis of biological effects of chemical upon its molecular structure. Molecular structure and biological activity are correlated by observing the results of systemic structural modifications**.** Structural activity relationship is qualitative not quantitative relationship.

8.2 QSAR:

It is method that gives the information about activity, reactivity, specificity, properties and characterization of an unknown set of molecules which is based upon the analysis of structures of molecules to their respective activity and property. It is the mathematical relationship between the biological activity and physicochemical parameters. QSAR try to identify and quantify the physicochemical properties of a drug and to check whether any of these properties has an effect on biological activity or not. Quantitative structure activity relationship (QSAR) is one of the widely used techniques in ligand based drug designing method.

A quantitative structure activity relationship related to quantitative chemical structure to a biological activity. QSAR plays an important role in drug discovery process because their application can save time and human resources. For the prediction of QSAR model several parameters are important. On One side some different statistical methods are used to check the linear and non linear behavior of data set. On another side selection techniques are used to reduce the model complexity. QSAR model can be useful in the discovery of new compounds with improved potency. The molecules which show interesting activity will be synthesized.

Table 8.1: Structural activity relationship v/s quantitative structure activity relationship.

Structural activity relationship	Quantitative structure activity relationship
Relationship between chemical or 3D of molecule and its biological activity.	Gives that idea that there is simple mathematical relationship between biological activity of drug and physicochemical properties.
It can help to insert new chemical groups into the biomedical compound and test the results.	QSAR attempt to finds consistent relationship between biological activity and molecular properties. So that these rules can be helped to evaluate the activity of new compounds.
It is done by X-rays and NMR techniques.	It is done by procedure known as linear regression analysis by the least square method**.**

Structural activity relationship	Quantitative structure activity relationship
Structure activity relationship is technique to find qualitative relationship between chemical structure and biological activity.	QSAR models are theoretical models that relate a quantitative measure of chemical structure to a biological property.

Importance of QSAR and drug design:

- To modify the chemical structure of the lead compound to retain the desirable biological activity while minimizing unwanted pharmacological, physical and chemical properties.
- QSAR studies can be applied to design, identify and synthesize new drugs or molecules to optimize absorption, distribution, metabolism, excretion and toxicity profile of identified molecules from various sources to cure the diseases.
- A major goal of Quantitative Structure Activity Relationship (QSAR) studies is to find a mathematical relationship between the activity under investigation, and one or more descriptive physicochemical parameters and descriptors related to the structure of the molecule.

QSAR parameters:

The parameters used in QSAR are measure of the potential contribution of its group to particular biological activity of the parent drugs.

- Lipophillic parameters: partition coefficient,
- Electronic parameters: Hammet constant, dipole moment.
- Steric parameters: Molar refractivity, verloop steric parameter.
- Polarizability parameters: molar volume, parachor.
- Miscellaneous parameters: Topological parameter.

Combinatorial chemistry:

The Combinatorial Chemistry is a scientific method in which a large number of chemical entities are synthesized by condensing a small number of chemical compounds together in all combinations defined by a small set of chemical reactions.

Combinatorial technologies produce new compounds in practically with unlimited number. Combinatorial chemistry is which collects the techniques for the synthesis of multiple compounds at same time. It is one of the important new technology developed by researchers in the pharmaceutical industry to reduce the time and cost associated with producing effective and competitive new drugs. It is technique by which large no. of different but structurally similar molecules are produced rapidly and submitted to pharmacological assay. This reaction uses same reaction conditions with same reaction vessels to produce large number of analogues.

8.3 Drug Discovery:

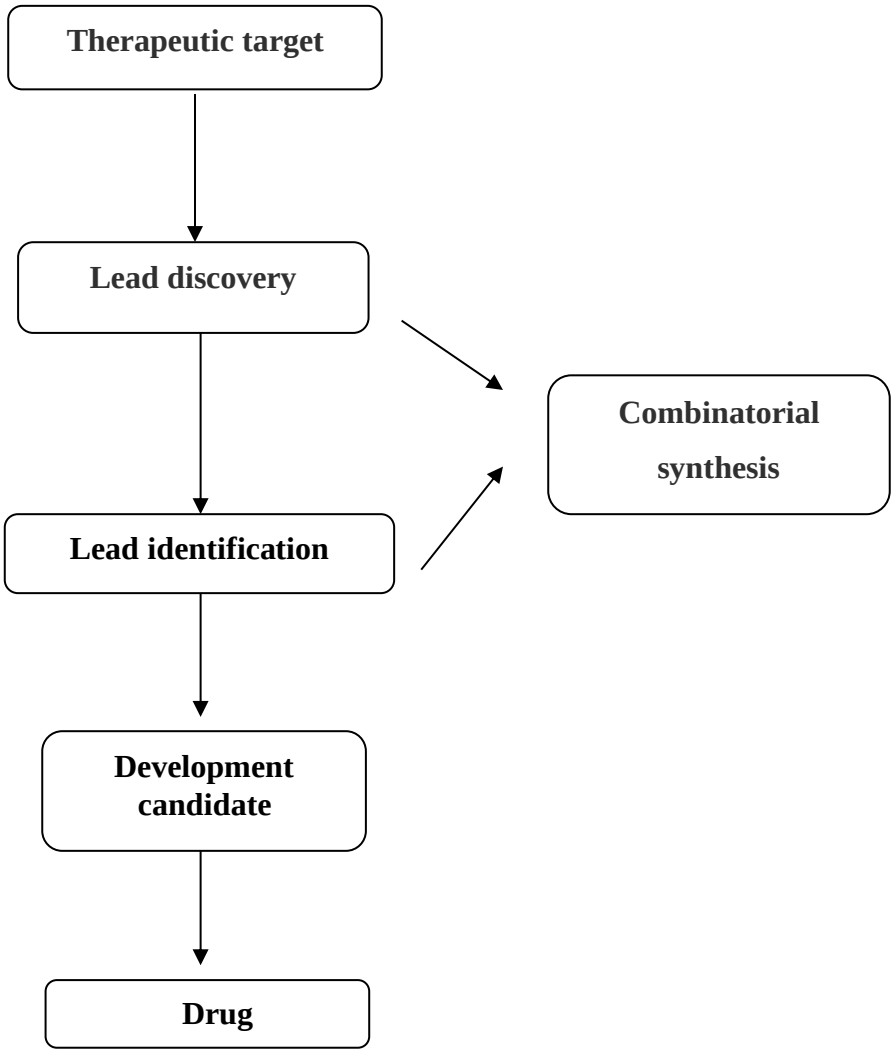

Figure 8.1: Drug Discovery

Strategies:

Conventional synthesis	Combinatorial synthesis
Only one compound can be synthesized at a time.	A range of compounds are synthesized at a time
Requires more time	Requires less time
More expensive	Less expensive
Slower lead generation	Faster lead generation

Role of combinatorial chemistry in drug discovery:

- By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.
- It provides immobilization strategies which allows high throughput and multiple parallel approaches to drug discovery.

Advantages of combinatorial chemistry:

- Mixed combinatorial synthesis produces chemical pool.
- More opportunities to produce lead compounds.
- From combinatorial chemistry the identification, isolation, purification and synthesis is very easy.
- Combinatorial approach can give million of compounds in same time as it will take to generate one compound by traditional method synthesis.

Techniques used in combinatorial chemistry:

A. Solid phase synthesis.

- Solid support method.
- Parallel synthesis.
  - a. Manual
  - b. Automated
- Mixed combinational synthesis.
- Mixed & split combinatorial synthesis.

B. Solution phase technique.

A. Solid phase synthesis:

In this synthesis, reactant is bound to insoluble resin bead, reagents are added to the solution in excess. The resulting products are isolated by using simple filtration which traps the bead while the excess reagent is washed.

Requirements:

a. Solid support.
b. Protective groups.
c. An anchor or linker.

Parallel synthesis:

It is process which is used to produce a single reaction product is produced in each reaction vessel. Parallel synthesis, individual peptides are synthesized in separate reaction vessels.

Mixed combinatorial synthesis.

- To use a standard synthetic method to produce a large range of different analogues where each reaction vessel or tube contains a mixture of products.
- The identities of the structures in each vessel are not known with certainty.
- By using mixed combinatorial synthesis lead molecule can be identified.
- It involved in the synthesizing large numbers of compounds quickly each mixture is tested for activity as the mixture.
- Inactive mixtures are stored in combinatorial libraries.
- Active mixtures are studied and are used to identify active component.

Mixed and split combinatorial synthesis:

The split –mix combinatorial synthesis is the rapid synthesis of larger libraries of compounds. On each polymer bead type of compound can be prepared. The split and combine approach is one of the classic strategies in combinatorial chemistry.

B. Solution phase technique:

It is the process in which allows reaction to accommodate solid support. It leads to the formation of mixture of product. This helps to find the development of new mixture.

Disadvantages:

- Difficult to remove unwanted material from reaction mixtures.
- Purification step is necessary at each step for each product.
- Other practical problems.

Table 8.2: Difference between solid phase and solution phase technique:

Sr. No	Parameter	Solid phase technique	Solution phase technique
1	Reagent	Excess	Optimum unless purification done.
2	Purification	Easy	Can be difficult.
3	Automation	Easy	Difficult.
4	Reaction	Suitable for new substance.	Suitable any organic reaction.
5	Scale-up	Expensive	Easy and inexpensive.
6	Dependence of reaction development	Mainly on -support -linkers	Time

Computer Aided Drug Design:

Drug design with the help of computer is very useful. It represents the computational methods and resources that are used to facilitate the drug design an discovery of new therapeutic solutions. It may be used at any of the following stages of drug discovery:

- Hit identification using virtual screening (structure- or ligand based design)
- Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc).
- Lead optimization, optimization of other pharmaceutical properties while maintaining affinity.

8.4 Conclusion:

In the medicinal chemistry, drugs are discovered by screening test of compounds, synthesized in laboratory or obtained from natural sources. Then Studies are conducted to get information on the mechanism of drugs action. QSAR is basically used to study the biological activities of drugs. It is also used to build models which can predict the physical and chemical properties and activities of organic compounds. A computational method give the information about drug structure with physical and biochemical properties of the drug and produces the efficacy of the drug. The computational methods used to model drug chemistry. It allows the observation in three –dimensions of a drug interaction with the protein or drug. Drug interaction with enzymes or receptors which leads to the structural features that are required in discovery and designing of new medicinally active drugs.

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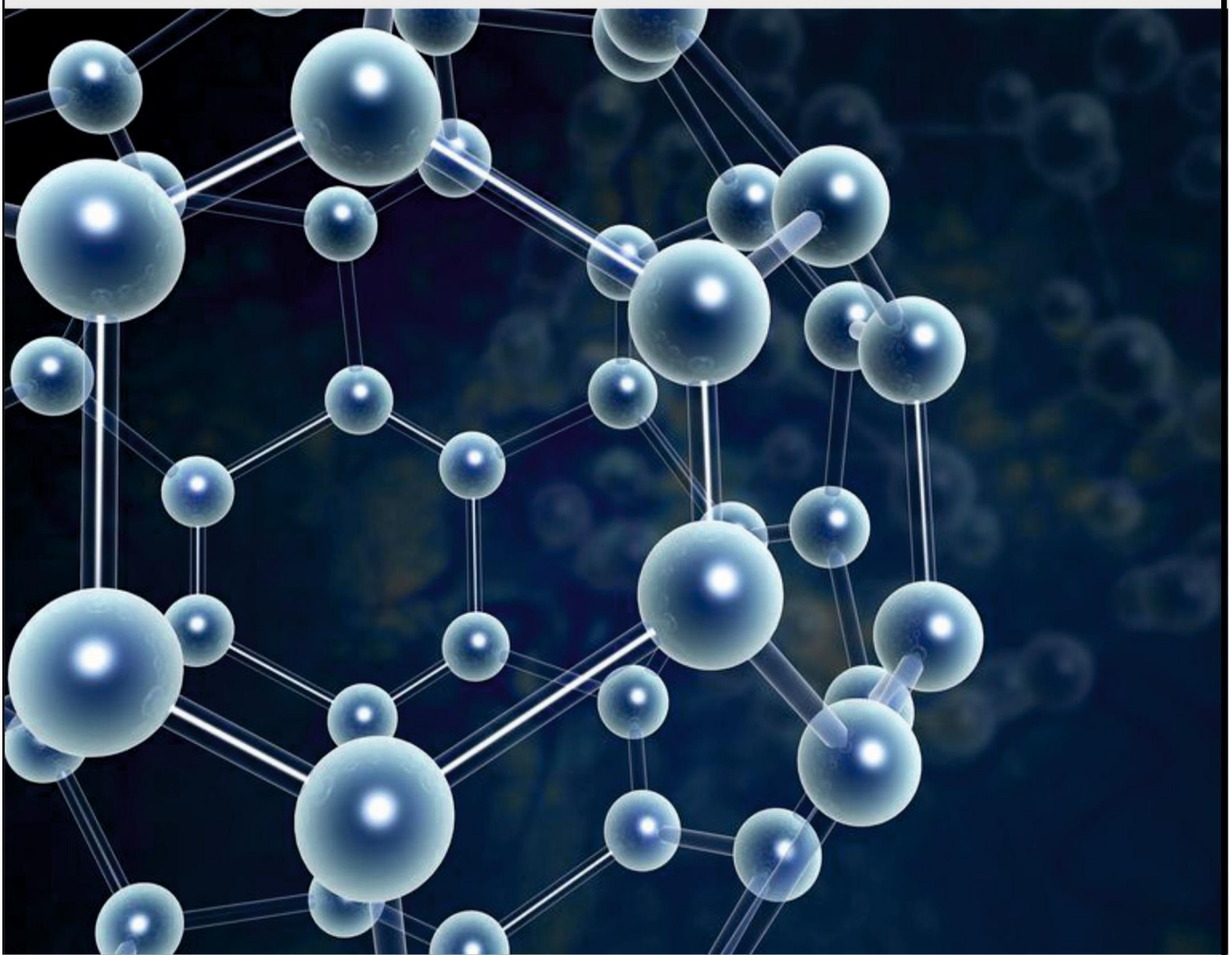
Kripa-Drishti Publications
A-503 Poorva Heights, Pashan-Sus Road, Near Sai Chowk,
Pune – 411021, Maharashtra, India.
Mob: +91 8007068686
Email: editor@kdpublications.in
Web: https://www.kdpublications.in

ISBN: 978-93-94570-79-5

Advanced Organic Chemistry Applications

Editor
Dr. M. R. Jayapal



ADVANCED ORGANIC CHEMISTRY APPLICATIONS

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Book Title: **Advanced Organic Chemistry Applications**

Editor By: **Dr. M. R. Jayapal**

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1st Edition

ISBN: **978-93-94570-79-5**

Published: **Jan 2023**

Publisher:

Kripa-Drishti Publications

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PREFACE

The manner of Organic Chemistry has changed somewhat since my days as a student in the early 2005s. Most notably, organic chemistry books offer more and better descriptions of topics in related fields such as Biochemistry and Materials Science, the internet allows one to search for information about specific topics, and computer software is readily available for modelling chemical structures and reactions. The overall level of sophistication has also risen for the presentation of traditional themes such as stereochemistry, bonding, reaction mechanisms, spectroscopy, and synthesis.

In spite of these changes, however, the mastery of Organic Chemistry as a course of study still requires a sound knowledge of the principles of molecular structure and chemical reactivity, which are topics introduced in most General Chemistry courses. With such a back-ground, a student studying organic chemistry begins to focus on a more limited set of atomic building blocks, particularly of carbon and its elemental neighbours. And while the study of a smaller portion of the periodic table might be expected to be easily manageable, understanding organic chemistry can still seem overwhelming because of the diverse way s that this handful of elements can combine and interact. To learn organic chemistry, one must grasp the recurring patterns that correlate the presented facts.

Toward that end, this textbook organizes and discusses applications of the patterns of chemical reactivity—which constitutes the majority of the subject matter—by combining information about the structures of functional groups (the reactive portions of a molecule) with the reaction mechanisms (pathways of chemical reactions) that these functional groups undergo. This approach differs from the one presented in many other texts, which describe every type of reaction that can occur for a given functional group; each approach has its advantages and disadvantages.

The one I have utilized here evolved from my objective to integrate discussions about biochemical processes with the types of reactions that are carried out in chemistry laboratories. With the use of two points of reference—structures and mechanisms—the similarities that associate biochemical and synthetic reactions can be appreciated more easily.

INDEX

ISBN: 978-93-94570-79-5

1. An Introduction of Polarography

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1.1 Introduction:

On February 10, 1922, Professor Jaroslav Heyrovsky carried out his pioneering experiment with a dropping mercury electrode from which polarography gradually evolved. Since then, polarography became a mature analytical method capable to adjust ever increasing demands on the sensitivity and selectivity and we believe that up to now mercury electrodes are among the best sensors for electroanalytical measurements[1,5]. Limits of determination gradually decreased from 10^{-5} M in the case of classical polarography[2], through 10^{-7} M for differential pulse polarography[3] to 10^{-11} M for adsorptive stripping voltammetry[4].

Development of mercury electrodes which proceeded from classical dropping mercury electrode[6] through mercury streaming electrode[7], hanging mercury drop electrode[8], static mercury drops electrode[9], mercury film electrode[10], mercury amalgam electrodes[11], mercury microelectrodes, chemically modified mercury electrodes[12], controlled growth mercury electrodes[13] and contractible mercury drop electrodes[14]. This process initiated by Professor Heyrovsky resulted in commercially available reliable mercury electrodes suitable for Nano molar and sub Nano molar concentrations. Further progress in this field can be documented by the above mentioned articles of Novotny and Kowalski and by papers of Gutz on versatile automatic mercury drop electrode[15-16].

Development of measuring techniques that proceeded from classical DC polarography[2], Through oscillopolarography[17], Kalousek's switcher[18], AC polarography[19], Tast polarography[20], Normal pulse polarography[21], Differential pulse polarography[22], Voltammetry[23], Cyclic voltammetry[24], Anodic stripping voltammetry[25], Adsorptive stripping voltammetry[26], Convolution techniques[27-28] and Elimination methods[29-30]. Development of preconcentration techniques on the surface of mercury electrodes enabling a substantial increase of sensitivity which proceeded from anodic stripping voltammetry and cathodic stripping voltammetry to adsorptive stripping voltammetry. The role of Professor Heyrovsky in the development of these methods cannot be underestimated. According to Zuman[31] the main contribution of Professor Heyrovsky consists in:

- Recognition of the importance of potential and its control;
- Recognition of analytical opportunities offered by measuring the limiting currents;
- The introduction of dropping mercury electrode as an invaluable tool of modern electroanalytical chemistry.

1.2 Principle of Technique:

Polarography is based on the unique characteristics of the current-voltage curves obtained with dropping mercury electrode, which was first introduced by Kucera[32] for electro capillary studies. In 1934 Ilkovic[33] derived an equation for the resulting constant. It deals with the measurement and interpretation of current-voltage curves when solution of electroactive substances is electrolyzed in a cell in which one electrode is polarisable i.e. mercury falling gravitationally drop wise from fine bore of capillary glass tube, while the other electrode remains non polarisable (saturated calomel electrode). Since the curves are graphical presentation of the dropping mercury electrodes, the apparatus is called 'polarograph' the curves as polarograms and technique is named as polarography. Thus, it is one of the most essential key to chemical analysis. The flow of current in the electrical circuit is observed only when the voltage is applied to electrodes changes at constant rate, raises the potential of a depolarizer present in the solution 10^{-5} moles/liter range. The current increases with the increasing negative potential of the electrode and during this time the concentration of the depolarizer on the surface of electrode decreases. When this concentration decreases to zero, current reaches to a constant value depending on the rate of depolarizer transport to the surface of electrode. In these conditions we have the maximum current which is often called limiting current.

Advantages of Dropping Mercury Electrode:

There are several advantages of the dropping mercury electrode.

- Each drop falling from the electrode exactly duplicates the behavior of the one that preceded it. This is because successive drops are born into solution of identical time, grow at a same rate and reach at the maximum size. Consequently, the currents are accurately reproducible from one drop to next.
- Solid products cannot accumulate on the electrode surface, changing its properties as it is possible with solid electrode.
- It is much less sensitive to mechanical disturbance than stationary electrode.
- High over potential of reduction of hydrogen ion or water on a mercury surface makes it to investigate processes that can occur only under strongly reducing conditions.

1.3 Applications of Polarography:

Polarography can be extensively applied in the field of inorganic analysis[34], organic chemistry[35], pharmacy[36], metallurgy, geology and archaeology[37], polymer chemistry[38], colloids and surface active substances[39], food chemistry[40], petroleum and fuel analysis[41], Trace analysis[42], rare earth analysis complex studies[43], trace determination of drugs[44-48], quantitative and qualitative analysis of organic compounds including drugs[49-54].

1.3.1 Analysis of Organic Compounds by Polarography:

Polarography has contributed significantly to the understanding of processes involved in the electrolysis of organic compounds. In organic chemistry, polarography can be used in the determination of equilibrium and rate constants, in studies of reaction mechanism, in the search of optimal conditions for some preparative reactions, in studies and comparisons of reactivity's of organic compounds and in correlations of structure with polarographic data.

From polarographic curves, identification of electrolysis with other methods may be used for elucidation of organic electrode process. Many organic functional groups undergo reduction or oxidation at dropping electrode and thus led themselves to polarographic determination. In general, the reactions of organic compounds at the dropping electrode are slower and are often more complex than those of inorganic ions; nevertheless, polarographic investigations can be useful for structure determination and for qualitative and quantitative analysis.

Reactions of organic substances at the dropping electrode usually involve hydrogen ions; a typical reaction can be represented by the equation.

$$R + nH^+ + ne^\ominus \rightleftharpoons RH_n$$

Where RH_n is the reduced form of the reducible compound R. As hydrogen ions (supplied from the solution) are involved in the reaction, the supporting electrolyte must be well buffered. Change in the pH of the supporting electrolyte may even lead to the formation of different reaction products. Thus, in slightly alkaline solution, benzaldehyde is reduced at -1.4 volts with formation of benzyl alcohol, but in acid solution (pH < 2), reduction takes place at –1.0 volts with formation of hydrobenzoin:

$$2C_6H_5CHO + 2H^+ + 2e^\ominus \rightleftharpoons C_6H_5CH(OH)CH(OH)C_6H_5$$

Some organic compounds can be investigated in aqueous solution. It is frequently necessary to add an organic solvent to improve the solubility. Suitable water miscible solvents include ethanol, methanol, ethane-1,2-diol, dioxane, acetonitrile and acetic acid. In some cases, a purely organic solvent must be used and anhydrous materials such as acetic acid, formamide and diethylamine have been employed. Suitable supporting electrolytes in these solvents include lithium perchlorate and tetra-alkyl ammonium salts R_4NX (R = ethyl or butyl; X = iodide or perchlorate).

The following functional groups can be expected to react at the dropping electrode.

C=C (When conjugated with another double bond or an aromatic ring), C□C (when conjugated with an aromatic ring), C–X (X = halogen), C=O (aldehydes, ketones, quinones), dicarboxylic acids in which the carboxyl groups are conjugated with each other, Peroxides, epoxides, C=N, Nitro, nitroso, azo groups, heterocycles with two or more nitrogen atoms in the ring, C=S, S–S and S–H (mercaptans give an anodic wave).

1.3.2 Polar Graphic Study of Metal Complexes:

The chemistry of metal complexes is undergoing a period of a rapid development and engaging the attention of many researchers. Its progress has received an added impetus due to its several applications in chemical, industrial, agricultural, biological and technological fields. Metals that are essential for plant growth and animal nutrition have been found to form complexes with materials present in organisms. Metal-chelate formation also plays significant role in the functioning of enzymes and processes like moderate dyeing in the textile industry and the tanning process as in the leather industry. Their applications in inorganic analysis are of many folds and include detection, determination, purification and solvent extraction through complex formation. Complex forming reagents are extensively applied masking agents in various titrimetric, spectrophotometric, polarographic, chromatographic and electrophoresis methods.

Historically, credit to study inorganic complexes by polarography goes to the pioneering work of Stackelberg, Frey-hold[55] and Lingane[56]. The classical method of analysis was thoroughly discussed by Kolthoff and Lingane[57] in the monograph on polarography and related electrochemical techniques which resulted in remarkable progress and is now extensively used in the study of complexes in solutions. Some of the general developments are presented and discussed by Irving[58], Koryta[59], Westwood and Crow[60-62] in their publications. Excellent reviews have also been published by Vlcek[63-64] on relation between electrochemical reactivity and structure of inert complexes. A beautiful review has also been written by Tamamushi and Sato[65]. The contribution of Lingane, Deford and Hume[66], Ringbom and Erikson[67-68], Kacena and Matousek[69] Schwarzenbach[70-71], Buck[72], Butler[73], Macovsch[74] and Crow are there for study of metal complexes. Schapp and MacMasters[75] have extended Deford and Hume's treatment for study of mixed ligand complexes in solution.

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ISBN: 978-93-94570-79-5

2. Organic Reactions

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Abstract:

The chemistry of carbon compounds is now referred to as organic chemistry. When the majority of the substances identified in this discipline of chemistry came from living organisms, the word " organic" was first used to characterize it.

The greatest component of chemistry is organic chemistry, which also ranks among the most popular disciplines in terms of both its factual base and its audience size. There are currently more than a million known organic compounds, and thousands more are constantly being found in nature or created in laboratories.[1]

Chemical processes involving organic molecules are known as organic reactions. Functional groups have a strong relationship with several of these reactions. Analysis of features including bond strength, steric hindrance, and the electron affinities of important atoms are all carefully considered in the general theory of these processes.

Covalent bonds found in organic compounds change most frequently during organic processes. These modifications could include bond cleavage, electric bond displacement, energy modifications associated with covalent bond formation, etc. We must.[2]

Keywords:

Covalent bond, steric hindrance, electron affinities, bond strength, energy modifications.

2.1 Types of Organic reactions:

A. Substitution reactions
B. Addition reactions
C. Elimination reactions
D. Rearrangement reactions

2.1.1 Substitution Reactions:

In a substitution reaction, an atom or group of atoms from a molecule are exchanged out for new ones while maintaining the molecule's original structural integrity. Free radical, nucleophilic, and electrophilic substitution reactions are those in which free radicals, nucleophiles, and electrophiles serve as reactive intermediates.[3]

A. Free Radical Substitution Reactions: For instance, methyl chloride is created when methane combines with chlorine in the presence of sunlight by replacing one hydrogen atom with a chlorine atom in a free radical substitution reaction. This reaction is known as a free radical substitution reaction because it uses free radicals as intermediates.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

This reaction involves the following steps:

- Cl-Cl $\longrightarrow$ Cl +. Cl
- CH_3 – Cl +. Cl $\longrightarrow$ $^{\cdot}CH_3$ + HCl
- $^{\cdot}CH_3$ + Cl- Cl $\longrightarrow$ H_3C – Cl +. Cl

This reaction may proceed further to replace remaining hydrogen atoms by chlorine to form CH_2Cl_2, $CHCl_3$ and CCl_4 by similar mechanisms.

B. Nucleophilic Substitution Reactions: A nucleophilic substitution process is one in which methyl chloride and aqueous potassium hydroxide react to produce methyl alcohol.

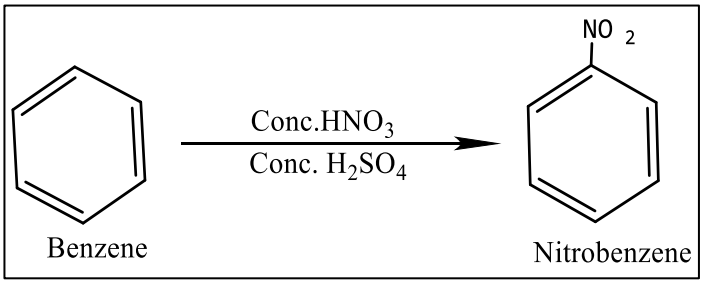
$$CH_3\text{- Cl} + KOH \longrightarrow CH_3OH + KCl$$

In this reaction replacement of Cl by a nucleophile (: OH^-) take place. Substitution reactions of alkyl halide involve nucleophilic substitution reactions.

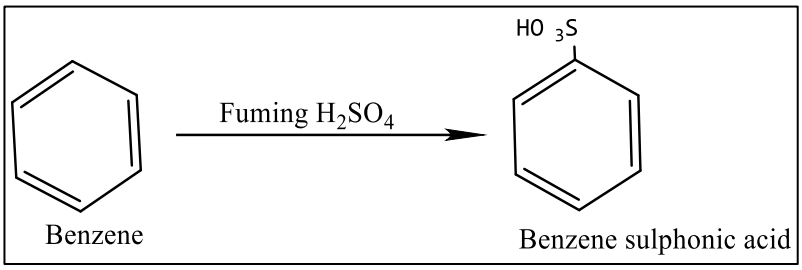
C. Electrophilic Substitution Reactions: Electrophilic substitution reactions include aromatic substitution processes like nitration, sulphonation, Friedel craft reactions, etc. These reactions involve replacement of nuclear hydrogen by an electrophile (Ex- NO_2, R^+ etc)[4]

Example: -

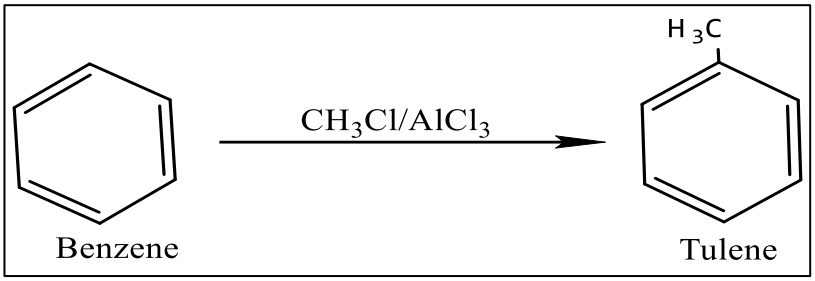
- Nitration



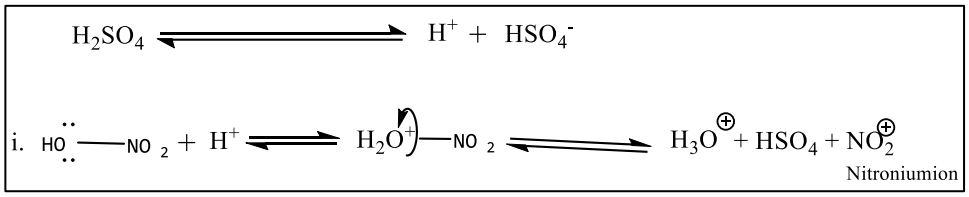
- Sulphonation

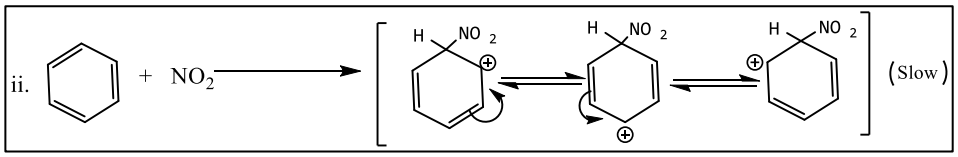


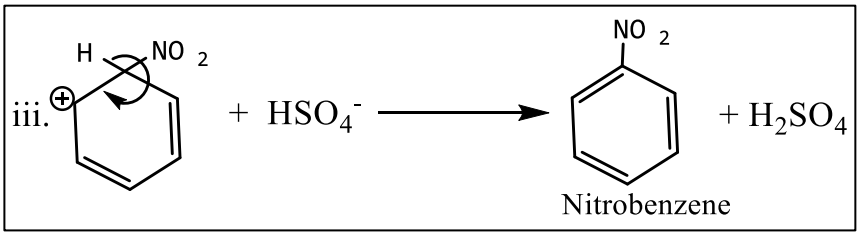
- Friedel craft reaction



- **Mechanism of Nitration:**

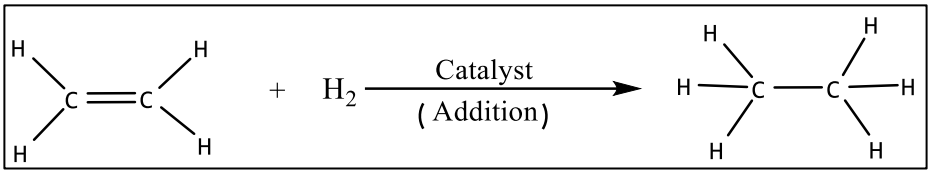






2.1.2 Addition Reactions:

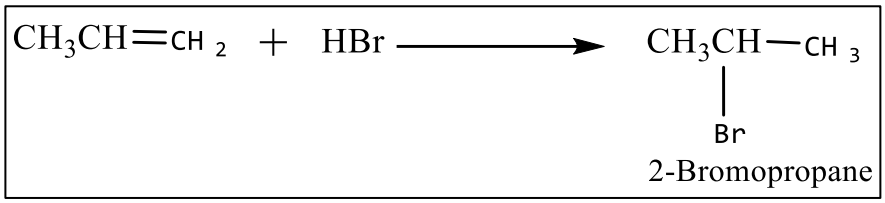
The chemical molecules with double or triple bonds that cause these reactions (unsaturated compounds). These substances easily incorporate hydrogen, haloacids, halogens, etc. into the end product while altering the molecule's shape. For example,



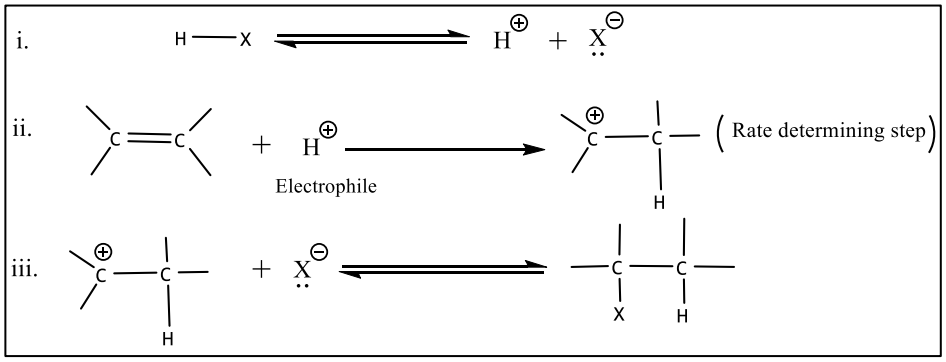
In these reactions, one pi bond, which is weaker than an alpha bond, breaks to produce two new sigma bonds, one on each carbon, which satisfy the valency criteria in the end product.

These reactions are of three types:

A. Electrophilic Additions: These reactions are known as electrophilic addition reactions because they are started by the addition of an electrophile during the rate-determining step. For example,



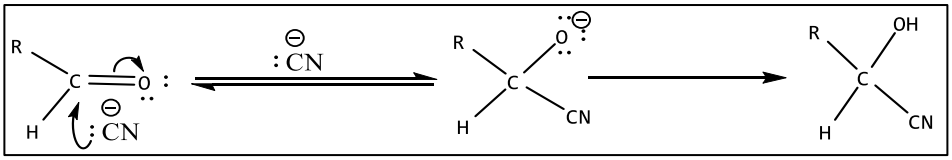
B. Mechanism: It is an electrophilic addition reaction, initiated by the electrophile (H^+) released from the HX. This reaction involves the following steps:



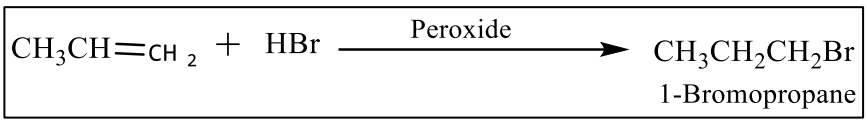
The rate determining step is step (ii) leading to the formation of a **carbocation.**

C. Nucleophilic Additions: Simple aldehydes and ketones' carbon-oxygen double bonds give rise to addition reactions that are typically nucleophilic in nature.

For example, addition of HCN to aldehydes

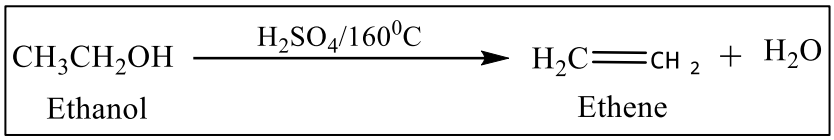


A. Free radical additions: - Free radical mechanism controls the addition reaction of HBr to unsymmetric alkenes (like propene) in the presence of peroxides to produce an anti-Markownikoffs product. Free radical addition reaction is the name given to this process.

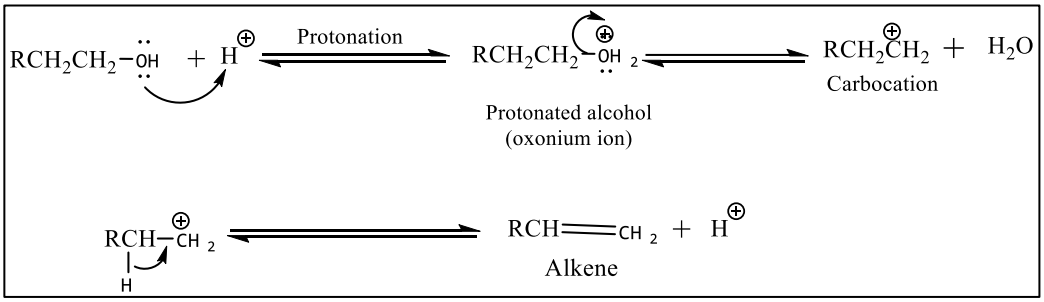


2.1.3 Elimination Reactions:

This reaction is the opposite of the addition reaction. A reactant molecule loses atoms or groups during an elimination process. These reactions result in compounds with many bonds.[5] For example,



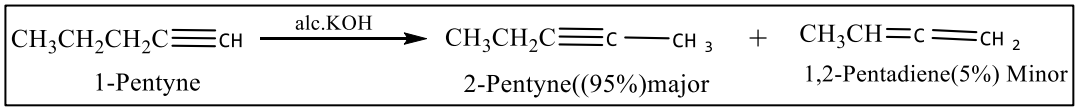
A. Mechanism: It involves protonation of alcoholic group followed by elimination of water and deprotonation.



2.1.4 Rearrangement Reactions:

An atom or a group of atoms may move from one area of a molecule to another area of the same molecule during a rearrangement reaction. Triple bond migration may also be involved.[6]

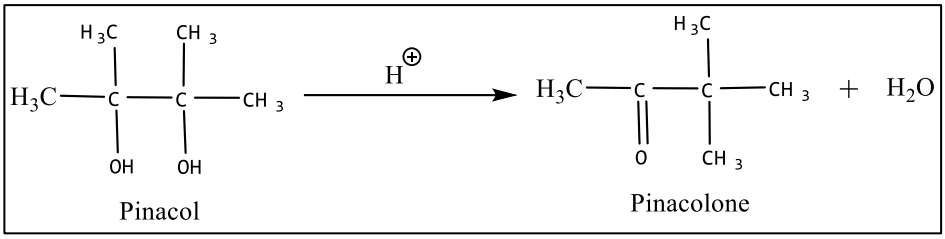
For example, 1-pentylene with alcoholic KOH tend to rearrange with migration or triple bond to form 2-pentylene as major product:



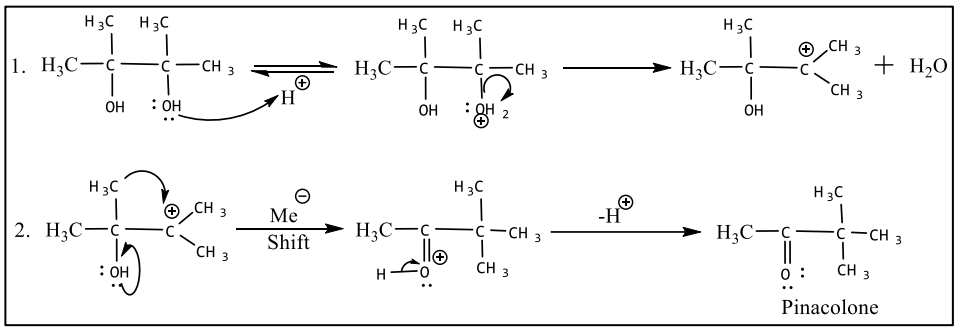
Some of examples of Rearrangement reactions,

A. Pinacol Pinacolone Rearrangement: It involves the dehydration of substituted vicinal diols (pinacols) under acid catalysis, followed by rearranging the carbon skeleton to produce ketones.[7]

For example,



Mechanism:

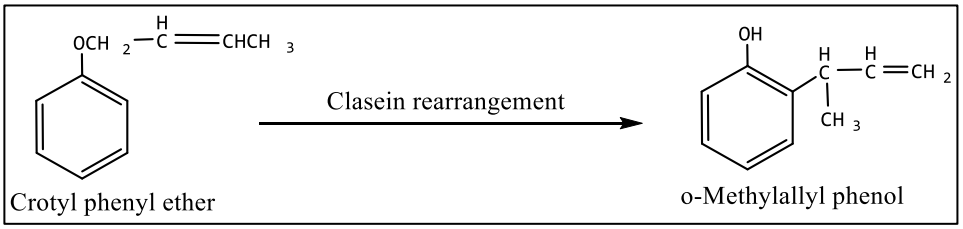


Step 1 involves protonation of that -OH group, which on elimination of water molecule gives most stable carbocation.

Step 2, carbocation undergoes a 1,2-methyl shit to the electron deficient carbon to generate protonated ketone.

B. Claisen Rearrangement: O-allyl ether of phenol undergoes a rearrangement to become o-allylphenol at a temperature of about 200^0C in the absence of any catalyst. The Claisen rearrangement of phenolic allyl ethers is the name of this thermal process.[8]

For Example,



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ISBN: 978-93-94570-79-5

3. Emerging Trends in Microwave Chemistry Assisted Extraction of Phytochemicals

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Learning Outcomes:

At the end of this chapter the reader will be able to understand:

- Introduction
- Microwave Chemistry: Principle, Benefits and Applications
- Microwave Assisted Extraction: Principle, Methodology, Advantages and Applications
- Microwave Aided Extraction Technology in Herbal Drug Research
- Microwave Assisted Extraction of Phytochemicals
- Studies using Microwave Assisted Extraction of Phytochemicals
- Conclusion

Abstract:

Plants are considered as natural factories for construction of wide range of phytochemicals. A large number of secondary metabolites like alkaloids, glycosides, tannins, phenolic compounds, resins and flavonoids are manufactured by plants. Developments in natural chemistry research led investigators to documentation and separation of diverse bioactive chemicals. These phytochemicals are widely used as therapeutic agents in treatment and management of various acute and chronic disorders and diseases. The superiority of active herbal preparation is considerably contributed by extraction techniques. Extraction is crucial and first most important step in the development of phytochemicals. Conventional extraction techniques reported to possess few limitations and disadvantages. The principles of microwave chemistry are useful in order to overcome few of the limitations of conventional extraction techniques. Hence in the Microwave assisted extraction has been introduced. This is an effective and new tool with numerous benefits as compared to the old-style approaches of extraction. The important benefits of microwave assisted extraction

are in terms of reduction in cost, time of extraction, amount of solvent used, and energy consumptions. This chapter give brief overview on basic approach, principle and applications of microwave chemistry. This chapters also emphasizes on the microwave assisted extraction techniques and its applications towards the development of phytochemicals.

3.1 Introduction:

The Microwave region is lie in the electromagnetic range between the radio waves and infrared waves. They have wavelengths between 0.01 and 1 meter, and functions in a frequency array between 0.3 and 30 Ghz. Usually a frequency of 2.45 Ghz is utilized for laboratory activities like to conduct the chemical reactions as this waves proper penetration depth which are suitable for the laboratory reactions. Beyond 30 Ghz wavelength frequency, the microwave frequency overlaps with the radio frequency.

Generally, the microwave electromagnetic range is distributed into two categories namely sub-bands including the lower microwave frequency called as L band and the higher frequency known as W band. L band microwave frequency is mainly used for the purpose of communication and W band frequencies are used for the analytical techniques such as spectroscopic characterization. Microwave chemistry is the branch of chemical science which involves the study and utilization microwave radiation to chemical synthesis.

Microwaves action as high frequency electric fields and mainly causes the heating of any material. It generates the mobile electric charges, such as polar molecules in a solvent or accompanying ions in a solid. Thus the microwaves are widely used in various industries including pharmaceutical, biotechnology, chemicals, petroleum and polymer industries.

The Microwave-assisted reactions are fast, clean, and economic and eco-friendly. The principles and approaches of microwave chemistry have been widely used in the natural products chemistry research as well to extract and isolate diverse chemical entities from natural sources like plants and minerals.

3.2 Microwave Chemistry:

In the year 1946, the technology of Microwave technology was originated and discovered. It was started with research performed by Dr. Percy Le Baron Spencer. He was performing laboratory examinations for a new vacuum tube known as magnetron. Magnetron is a device that produces an electromagnetic radiation.

During this experiment, accidentally he discovered that a candy bar in his pocket liquefied on exposure to radiations of microwave. In the year 1947, Dr. Spencer established the idea and recognized that microwaves might be used as a technique of heating.

Then, he intended the first microwave oven for domestic practice. Subsequently, in future years the expansion of microwave radiation and its applications were studied. Table 3.1 provides the information about development and evolution of Microwave chemistry.

Table 3.1: Development and Evolution of Microwave Chemistry

Sr. No.	EVOLUTION	YEAR
1	Discovery of Microwave radiation as heating method	1946
2	Introduction of first commercial domestic micro oven	1947
3	Development of first laboratory useful micro oven instrument	1978
4	Generation of microwave radiations to dry organic materials	1980-1982
5	Utilization of microwave radiation for analysis of chemicals	1983-1985
6	Publication of research papers related to applications of microwave radiation in synthesis of chemicals	1986
7	Emergence and development of Microwave Chemistry as a field of study due to its useful applications in chemical synthesis	1990
8	Development of first high pressure vessel for conducting full digestion of oxides, oils and pharmaceutical samples.	1990
9	Synthesis of chemicals based on microwave radiations using batch system reactor and single mode cavity system	1992-1996
10	Publication of book titled Microwave Enhanced Chemistry-Fundamentals, Sample Preparations, and Applications	1997
11	Introduction of first commercial microwave synthesizer to carry out the chemical preparation.	2000
12	Conduct of various research using microwave chemistry and its applications, commercialization, industrial utility, publication of research papers.	2022

3.2.1 Principle of Microwave Chemistry:

Microwave chemistry is the branch of chemistry that deals with study and applications of microwave radiations to conduct chemical reactions or chemical synthesis and chemical analysis. The approach of Microwave-assisted synthesis works on the basis of aligning dipoles of the substance in an external field via the excitation fashioned by electromagnetic radiations of microwave and is generally performed in mixture with an identified synthesis scheme.

This technique is moderately beneficial as the synthesis development can be modified to produce product with many advantages. The procedure of alignment or orientation of substance by the external electrical field may result in the creation of internal heat which is accountable for a decrease in processing time and energy requisite. It is particularly due to the heating consistency of microwaves. The reaction time can be fairly condensed by accepting microwave-assisted preparations.

A. Benefits of Microwave Chemistry:

Microwave chemistry has many benefits as mentioned below:

- Microwave radiation are extremely effective and used as heating source in chemical synthesis.
- Microwave chemistry is helpful in emerging the cleaner synthetic routes and procedures.
- Microwave chemistry helps to enhance the rate of chemical reactions and improve the percentage yield of product.
- Microwave chemistry helps to achieve the better reproducibility of reactions.
- It helps to deliver efficient and uniform heating to the chemical reactions.
- It also helps to provide the selective heating in a chemical synthesis schemes.

B. Applications of Microwave Chemistry:

The concept and approaches of microwave chemistry is widely used and applicable in various industries. The wide range of applications of microwave chemistry and related techniques are useful in various fields. Figure 3.1: Shows The Applications of Microwave Chemistry in Various Areas.

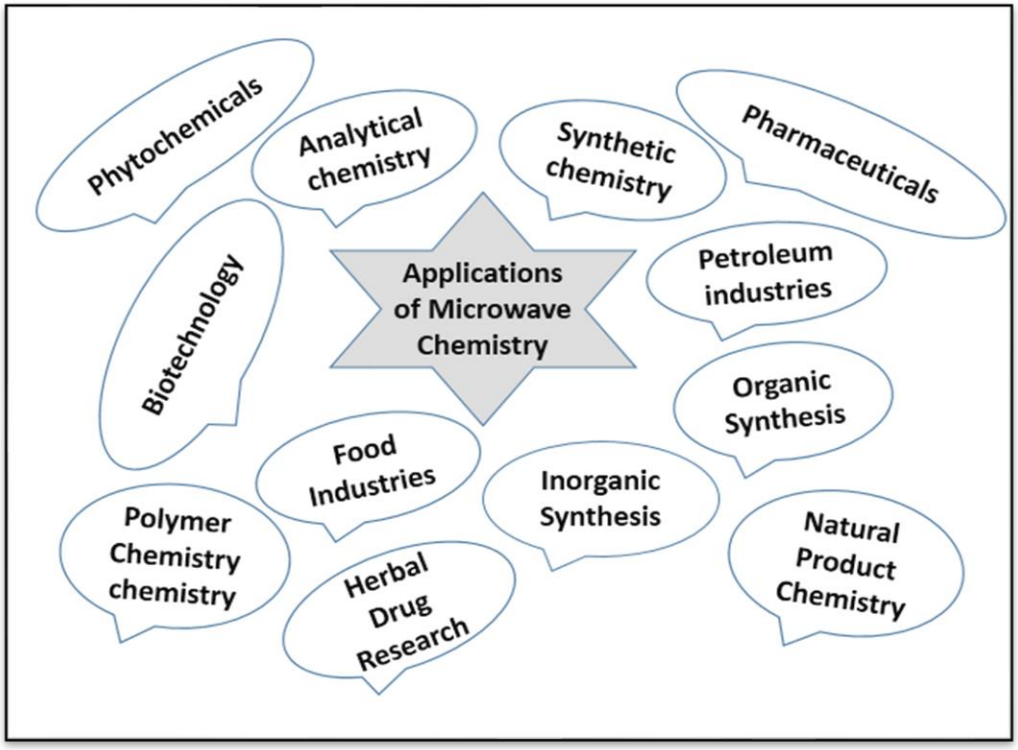


Figure 3.1: Applications of Microwave Chemistry in Various Fields

a. General Applications: The concept of microwave chemistry is widely used in various industries like biotechnology, pharmaceuticals, petroleum, plastics, chemicals and food industries. Various general applications of microwave chemistry are listed as below:

- The microwave chemistry is useful in the field of analytical and synthetic chemistry
- It has wide range of applications in natural products chemistry research.
- Microwave heating is extensively used for ashing in the petroleum and fuels, plastics, pharmaceuticals and food industries.
- Microwave digestion systems are used in analytical laboratories for sample decomposition and preparation.
- Microwave radiation used in trace and ultra-trace metals analysis.
- Microwave extraction is widely used in herbal drug research.
- Microwave assisted extraction systems are used to conduct routine solvent extractions of soils, sediments, sludge, polymers and plastics, pulp and paper, biological tissues, textiles and food samples.
- Microwave assisted moisture analysis has been widely used in the food and beverage, chemical, environmental, organic and pharmaceutical industries.
- Microwave moisture analysis is specifically applied at product development stages such as process and quality control, testing of raw materials, intermediate and finished products.

b. Applications in Chemical Synthesis: The application of microwave radiation are widely useful in the synthesis of large number of chemical moieties. It is widely used in the organic and inorganic synthesis in laboratories. The Microwave-enhanced preparations help the scientist to perform his work faster, get higher yields, and enhance the purity of product. Apart from this due to the advanced instrumentation and innovative research in Microwave chemistry, it has been observed that the yield of product is been scaled up from mg to kg. The techniques of microwave chemistry play valuable role in the organic and inorganic synthesis and few of the important applications are listed as below:

- **Applications in Organic Synthesis:** Organic synthesis can be defined as the synthesis of a preferred organic molecule by using precursors. The Microwave assisted organic preparation is one of the novel research area in the organic preparations as it gives better results with many advantages over the conventional routes and hence Microwave organic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in organic synthesis are highlighted as below:

- The Microwave assisted organic preparations are widely used in the pharmaceuticals companies, mainly in order to develop the molecules in the optimization of lead stage in the drug development.
- Literature reported that the scientist has been successfully used the approach of microwave synthesis in conduct of large number of named chemical reactions. Few of these reactions conducted using microwave techniques are listed below:

    - Condensation reactions
    - Cyclisation reactions

- Cycloaddition reaction
- Dehydration
- Diels Alder reaction
- Epoxidation
- Esterification

- Heck reaction
- Hydrogenation of [beta]-lactams
- Hydrolysis
- Mannich reaction
- Protection and deprotection of functional groups
- Reduction reactions
- Suzuki reaction

- **Applications in Inorganic synthesis:** Inorganic preparations can be defined as the preparation of a preferred inorganic compound from suitable precursors. The Microwave assisted inorganic compound synthesis is one of the innovative research region in the inorganic preparations as it gives better results with many advantages over the conventional routes and hence Microwave inorganic preparations are found to exert great role in the synthetic laboratories. The important applications of microwave synthesis in the field of inorganic synthesis are highlighted as below:

- The Microwave assisted inorganic preparations are extensively used in the pharmaceuticals companies, mainly in order to develop the inorganic molecules.
- Microwave chemistry is widely used in the preparation of organometallic derivatives.
- Microwave chemistry is also used in the synthesis of coordination compounds.
- It is used in the synthesis of intercalation molecules.
- It is also used in the preparation of ceramic products.

c. Applications in Polymer Chemistry: Polymer chemistry is one of the important field in the chemistry and it is mainly used in the preparation of Polymer products.

- The concept and approaches of microwave chemistry is widely used in the development of polymers and related products.
- The approaches of microwave techniques are also widely used in order to conduct the polymerization reaction.

3.3 Microwave Assisted Extraction:

The microwave assisted extraction is a model and newest green approach to an analytical method in which microwave radiation frequency is used for the extraction of chemical compounds or isolates particularly from plant materials. This technique utilized to extract the samples or chemical compounds from biological matrices for the purpose of its further analysis. Microwave assisted extraction is a procedure of utilizing the microwave energy to heat liquids in connection with a sample in order to distinct the chemical from the matrix into the liquid. Earlier microwave ovens are utilized for the digestion of samples for metal

analysis. All microwave ovens (Home or the laboratory used) are usually operate at 2.45 GHz frequency. The microwave region found to exists at frequencies of wavelengths from 0.3mm to 1m or 100 GHz to 300 MHz.

Principle of Microwave Assisted Extraction: The basic principles of the microwave assisted extraction method are different from traditional methods of extraction like solid-liquid or simple extraction techniques. As we know the electromagnetic radiations are known to cause the cell structure and this leads to the extraction. When the microwave radiation is passed through the matrix or plant materials, it causes the molecular communication with the wave. Thus the microwave radiation is converted into heat energy that supports the mass transfer from plant cell or material into the solvents. By using this principles, the phytochemicals can be extracted from plant materials by using microwave radiation. The traditional solvent extraction techniques from plant materials trust on the appropriate assortment of solvents and the use of thermal energy and agitation to recover the mass transfer and increase the solubility of the anticipated agent. Hence new system of microwave assisted extraction helps to condense the extraction time, less solvent ingesting, decrease the contamination and superior attention for thermolabile chemicals have added consideration.

Methodology: In order to perform the microwave assisted extraction two methods are utilized using different devices mainly:

- Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System
- Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System

a. **Open Microwave Assisted Extraction System/Atmospheric Microwave Assisted Extraction System:** In case this method the sample is situated in an open vessel to which a suitable organic liquid is placed. The microwave radiation produced from the magnetron is focused by the waveguide onto the sample/liquid, thus producing the liquid to boil. The hot liquid is then arising into interaction with a water cooled reflux condenser. This effects the liquid to condense and reappearance to the vessel. This procedure is recurrent for a little period of time so allowing compounds of interest to be come out from the sample material into the liquid.
b. **Closed Microwave Assisted Extraction System/Pressurized Microwave Assisted Extraction System:** In this case, the microwave radiations enter into the oven, and are detached by a mode stirrer. The mode stirrer permits an even delivery of microwaves within the oven. In this approach the sample and liquid are situated within the closed container which is typically prepared of microwave transparent resources such as polymers and their derivatives.

3.3.1 Advantages of Microwave Aided Extraction:

A prospective substitute to old-style solid liquid extraction method is the microwave assisted method. Microwave assisted techniques has good number of compensations over the traditional extraction and few of them are listed as below:

- Microwave assisted extraction technique helps to extract multiple samples for at a time.
- Microwave supported extraction method requires small quantity of liquid for extraction.
- Microwave aided extraction technique carries the extraction in very short period of time.
- Microwave assisted extraction gives the Improved yield.
- This technique gives improved accuracy in the results.
- This approach is suitable for the thermolabile chemical extraction.
- It requires remarkably less extraction period and the time of extraction usually extending from few seconds to few minutes.
- It requires very less amount of liquid in extraction and amount is a few milliliters.
- It shows also the better precision due to the automation of the apparatus.
- It is useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the improved mass transfer mechanism due to the agitation of sample vessels.

3.3.2 Applications of Microwave Supported Extraction Techniques:

The wide range applications of microwave aided extraction technology are listed as below:

- The microwave assisted technique is useful in order to extract large number of phytochemicals from the plant materials.
- It is widely used technique in the extraction of sample in herbal drug industries.
- It has showed the utilization in extraction of sample or analyte from the biological matrix in the bioanaytical laboratories in the clinical research.
- In the analytical research and development department of pharmaceutical industries this approach is extensively used.
- This approach is used in order to extract the secondary bioactive chemicals from the plant materials including alkaloids, glycosides, tannins, polyphenols, flavonoids, terpenes, lignans and phenolic derivatives.
- The closed vessel microwave method is used for the extraction of terpenes from plant material.
- The extraction of imidazolinone herbicides and sulphonylurea herbicides has been carried out and reported in the literatures.
- It has been also used in the extraction of fungicides like hexaconzole from weathered soil.
- The extraction of additives polypropylene and polyethylene has been achieved in the polymer chemistry and related research.
- It has been widely used in the food industries in the preparation of vitamins in foodstuffs.
- It can be used for determination of various metals and metallic compounds like Zn, Pb, and Cu from soils.
- Microwave aided extraction is a consistent source of extraction of phytoconstituents.
- It also can be used for the extraction of essential oils from plant sources.
- This technique also used in the analysis of heavy metals and other pollutants present in the different type soils.
- Microwave supported extraction is used in the synthesis and preparation of pharmaceuticals samples in the pharmaceutical industries.

3.4 Microwave Aided Extraction Technology in Herbal Drug Research:

Herbal medicines are also known as phytomedicines and they have been widely used by human culture. The plants are considered as natural factories for manufacture of numerous phytochemicals or plant compounds. A large quantity of secondary metabolites like alkaloids, glycosides, tannins, phenolic derivatives and flavonoids are manufactured by plants.

They act as a great source in the development of modern medicines. The advancements in natural chemistry sciences directed researchers to documentation and isolation of diverse bioactive phytocompounds. The one of the most important step in the development of herbal medicines include the extraction of plant samples. Based on the basis of physical nature and chemical properties of phytochemicals, several approaches are in procedure to gain the crude extract. Few of the conventionally used extraction techniques in herbal drug industries are listed as below:

- Infusion
- Digestion
- Decoction
- Percolation
- Maceration
- Soxhlet Extraction etc.

The above mentioned extraction techniques are used for the extraction of plant chemicals from plant material but at the same time they are also associated with some limitations and disadvantages like:

- Extraction time is more
- Solvent consumption is more
- Soxhlet extraction method is not suitable because in the method the targeted compound may undergoes the decomposition due to usage of high temperature.
- The traditional extraction technique carries the extraction in more time.
- The traditional extraction technique may give the less yield.
- This technique gives less accuracy in the results.
- This approach is not suitable for the thermolabile chemical extraction.
- It requires remarkably more extraction period and the time of extraction usually extending more than hours.
- It requires more amount of liquid in extraction.
- It shows also the less precision due to the non-automation in the extraction apparatus.
- Many time it is not useful to extract heavy metals and pesticide deposit present in very minute units.
- It shows the less mass transfer mechanism due to the poor agitation of sample vessels.

In order to overcome one or other limitations of the conventional methods the approach of microwave assisted tool has emerged due to its wide range of advantages as discussed earlier in this chapter.

A. Emerging Trends in Microwave Aided Extraction: A Competent and Modern Approach for Pharmaceuticals and Botanicals:

The microwave aided extraction is attentive and targeted technique of extraction of plant chemicals and can be effortlessly joined with other analytical devices like chromatographic techniques. Its treatment is additional made easier due to the automation of the apparatus. This approach is new and widely used in order to develop the modern medicines and pharmaceuticals from the various botanicals. There are many recent advancements and emerging trends in the development of microwave assisted solid extraction techniques from natural matrices. Some recent trends and applications are discussed in this chapter under below headings:

- Development of marker compounds
- Assessment of plant productivity
- Extraction of plant chemicals for drug development and its commercial applications.

a. Development of Markers: The microwave driven extraction tool is also reported for the development of marker compounds from the plant materials. Literature reported various methods and compound which are extracted and isolated using this approach and successfully used for marker based standardization of phytomedicines and related products**.** Few of the marker compounds extracted using microwave techniques are listed as below:

- Vitexin
- Isovitexin

b. Assessment of Plant Productivity: The microwave driven extraction offers the opportunity for performing the multiple extractions which is suitable for the fast screening of an abundant set of samples to assess the efficiency of organisms. For example, in order to compare amount of coumarin and related compounds like melilotic acid, and o-coumaric acid, the microwave assisted technique can be used also it can be used to analyze the productivity of *Melilotus officinalis* plant.

c. Extraction of plant chemicals for drug development and its commercial applications: The plant compounds isolated from the medicinal plants are widely used in the management and treatment of various diseases and disorders. The plant secondary metabolites include alkaloids, flavonoids, tannins, terpenes, polyphenols and many other functional derivatives. The microwave assisted extraction tool has been reported in the literatures in order to extract these plant secondary chemicals with better extraction and activity reports. Few of the examples of such microwave assisted extracted chemicals are discussed as below:

- **Extraction of Alkaloids:** The alkaloids are a famous class of secondary metabolites characterized by the presence of basic nitrogen. These class of compounds are widely used as therapeutic agent in very small amount. Over the years, many active alkaloids have been extracted microwave irradiation tools. Few important examples of execrated alkaloids by this tool are listed as below:

- Extraction and isolation of ephedrine, cocaine, and ergot alkaloids has been reported by using microwave extraction tool.
- An efficient microwave supported extraction protocol as a drug discovery process has been reported for the extraction and isolation of bioactive alkaloids like neferine, dauricine, liensinine, isoliensinine, nuciferine from *Lotus plumule* plant.
- The simultaneous microwave assisted extraction protocol have been developed for the collection of cocaine, cocaethylene, benzoylecgonine, morphine, 6-monoacethylmorphine, and codeine from human urine, hair, and vitreous humor samples.
- The microwave aided aqueous two phase extraction protocol has been reported for the rapid and simultaneous extraction and separation of alkaloids like oxymatrine, Matrine, 5α-hydroxysophocarpine, sophocarpine, oxysophocarpine, cytisine, N-methylcytisine, sophoranol, and sophoridine etc. from the plant *Radix Sophorae tonkinensis*.
- Recently literatures have reported the microwave supported extraction protocol for multicomponent analysis and the extraction of Berberine and polyphenol chemicals from various plant species of *Berberis*.
- Microwave extraction tool also has been used for the extraction of cocaine and benzoylecgonine from the leaves of *Erythroxylum coca.*

- **Extraction of Stilbene-based Polyphenolic Chemicals:** The Stilbene-based polyphenolic chemicals have been widely used as antibacterial, anti-inflammatory, hypolipidemic, cardiovascular, anti-diabetic, anti-ulcer, hepatoprotective, and anticancer agents. The few examples of useful Stilbene-based Polyphenolic Chemicals extracted by using microwave radiations includes: *trans*-resveratrol (3, 5, 4′-trihydroxystilbene), pterostilbene, viniferin, and other polyphenolic-stilbene derivatives etc.
- **Extraction of Terpenoids:** The Terpenes and isoprenoids, in general, expanded much consideration for their many biological functions like hormones, aliphatic tissue anchors, upholding tissue structure, biotic roles like defense compounds, insect or animal attractants, and wide medicinal uses such as flavors, fragrances, and drugs etc. Few examples of terpenes and related derivatives which are extracted using microwave techniques are listed as below:
    - Artemisinin from *Artemisia annua*
    - Paclitaxel from *Taxus baccata L.*

3.5 Microwave Assisted Extraction of Phytochemicals:

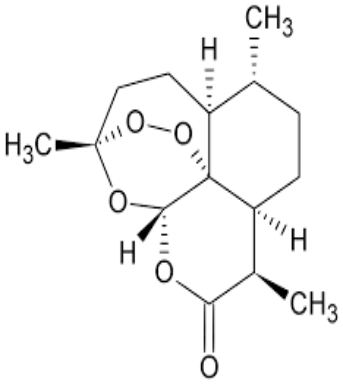
The extraction includes separating dissolvable chemical from non-dissolvable material using suitable liquids. There are two groups of extraction techniques reported for phytochemicals collection namely the traditional and modern extraction techniques. The list of traditional extraction methods includes the Soxhlet, soaking, maceration, digestion, decoction etc. These traditional extraction tools are associated with some limitations. In order to overcome the limitations of older extraction techniques few modern extraction techniques are evolved which includes turbo-fast blending, sonication, ultrasonic aided, subcritical, supercritical, enzyme assisted, pressure assisted, and microwave assisted techniques. Out of all these listed modern methods of extraction, the microwave supported

extraction has established the highest responsiveness due to its condensed consumption of liquid, less operation time, good reproducibility, improved recovery, upright selectivity, and condensed sample manipulation. In recent years, the microwave assisted extraction is usually used in gaining the chemicals of bio origin from plant materials. This has significantly improved the total attention in expansion and growth of research areas in plant chemistry research. It is a green expertise that is operational for taking out the plant compounds from plant sources. The microwave supported extraction has been employed in several ways to extract bioactive compounds from different plant samples. The isolates from these plant materials are being used in nutraceuticals and pharmaceutical uses. The microwave irradiation is mostly used to resolve some of the drawbacks associated with traditional methods. Table 3.2 presents some of the previous studies and the list of phytochemicals extracted from plants using microwave aided technology. The chemical structure of selected phytochemicals extracted using approach of microwave chemistry are given in Karnataka, India.

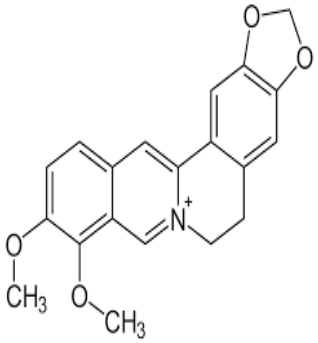
Table 3.2: List of Phytochemicals Extracted by Microwave Chemistry Approach

Sr. No.	Phytochemicals	Source of Plant
1	Artemisinin	*Artemisia annua* L.
2	Berberine	*Berberis aristata*
3	Coumarin	*Melilotus officinalis*
4	Caffeine	Green tea leaves
5	Carvone	*Carum carvi* L.
6	Carvone	*Mentha crispa* L.
7	Curcumin	Turmeric plant
8	Eugenol	*Ocimum basilicum* L.
9	Glycyrrhizic acid	Licorice roots
10	Isorhamnetin-3-O-rutinoside	Sea buckthorn
11	Limonene	*Carum carvi* L.
12	Limonene	*Mentha crispa* L.
13	Linalool	*Ocimum basilicum* L.
14	Monoterpenes	*Lavandula angustifolia* Mill.
15	Oxygenated monoterpenes	*Lavandula angustifolia* Mill.
16	Pectin	Grape fruis

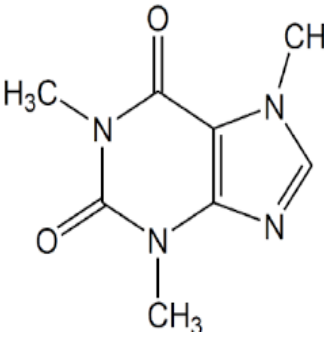
Sr. No.	Phytochemicals	Source of Plant
17	Phenolics chemicals	*Cinnamomum zeylanicum*
18	Polyphenols	Green tea leaves
19	Quercetin	Cranberry
20	Quercetin 3-O-Glucoside	Sea buckthorn
21	Sesquiterpenes	*Lavandula angustifolia* Mill.
22	Silybinin	*Silybum marianum* (L.)
23	Triterpene saponins	*Xanthoceras sorbifolia* Bunge.
24	5,8-Dihydroxycoumarin	Sweet grass leaves
25	5-Hydroxy-8-O-β-D-glucopyranosyl-benzopyranone	Sweet grass leaves



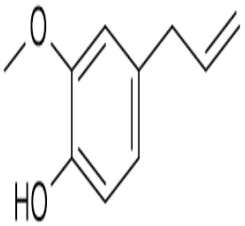
Artemisinin



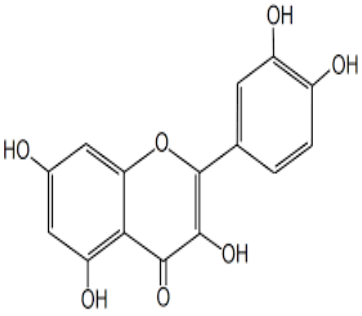
Berberine



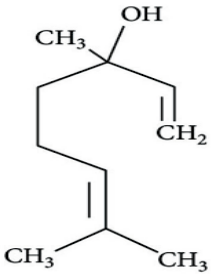
Caffeine



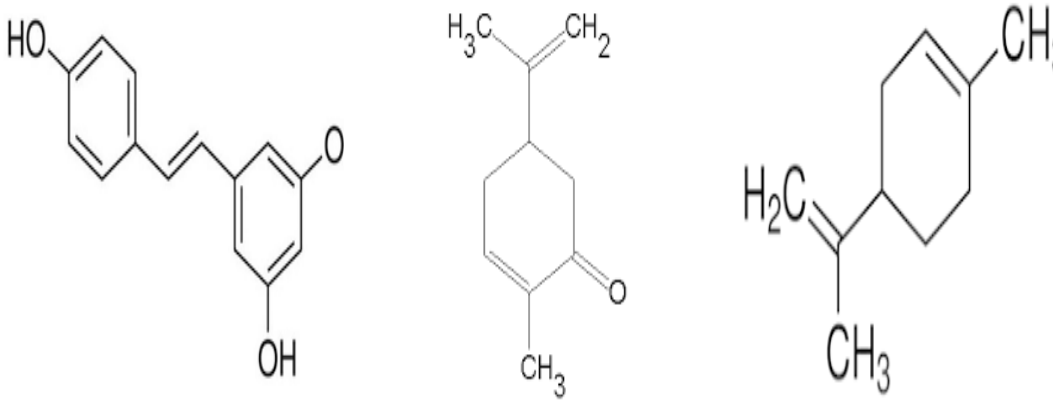
Eugenol



Quercetin



Linalool



Resveratrol **Carvone** **Limonene**

Figure 3.2: Structures of Phytochemicals Extracted by Microwave Chemistry Approach

3.6 Studies Using Microwave Assisted Extraction of Phytochemicals:

a. **Microwave Aided Extraction of Plant Chemicals from Ficus racemosa:** This research was conducted and published in the literature to optimize the microwave aided extraction procedure for the pulling out of plant chemicals from fruits of Ficus racemosa, which is measured as an underutilized and extreme basis of numerous polyphenols. The extreme phytochemical characteristics were found in the optimized conditions using 30 second of time 3.5 of pH, and 360.55 W microwave power using microwave oven. The research work further identified and quantified the presence of ascorbic acid, catechin, gallic acid, tannic acid, and quercetin. The research showed that F. racemosa can be positively applied for the extraction of phytochemicals by microwave supported extraction technique, which can be further used in food and pharmaceutical productions.
b. **Microwave Aided Extraction of Plant Chemicals from *Nonea pulmonarioides:*** In this research investigation the microwave supported extraction tool was selected to isolate the secondary plant chemicals from *Nonea pulmonarioides*. They suggested that the microwave chemistry approach in extraction is an efficient method. In this study of *N. pulmonarioides*, extracted using microwave extraction technique they found that the faster extraction was obtained in 5 minutes of time with an more yield than the maceration extraction technique. The phytochemical screening specified the existence of several classes of plant secondary compounds.

3.7 Conclusion:

The microwave assisted extraction technique has quickly grown during the latest periods as a technique for the extraction of secondary plant compounds which are of pharmaceutical and nutraceuticals attention. This is a model and innovative approach utilized for the extraction of phytochemicals due to several advantages like less extraction time, decrease in the solvent consumption, more precision and accuracy in results, better yield, and

multiple sample extraction etc. This technique has proven to be operative in all features, including inexpensive and practical, compared to old-style extraction practices. Microwave supported technology showed the effective role in the extraction of plant secondary chemicals including alkaloids, flavonoids, terpenes, polyphenols, Coumarin derivatives, and saponins etc. The advanced instrumentation leads to better extraction and it has helped to develop the modern medicines for management of various diseases and disorders. Hence microwave assisted extraction technique is considered to be an emerging trend and one of the model approach in the field of natural products chemistry research especially it has gained more attention and scope in the phyto chemistry and drug development research.

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ISBN: 978-93-94570-79-5

4. Application of Synthesized Ion Exchanger Tin (IV) Vanadomolybdate

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Abstract:

The distribution coefficient of Tin (IV) vanadomolybdateion exchanger for various metal ions revealed that the exchanger is selective for Ni2+ and Cu2+ ions, by the help of KD values. Binary separation of some important metal ion pairs was achieved. The ion exchanger may also be employed in the removal of transition metal ions from their aqueous solution. The effective separation of Ca2+and Mg2+ ions from hard water and the removal of colour metal ions were also achieved.

Keywords:

Distribution coefficient, Binary separation, Water softening, Removal of transition metal ions.

4.1 Introduction:

Ion exchange[1,2] is the process in which ions are exchanged between a solution and an insoluble solid. Ion exchange serves as one of the most important analytical technique for the separation of charged species from a solution that would ordinarily be very difficult and time consuming. Ion exchange process may be done with the help of an ion exchanger, interchange of ions of the same charge by other ions[3]. The earliest systematic studies of ion exchange were described with base exchange in minerals present in the soil[4].Ion exchanger may be natural or synthetic. Most natural ion exchangers like zeolites are crystalline materials having cation exchange properties. First synthetic industrial ion exchanger was reported in 1905[5]. In recent years' various zeolites with completely regular crystal structure have been synthesized and these products are exact counterparts of the natural materials. The examples of such kind of material include zeolite 4A[6] and zeolite A[7]. Now a day's synthetic inorganic ion exchangers have drawn the attention since they are less sensitive to higher temperature and to different chemicals and are also selective to certain ions. Further it was shown that three component ion exchangers show a better IEC than the two component ion exchangers. Tin (IV) based ion exchangers have been studied in detail previously by Varshney et al[8]. Various two component ion exchangers based on tin (IV) were reported in the literature[9-14]. Similarly, some examples of three component ion exchangers reported are stannic (IV)silicomolybdate[15], stannic(IV)arsenosilicate[16], stannic(IV)iodophosphate[17], stannic(IV)molybdophosphate[18], stannic(IV)phospho-tungstate[19] and stannic(IV)arsenophosphate[20]. Trace element can be removed from water by a range of physicochemical method such as membrane filtration, precipitation and ion exchange[21].

The present work is concerned with the application of Tin (IV) vanadomolybdate ion exchanger the synthesized ion exchanger finds several applications in analytical chemistry. Ion exchanger process is applied in several cases for separation of Ions that interfere in many analytical procedures may be removed. Some important application of ion exchanger is binary separation of metal ions, water softening and removal of colour metal ions.

4.2 Requirements:

A. Glasswares: Burette converted into column, Funnel, Glasss wool, Burette stand, Chemical balance, Oven, Mangnetic stirrer, Pipette, Beaker, Glass rod, Test tube with Test tube stand. All glass ware that is used throughout the experimental work was Borosil mark.

B. Reagents and Chemicals: Sodium hydroxide, Lead nitrate, Bismuth nitrate and EDTA were Qualigens product. All the acid that is Perchloric acid Hydrochloric acid, Nitric acid were also Qualigens product. Chemicals such as Zinc acetate, Cobalt acetate, Copper acetate, Nickel acetate, Ammonium chloride were also used in the experimental work.

4.3 Experimental:

A. Distribution Behavior:

In order to examine the affinity of tin (IV) vanadomolybdate towards various metal ions, distribution coefficient (k_d) values for ten metal ions were determined by batch process[22-28]. In this process ten equal portions 0.50g each of the exchanger were treated separately with 25ml of 0.1M aqueous metal salt solutions. The mixtures were then kept for twenty-four hours at room temperature and subsequently determination of metal ions was done by titrating the solutions against the standard solution of EDTA (Complexometric Titration)[23] with the help of appropriate indicators. The k_d values as given in Table 4.1 were calculated according to the formula-

$$K_d = \frac{I - F}{F} \times \frac{V}{W}$$

Where, I – Initial volume of the EDTA solution used

F – Final volume of the EDTA solution used

V – Volume of the metal ion solution taken

W – Weight of the exchanger

Table 4.1: Distribution Coefficient for Different Metal Ions with TVM

Sr. No.	Metal ions	Form	K_d(ml/g)
1	Ca^{2+}	Carbonate	2.54
2	Mg^{2+}	Acetate	6.11
3	Zn^{2+}	Acetate	5.33
4	Cu^{2+}	Acetate	12.25
5	Mn^{2+}	Acetate	0.40
6	Co^{2+}	Acetate	0.20
7	Ni^{2+}	Ammonium sulphate	23.67
8	Pb^{2+}	Nitrate	5.09
9	Bi^{3+}	Nitrate	10.73
10	Cd^{2+}	Chloride	6.36

4.4 Separations Achieved:

The values of separation factor for different metal ion pairs obtained for the exchanger were greater than three and the values are obtained by using following formula.

$$\alpha_B^A = \frac{K_d\ Value\ of\ A}{K_d\ Value\ of\ B}$$

Where

α_B^A is separation factor

A. Binary Separation:

The ion exchanger Tin (IV) vanadomolybdatewas also employed for binary separations of Ni-Pb, Zn-Co, Ni-Co, Ni-Mn, Ni-Mg, Cu-Co Combination as indicated by the value of separation factors for these metalions pairs. In binary separations. 0.50g of the exchanger in H^+ form was packed in glass columns. The column was washed with demineralized water and then metal ion mixtures were poured in column separately. The absorbed metal ions were eluted with appropriate eluents one by one. The flow rate of the effluent was maintained at 1ml/min through the elution process. The effluents were collected separately in different conical flasks and metal ions concentration were determined (Complexometric Titration) against disodium EDTA salt solution using suitable indicators[24-28]. The results are summarized in Table 4.2.

Table 4.2: Binary Separation Achieved with The Help of Tin(IV)Vanadomolybdate

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ni^{2+}	8217	8158	99.21	- 0.79	50ml	0.1M $HClO_4$
	Pb^{2+}	2279	2279	100	0.00	40ml	0.1M HNO_3
2	Zn^{2+}	1831	1766	96.45	- 3.55	40ml	0.2M $HClO_4$
	Co^{2+}	707.16	650.23	91.94	- 8.05	60ml	1.0M NH_4NO_3
3	Ni^{2+}	8217	8334	101.42	+1.42	40ml	0.001M HNO_3
	Co^{2+}	707.16	707.16	100	0.00	60ml	0.1M HNO_3 +0.5M NH_4OH
4	Ni^{2+}	8217	8275	100.71	+ 0.71	50ml	1.0M NH_4Cl + 0.1MHCl
	Mn^{2+}	1540	1428	92.72	- 7.27	30ml	

Sr. No.	Metal ion pairs	Amount loaded(μg)	Amount found(μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
							0.1M HCl
5	Ni^{2+}	8217	8099	98.56	- 1.44	80ml	1.0M HNO_3
	Mg^{2+}	1944	1871	96.24	- 3.76	70ml	0.4M NH_4NO_3
6	Cu^{2+}	2923	2796	95.65	- 4.35	50ml	0.2M HNO_3
	Co^{2+}	707.16	707	99.84	- 0.27	60ml	0.2M $HClO_4$

B. Water Softening:

Hardness causing $Ca^{2+}$and Mg^{2+}were also removed with help of Tin (IV) vanadomolybdate. Column operation was used for the removal of metal ions. The hardness of the water sample was determined by complex metric titration method, in which Eriochrome Black-T was used as an indicator. In water softening, definite volume of hard water sample was passed at rate of 10 drops per minutes through the column maintained the bed of ion exchanger in column. This process is repeated for three times. Hardness causing calcium and magnesium loaded in the column were eluents using 1M HNO_3 and 0.01M $HClO_4$ as eluents respectively. The elution rate was maintained at 5 drops per minute. The eluted Ca^{2+} and Mg^{2+} amount was determined by quantitatively with appropriate indicators. The results are shown in Table 4.3.

Table 4.3. Removal of Ca^{2+} and Mg^{2+} With the Help of TVM

Sr. No.	Metal ions	Amount loaded(μg)	Amount found (μg)	% of Metal ion eluted	% Error	Total elution volume	Eluent used
1	Ca^{2+}	240.5	218	90.65	-9.35	50ml	1.0M HNO_3
2	Mg^{2+}	1775	1750	98.59	-1.41	50ml	0.01M $HClO_4$

C. Removel of Transition Metal Ions:

Application of the exchanger in removing the metal ions from different water samples was done using by Column method. The determination of Co^{2+}, $Ni^{2+}$and $Cu^{2+}$was done ascertain the amount of these ions in their aqueous solutions. The method of determination was done on the basis of two types. In qualitative determination, different definite volumes of the three solutions were loaded on the ion exchanger packed in three different columns.

The flow rate of ten drops per minutes was maintained the solution were passed three times through the exchanger. The effluents of the three columns were collected in three different containers. The presence of the metal ions in all the containers was confirmed by performing qualitative analysis as given in Table 4.4. All the qualitative test was found to be negative.

Table 4.4: Qualitative Tests for Transition Metal Ions for TVM

Sr. No	Metal ion	Colour of the salt solution before passing through exchanger	Colour of the salt solution after passing through exchanger	Detection of metal ion in the effluent
1	Ni(II)	Green	Colorless	a) Effluent NaOH Solution- No Precipitate Ni(II) absent b) Effluent Ammonia- No Precipitate Ni(II) absent
2	Co(II)	Pink	Colorless	Effluent + Sodium hydroxide Solution-No Precipitate Co(II) absent
3	Cu(II)	Blue	Colorless	a) Effluent NaOH Solution- No Precipitate Cu(II) absent b) Effluent Ammonia- No Precipitate Cu(II) absent

For quantitative determination of metal ions, suitable eluents were passed through all the columns containing loaded exchanger.

After elution process the amount of metal ions was determined by complex metric titration using suitable indicators. The results are shown in Table 4.5.

Table 4.5. Removal of Transition Metal Ions with The Help of TVM

Sr. No.	Metal ion	Amount loaded (μg)	Amount found (μg)	% of Metal ion eluted	% Error
1	Co^{2+}	707.16	665.45	94.10	-5.89
2	Ni^{2+}	8217	8092	98.48	-1.52

Sr. No.	Metal ion	Amount loaded (µg)	Amount found (µg)	% of Metal ion eluted	% Error
3	Cu^{2+}	2923	2798	95.72	-4.27

4.5 Result and Discussion:

The study of the values obtained for distribution coefficient revealed that the material shows high selectivity for Ni^{2+} and Cu^{2+} for which the k_d values were 23.67ml/g and 12.25ml/g respectively. The distribution coefficient for the metal ions (Table 1) follows the sequence-

$Ni^{2+} > Cu^{2+} > Bi^{3+} > Cd^{2+} > Mg^{2+} > Zn^{2+} > Pb^{2+} > Ca^{2+} > Mn^{2+} > Co^{2+}$

In binary Separation of different combinations were quite successful through ion exchanger. The exchanger removed different metal ions to different extent such as 650.23µg Co^{2+} was removed out of 707.16µg Co^{2+} while 8334µg Ni^{2+} was removed out of 8217µg Ni^{2+}. The removal is seen from 91.94% to 101.42%. In Ni –Pb separation, the difference between loaded amount and amount found show that lead is 100% eluted with 0% error and nickel is eluted to 99.21% with -0.79% error. The recovery ranges of nickel is present in all combination from 95-100% and the results are summarized in Table 2.

The synthesized ion exchanger Tin(IV)vanadomolybdate can removed Ca^{2+} and Mg^{2+} from hard water and it may helpful in water softening. The results for these ion exchanger implies that Mg^{2+} can be removed from hard water up to 98.59% and removed of Ca^{2+} is 90.65% and the results are shown in Table 3.

The role of the ion exchanger is found to be useful in decontamination of the chemicals. Detection of the metal ions are (qualitative analysis) made it possible decide the determination process. The results are shown in Table 4. Quantitative determination of metal ions in a sample helped in knowing the amount of metal ion present which in turn was helpful to decide the exchange process. The observation table clearly indicates that Tin (IV) vanadomolybdate was found to be able to decontaminate cobalt 94.10%, Nickel 98.48% and 95.72% Copper respectively. The results are shown in Table 5.

4.6 Conclusion:

In the present work the analytical applications are performed for Tin (IV) vanadomolybdate. The ion exchanger possesses selectivity for trace metals such as, Ni^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+}. The ion exchanger is also employed for the binary separation of heavy metals present in aqueous media and also used as in water softening.

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ISBN: 978-93-94570-79-5

5. Biomaterials: Review and Applications

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Abstract:

Since it has been around for almost 50 years, the science of developing biomaterials is not a recent one. The study of biomaterials is known as biomaterial science. It is a contentious field of study that has expanded consistently and dramatically throughout the duration of its existence, with various companies investing sizeable sums of money in the development of new products. Biomaterial science encompasses tissue engineering as well as biology, chemistry, and materials science.

Keywords:

Biomaterials, Review

5.1 Introduction:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. When applied to a more interactive application, such as hydroxyapatite-coated hip implants (such as the Furlong Hip, manufactured by Joint Replacement Instrumentation Ltd. in Sheffield), biomaterials can be either benign or bioactive. One such instance is Sheffield, where such implants can endure up to twenty years. Additionally, biomaterials are regularly utilized in medical procedures, dentistry, and drug delivery.

Although it has been challenging to define the term "biomaterial," more commonly " working definitions that are recognized include: A biomaterial is any material, natural or man-made, that comprises whole or part of a living structure or biomedical device that performs, augments, or replaces a natural function."

A. Applications:

- Joint replacements
- Blood vessel prostheses
- Bone cement
- Bone plates
- Bone cement
- Artificial ligaments and tendons
- Dental implants for tooth fixation
- Contact lenses
- Cochlear implants

Here are the 2 examples.

first intraocular lens

Basic components: Silicone and PMMA (acrylic).


Combining long-term biocompatibility with optical performance is difficult.

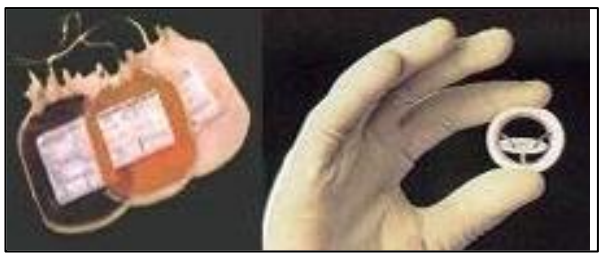



B. Artificial Hip Joints:

Stainless steel, titanium and its alloys, and UHMWPE are the basic materials. Prevention of wear and loosening over long durations (10–15 years) is a challenge.

C. Substitute Heart Valves:

D. Indian Chitra Heart Valve:



E. Vascular Grafts:

Dacron, Teflon, and polyurethane are the basic materials.

Maintenance of mechanical integrity and long-term blood compatibility are obstacles (avoidance of blood clotting).

The proximal load transfers for the human complete hip system shown below is provided by a titanium, dual tapered stem design, significantly lowering possibility of the calcar resorption and proximal hypertrophy Not a fool! System offers a straight stem design and an anatomic fit. Polyethylene serves the function of cartilage in this application. Biomet Corporation is the cited to learn more about hip replacement and the situations under which it is performed, visit the Medline Plus website (many great illustrations).

5.2 Some Commonly Used Biomaterials 2:

a. Silicone rubber
b. Dacron
c. Cellulose
d. Poly (methyl methacrylate)
e. Polyurethanes
f. Hydrogels

g. Stainless steel
h. titanium
i. Alumina
j. Hydroxyapatite
k. Collagen (reprocessed)

Applications:

- Catheters, tubing
- Vascular grafts
- Dialysis membrane
- Intraocular lenses, bone cement
- catheters, Pacemaker leads
- Opthalmological devices, Drug delivery
- Orthopedic devices, stents
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Orthopedic & Dental devices
- Ophthalmologic applications, wound dressings

A. Protein-Surface Interactions in Biomaterials:

The underlying cause of medical device biocompatibility—or lack thereof—is protein–surface interactions. Proteins quickly adsorb onto the surface of a solid substance that comes into contact with a fluid containing soluble proteins, like a catheter, stent, hip joint replacement, or tissue engineering substrate (such as blood, interstitial fluid, cell culture media). Within seconds to minutes, this saturation happens. Because of this, living cells actually make touch with the molecular structure of a biomaterial when they approach its surface. Living cells are larger than proteins and move more slowly adsorbed protein layer rather than the surface of the material itself. Of course, cells cannot "see" the layer of adsorbed proteins; instead, they probe their environment using membrane-bound receptors that can bind to specific bioactive features that the adsorbed proteins provide.

Following their binding, these receptor-protein interactions are then conveyed through the cell membrane via a number of carefully regulated molecular mechanisms in such a way as to excite particular intracellular activities that ultimately define the response of a cell. As a result, how bioactive locations differ offered by the protein layer that is absorbed is the most essential factor in determining cellular response.

The number, kind, and packing arrangement of proteins that are adsorbed as well as it is possible to control their packing, conformation, and direction on the biomaterial's surface. The emphasis will be on showcasing a few among the most fascinating relatively recent techniques that have been developed and applied to increase our comprehension of the sub molecular principles underpinning how surface chemistry impacts the orientation, conformation, and organisation of adsorbed proteins.

If we want to move past moving from the mostly trial-and-error-based surface design of the present to a future where surfaces are purposefully created to directly regulate adsorbed protein bioactivity, and hence govern cellular response, we must continue to develop our understanding of these processes. Though conceptually straightforward, the vast variety has been made possible—and continues to be made possible—by the complex structural features of soluble proteins found in physiological fluids. —a very difficult subject.

B. Computer Simulation of Protein Adsorption to a Material Surface in Aqueous Solution: Biomaterials Modeling of a Ternary System.

Because biomaterials frequently come into touch with the body or body fluids, crucial aspects like biocompatibility and bio reactivity are controlled by interfacial processes, particularly protein adsorption. A mechanistic understanding of the interactions the development of biotechnology tools like DNA/protein micro arrays and micro fluidic systems will also require the improvement of the interface between biological macromolecules and material surfaces. As a result, the atomistic characterization of structure function correlations at the interface between biological macromolecules and materials surfaces will be crucial for the development of a wide range of bioengineering and biotechnology applications in the future.

They used typical computer modelling software to simulate protein adsorption to a material surface in water. Bovine pancreatic trypsin inhibitor was used to model a multi-component system in which a hydrated protein was present (BPTI), comes into contact with a MgO surface in pure water, molecular dynamics and local minimization were used. In water and in living things, soluble proteins are known to bind to charged substance surfaces. In three distinct initial protein orientations, the simulations demonstrate the binding of BPTI with binding energies of 242, 350, and 241 kcal/mol to MgO in water. Our research shows that in this watery environment, there is hardly any interaction between the atoms of the protein and those of the surface. The solvation layer facilitates important surface binding mechanisms in the interphase (double-layer) area. Although this fact is often not explicitly taken into consideration in the protein adsorption literature, it is anticipated on the basis of traditional electrochemical theory.

C. Carbohydrate derived protein resistant biomaterial:

The Side-chain polyethers obtained from carbohydrates can be made using monomers made from naturally occurring carbohydrates to condensation polymerize. These substances are biodegradable, resistant to proteins, and allow for functionalization in places other than the chain ends. To accomplish desired protein resistance, biodegradability, and/or functionalization, the compounds of the present invention may be formed, at least in part, into various devices, apparatus, and manufactured goods.

D. Hard Tissue: Biomaterial Interactions:

Because bone and cartilage are prone to damage, biomaterials—artificial and modified natural materials—have been effectively employed for many years to replace and/or regenerate these tissues. Science has lately developed the idea of tissue engineering, which

combines the use of biomaterial-based scaffolding, cultured cells, systemic and/or local hormones/mediators, and, more recently, genetic modulators, to try to restore damaged tissues. Since many years ago, musculoskeletal illnesses and disorders have been treated extensively with tissue engineering products, which are essentially biomaterials of various shapes and forms. Currently, materials for replacing bone, cartilage, and joints include ceramics made of hydroxyapatite (HA), calcium phosphate, and polymers like polymethyl methacrylate, as well as metals like titanium, cobalt-chrome, and steel in pure and/or alloy form.

E. Modeling and Simulation of Biomaterials:

Simulation and modelling are being used more and more in materials research. The authors of this paper cover modelling and simulation applications in the emerging subject of biomaterials. The authors don't cover biochemical or biological applications in order to somewhat condense the subject; instead, they concentrate on the structure and characteristics of biomaterials. an explanation of how molecules and groupings of molecules can be studied using atomistic level simulation. After that, we concentrate on simulations of structure and behaviour at the mesoscale, followed by a brief discussion of continuum scale methods.

F. Nano Biomaterials:

Enzymes have been included in detergent recipes for a very long time to help combat particularly difficult filth. Chemical engineer Jonathan Dordick of Troy, New York's Rensselaer Polytechnic Institute is advancing the fight against dirt by employing nanotechnology to create a self-cleaning plastic in which the enzyme molecules are a fundamental component of the substance. The enzymes in the plastic attack bacteria and other pathogens when they come into touch with it, preventing them from adhering to its surface.

G. Bioengineering of Improved Biomaterials Coatings for Extracorporeal Circulation Requires Extended Observation of Blood Biomaterial Interaction under Flow.

Cardiopulmonary bypass systems are frequently hindered by the thrombus development and also infection after prolonged use. The CPB circuitry's insufficient hem compatibility is one cause of several of these issues. In biomaterials science, creating true long-term hem compatibility of biomaterial surfaces is largely unexplored territory. For instance, the bulk of studies evaluating the interactions between blood and biomaterials under flow using the well-known Chandler loop model have only been described for a maximum of two hours.

Two commercial CPB tubings with hem compatible coatings were thoroughly compared in this study with one uncoated control. Examining human whole blood from four separate donors while it was flowing for five hours, analyzing luminal surfaces with scanning electron microscopy, and timing the formation of thrombin were all part of the study. The research showed that the tubing's hem compatibility varied. Furthermore, it seemed that one could only tell one biomaterial covering from another after several hours of blood contact.

Platelet counting, myeloperoxidase quantification, and scanning electron microscopy were the most efficient methods. It is believed that these findings are relevant to the bioengineering of extracorporeal devices that are intended to work for lengthy periods of time in contact with blood.

H. Protein-Based Vascular Tissue Engineering Advances:

Vascular tissue engineering is driven by improved blood artery replacements are clinically necessary, especially for small-diameter applications. Although the blood vessel's form and function are well known, because it is a complicated tissue, it has been difficult to create engineered tissues that are suitable for widespread clinical application. This article discusses vascular tissue engineering techniques that use proteins as the primary matrix or "scaffold" material to create fully biological blood vessel substitutes.

This review specifically discusses the following four vascular tissue engineering methods: Protein hydrogels with cells, crosslinked decellularized natural tissues, self-assembled scaffolds, and protein scaffolds are the first four types of materials. These approaches' benefits and limitations are highlighted together with recent developments in each of these field.

I. Biomaterials: where we have been and where we are going:

The field of biomaterials has had sustained expansion with the steady introduction of fresh concepts and fruitful branches since its founding just over 50 years ago. This assessment outlines our progress to date, the current state of the art, and potential future developments. Here, they highlighted some of the most recent developments in biomaterials with the goal of regulating biological reactions and ultimately promoting healing. Biologically inspired materials that mimic natural processes, the creation of sophisticated three-dimensional (3D) architectures to provide clearly defined patterns for diagnostics, the synthesis of synthetic materials with regulated qualities for medication and cell carriers, and precision immobilization of signalling groups on surfaces are all included in this new generation of biomaterials.

J. Biomaterials for Blood Contacting Applications:

Biomaterials should be taken into account for applications involving blood contact while also considering blood-biomaterial interactions, blood response parameters, and evaluation techniques.

When analyzing blood-biomaterial interactions, factors such protein adsorption, platelet responses, intrinsic coagulation, fibrinolytic activity, erythrocytes, leukocytes, and complement activation can be taken into consideration. Blood response to a biomaterial in a therapeutic environment is influenced by the biomaterial's structure, the presence of an antithrombotic agent, the patient's condition as indicated by the disease and pharmacological therapy, and the particulars of the application. Ex vivo and in vitro procedures are important for biomaterial development, and there are choices for clinical, in vivo, ex vivo, and in vitro evaluation of biomaterials.

K. Biomaterials in Canada: The first four decades:

The 1960s saw the start of Canadian biomaterials research. Significant advancements in a wide range of fields, over the past 40 years, a variety of biomaterials have been developed, including dental, orthopedic, cardiovascular, neurological, and ophthalmic materials. Canadians have also been involved in the tissue engineering derivative industry. The federal and provincial governments provide the majority of the funding for the biomaterials laboratories that are now present at universities and other research institutions from coast to coast. Initiated in 1971, the Canadian Biomaterials Society has contributed significantly to the growth of the industry. In 1996, the Society hosted the Fifth World Biomaterials Congress in Toronto. An overview of Canadian researchers' work during the previous four decades is provided. The scientific field of biomaterials and tissue engineering is deemed to be mature and robust in Canada and is predicted to remain so in the future.

L. Future directions in biomaterials:

The field of medicine has greatly benefited from biomaterials. However, there are still several difficulties. This essay examines three pertinent topics with significant medical issues. First, drug delivery systems; important factors to take into account are interactions between pharmaceuticals and polymers, drug transformation, drug diffusion characteristics, and, if polymer degradation occurs, the products of polymer degradation through polymer matrices. New tailored polymers are also being developed for specialized applications including vaccination and pulsatile release. Second, how cells interact with polymers, including what happens to inert polymers, how to use polymers as templates for tissue regeneration, and how to investigate polymers that make cell transplantation easier. The third category is orthopedic biomaterials, which includes fundamental research on the behaviour of chondrocytes, osteocytes, and connective tissue-free interfaces as well as applied research using computer-aided design of biomaterials and the production of orthopedic biomaterial.

M. Smart Biomaterials Design for Tissue Engineering and Regenerative Medicine:

Tissue engineering (TE), a significant approach in regenerative medicine, has been an active area of scientific research for almost three decades. However, due in part to the small number of biomaterials that have been given human use approval, the clinical application of TE technology has been somewhat constrained.

Even though a lot of great biomaterials have been created recently, their implementation into clinical practice has been delayed. Since biodegradable polymers were initially licensed for use in humans over 30 years ago, many researchers still utilize them today.

N. Systematic Effects of Biomaterials:

The tissue reaction at the implant site is typically the main focus of analyzing the host's reaction to implanted biomaterials. Similar to how looking at battles out of their historical context can lead to incorrect judgements, this can also.

A larger perspective reveals a number of potential and actual systemic consequences of a bacteriological, immunological, metabolic, and carcinogenic character. The absence of epidemiological data makes it difficult to identify these impacts in patients.

O. Biomaterials and Biomedical Devices:

The variables crucial to the integration of biomaterials and technology into tissue are covered in this review. Surface modification approaches and surface-sensitive analytical techniques are mentioned. The effectiveness or biocompatibility of specific biomaterials and devices are assessed using in vitro procedures. There is discussion of current and future directions in dialysis, artificial organs, plasma and cytapheresis, artificial blood or bone substitutes, orthopaedic prostheses, dental materials, neural prostheses, and cardiovascular materials.

P. Biomaterials for Healthcare:

Animal-derived islets were encased in a device with a membrane composed of polycarbonate and a support. The encapsulation chamber was given an extracellular matrix to prevent the islets from congregating. By interconnecting 20 devices, it was possible to implant up to 20 000 pancreatic islets, as needed for testing on a mini-pig in a plate-type support. After up to 92 days following implantation, the biocompatibility of sterile macro devices was examined in normal mini-pigs. Despite the generation of fibrosis, the peripheral immune system did not significantly change or show any signs of an inflammatory response.

Q. Optimization Studies on the Features of an Activated Charcoal supported Unease System:

The enzymatic hydrolysis of urea has been made possible by the successful adsorption of urease onto activated charcoal derived from petroleum. The enzyme support system has been plasma polymerized to coat hexamethyl disiloxane, resulting in a biocompatible surface. Electronic Chemical analysis using spectroscopy and scanning electron microscopy methods were used to evaluate the effectiveness of the resultant coat. Studies on the urease's adsorption, activity, and stability on the support have been made in an effort to improve the properties of the urease supported by charcoal and increase its accessibility for usage in clinical applications.

R. Bioactive Specific Biomaterials: Present and Future:

In order to interact specifically with living systems, bioactive biomaterials are replaced with specific chemical functional groups carried by the macromolecular chain and made of synthetic or artificial polymers.

These polymers, which can be soluble or insoluble, are made from dextran and polystyrene. When these modified polymers come into contact with circulating blood, they have low thrombogenicity because they may be endowed with anticoagulant heparin-like characteristics. It has been specifically designed for other functional polymers to interact with immune system elements.

Other polymers can influence cell development and biological activity or only biological activity when in contact with cells, without necessarily changing all of the features of the cells. From the aforementioned ideas, it is conceivable to show that the biological features of these polymers correlate with a statistically random chemical group distribution along the macromolecular backbone.

S. Macromolecular Engineering of Fluorinated Polymers and Hybrid Composites for Dental Resoration Application:

Investigated were novel polymeric materials that shrink less during polymerization and have low surface energy. New fluorinated ring-opening monomers were synthesised in order to produce the requisite polymers and composite resins. Different polymeric and co-polymeric systems' properties, including reactivity, chemical composition, thermal behaviour, and surface features, were thoroughly investigated. Even at comparatively low fluorinated chain side group concentrations, the ordering of the fluorinated groups caused the polymers to form liquid crystalline mesophases. Surface studies showed the existence of uniform, well-ordered surfaces with low surface tension due to the fluorine enrichment of the air-polymer interface. Fluorinated ring-opening monomers and crosslinkers were used to create dental composite resins. The function of the components in the resin formulations was evaluated in terms of bacterial adhesion, surface topography and composition, and mechanical properties. Without appreciably changing the mechanical properties, the introduction of fluorinated groups resulted in a significant decrease in volume shrinkage. There was a suggested relationship topography, surface energy, and fluorine surface segregation.

T. Toward A Suture Less Vasovasostomy: Use of Biomaterials and Surgical Sealants in A Rodent Vasovasostomy Model:

Vasectomy reversal has become a routine treatment with an annual reversal rate of 3% to 8% and 500,000 to 800,000 vasectomies performed. The gold standard for surgical vas reconstruction is still a two-layer microsurgical vasovasostomy. The process is time-consuming and technically difficult. They discovered how biomaterials and surgical sealants might cut down on the amount of sutures needed, improve the water tightness of anastomoses, and shorten operating times.

5.3 Conclusion:

A substance that has been altered for usage in a medical environment is essentially a biomaterial. Biomaterials may be bioactive or serve a benign purpose, such as in the construction of a heart valve such as hydroxyapatite-coated hip implants, which last up to twenty years and are used for more interactive purposes.

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ISBN: 978-93-94570-79-5

6. Supramolecular Chemistry, Types of Supramolecular Systems and Its Applications

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6.1 Supramolecular Chemistry:

Supramolecular chemistry, also known as "chemistry beyond the molecule", is a fast-expanding discipline concerned with the chemical interactions of molecules. Recent years have seen a substantial increase in interest in this topic as a result of the possibility of developing novel materials and systems with distinct functions. In this chapter, we will discuss the fundamental concepts of supramolecular chemistry, recent trends and advancements in the field, and potential future applications. Supramolecular chemistry is fundamentally concerned with the interactions between molecules that take place via non-covalent interactions [1], such as hydrogen bonding, metal coordination, hydrophobic interactions, etc., [2]. Through their interactions, molecules can create intricate structures known as supramolecular assemblies, which can exhibit their unique properties. And behavior is different from those of the individual molecules.

One of the main goals of supramolecular chemistry is to design and synthesize molecules that can self-assemble into well-defined structures. These structures can have a wide range of functions, such as the ability to store and release energy, conduct electricity, or act as catalysts. [3] Supramolecular chemistry has several important applications in various fields such as medicine, materials science, nanotechnology, etc.

In medicine, supramolecular systems can be used for targeted drug delivery, as the self-assembling nature of these systems allows for specific targeting of diseased cells. In materials science, supramolecular systems can be used to create new materials with improved mechanical and thermal properties. In nanotechnology, supramolecular systems can be used to create nanoscale devices with a range of applications. [4]

In recent days, supramolecular chemistry is focused on the development of new materials and devices with improved properties and also the development of new synthetic methods and characterization of supramolecular systems. In addition, the development of new theories and models can easily understand their behaviour in the application of these systems in real-world problems, due to the numerous applications and the potential for further discovery, supramolecular chemistry remains a rapidly growing and exciting field.

6.2 Mechanically Interlocked Molecules (Mims):

Mechanically interlocked molecules (MIMs) are a class of supramolecular compounds that are held together by non-covalent interactions, such as hydrogen bonding, electrostatic interactions, and van der Waals forces [5]. There are several different types of MIMs, each with its own unique properties and potential applications. Some of the most well-known types of MIMs are discussed in this chapter.

A. Rotaxanes:

Rotaxanes are a class of molecular structures that consist of a macrocycle, or large ring, that surrounds a smaller and linear component called an axle. The axle is able to move within the macrocycle but it is prevented from completely escaping from the macrocycle due to the presence of one or more stoppers, like bulky groups, that are attached to the axle. This unique mechanical bond between the macrocycle and the axle makes rotaxanes an attractive subject for research in the field of supramolecular chemistry. The structure of rotaxanes resembles A dumbbell-shaped molecule with a ring trapped between its two ends.

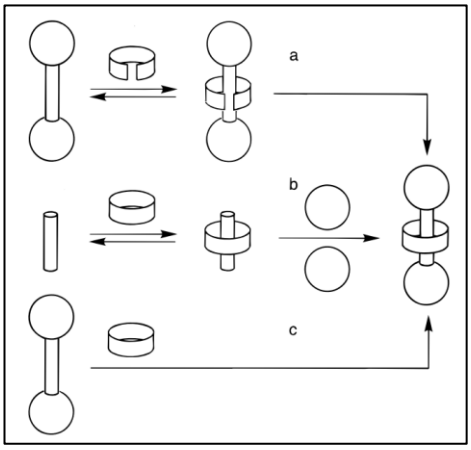

Figure 6.1: Three different approaches to the construction of rotaxanes: (a) “clipping”; (b) “threading”; (c) “slippage” [5].

Rotaxanes have been shown to have potential applications such as drug delivery [6], chemical and biological sensors [7], and data storage [8] due to their ability to undergo dynamic changes in conformation and responsive behavior to external triggers. Furthermore, rotaxanes also have the potential for use in molecular machines and devices as their mechanical bond allows for rotational motion and/or translation of the axle [9].

B. Catenanes:

Catenanes are a class of molecular structures in which two or more interlocked macrocycles are connected in a "chain" formation. They are similar to rotaxanes, but with multiple macrocycles linked together. Catenanes are named based on the number of interlocked rings, e.g. a [2] catenane consists of two interlocked rings (Figure 6.2). The "ane" ending of the term is a reference to alkanes, and catenanes are typically considered to be organic compounds, although they may not always consist of hydrocarbon groups. In situations where the interlocked ring system can act as a ligand for a metal centre, the terms [n] catenand and [n] catenate may also be used, in analogy with the terms cryptand and cryptate. The term "catenand" refers to the free ligand that forms a catenate complex in the presence of metal ions [10].

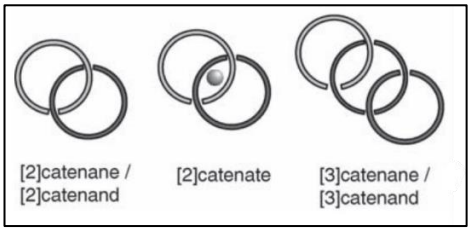

Figure 6.2: Nomenclature and schematic representation of Catenanes [10].

The synthesis of catenanes can be challenging, but various methods have been developed, including template-directed synthesis, mechanically interlocked synthesis, and chemical synthesis [11]. Catenanes have potential applications in fields such as molecular electronics, drug delivery, and as molecular machines. Their unique properties, including their ability to perform mechanical movements in response to external inputs, can be utilized for switching and sensing purposes. They have also been explored as molecular shuttles, molecular switches, and artificial muscles [12].

C. Clathrates:

Clathrates are a class of molecular structures in which a host molecule encapsulates or "traps" a guest molecule inside a cage-like structure. The host molecule forms the walls of the cage, and the guest molecule is held inside by non-covalent interactions such as hydrogen bonding or van der Waals forces.

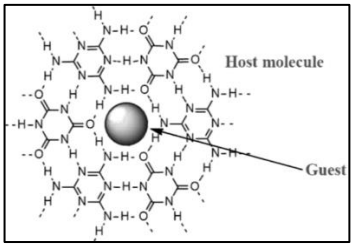

Figure 6.3: Schematic representation of Clathrates

Clathrates have been found in various forms of matter such as gases, liquids, and solids. In the field of chemistry, clathrate hydrates are known for their ability to trap gases such as methane and carbon dioxide, making them of interest for natural gas storage and carbon capture [13]. They also have potential applications in various fields such as drug delivery, catalysis [14], storage of gases like natural gas, hydrogen, and others in solid form, treatment of wastewater and concentration of organic mixtures, as well as separations and storage of gas mixtures. Clathrates are a topic of ongoing research, and the full potential of these structures is yet to be fully understood and harnessed. Further research is needed to develop new synthetic methods and to better understand the properties of these complex structures.

D. Cavitands:

Cavitands are a class of molecular structures that are characterized by a "cavity" or a hollow interior space. These cavities are formed by the arrangement of atoms or chemical groups in a specific way, and they can be either hydrophobic or hydrophilic in nature, which has potential applications in various fields like molecular sensors [15], catalysis, drug delivery, and separation science. In separation and purification, cavitands can be used to sort and isolate specific molecules, such as proteins and enzymes, based on their size and shape. They have also been explored as scaffolds for the formation of supramolecular assemblies, and in the field of host-guest chemistry as receptors for specific molecules [16].

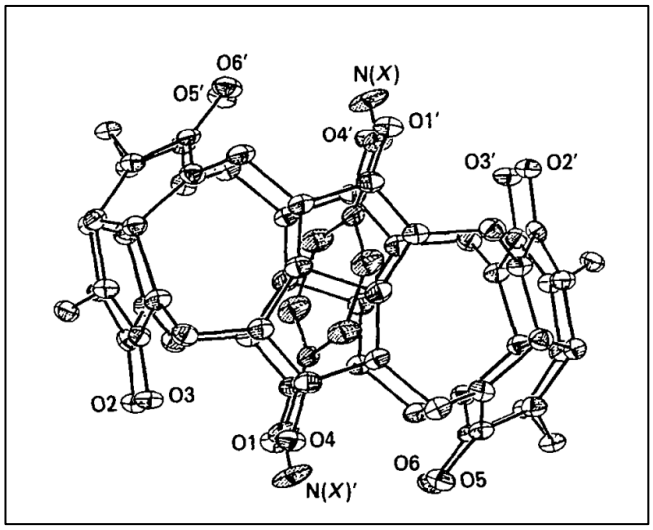

Figure 6.4: A cavitand (cucurbituril) bound with a guest p-xylylenediammonium [16].

F. Cryptands:

Cryptands are a class of molecular structures that have found significant application in the field of supramolecular chemistry. They are characterized by a "crypt" or a hollow cavity that can selectively bind or "capture" specific guest molecules within it. The structure of cryptands is composed of a macrocyclic ring with a number of binding sites that can interact

with specific guest molecules via non-covalent interactions viz., hydrogen bonding or electrostatic interactions. In supramolecular chemistry, cryptands have been used to form various types of assemblies, including host-guest complexes, supramolecular polymers, and supramolecular gels. They have also been explored as receptors for specific molecules, such as small ions or metal ions [17].

Cryptands have numerous applications in a variety of fields such as chemistry, biochemistry, materials science, etc. Their ability to selectively bind specific guest molecules makes them attractive for use in chemical separations, and the formation of supramolecular assemblies can be used to create new materials with specific properties. These molecules are valued for their high selectivity and specificity in recognizing cations, anions, neutral molecules, and even isotopes. They play a crucial role in ion transportation studies and are used as stationary phases in column chromatography for separating cations, anions, and isotopes. In addition, they are utilized in the study of redox systems, photo physical properties, non-linear optics, amphiphiles, sol-gel materials doping, and as structural directing agents in synthesis [18].

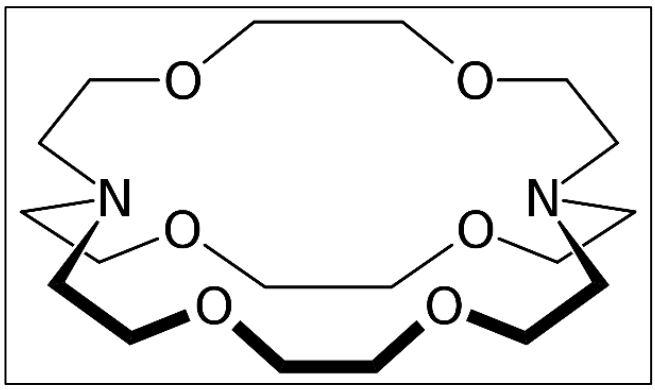

Figure 6.5: Structure of [2.2.2] Cryptand

6.3 Molecular Self-Assembly:

Molecular self-assembly is a fundamental concept in supramolecular chemistry that refers to the process by which individual molecules come together to form ordered structures without any external inputs. This process is driven by non-covalent interactions such as hydrogen bonding, electrostatic interactions, and van der Waals forces. Self-assembly has been used to create a wide range of structures including, but not limited to, vesicles, fibers, gels, and even more complex supramolecular systems [19]. The ability to manipulate and control the self-assembly process is of great interest in supramolecular chemistry, as it allows the creation of new materials with specific properties [20]. Self-assembly can be directed by various strategies such as the use of pre-designed templates or by controlling the chemical composition and stoichiometry of the system. The utilization of self-assembling peptides, small molecules, and lipids is also gaining recognition as a flexible approach to creating new materials with specific characteristics [21]. Molecular self-assembly is an active area of research in supramolecular chemistry and has potential applications in fields such as materials science, nanotechnology, biotechnology, etc.

A. Micelles:

Micelles are a form of supramolecular structures that are composed of a core of hydrophobic units surrounded by a shell of hydrophilic groups. They form spontaneously in water-based solutions and are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Micelles are of great interest in supramolecular chemistry due to their ability to encapsulate hydrophobic molecules and act as a carrier for drugs and other hydrophobic molecules, allowing for targeted drug delivery and improved bioavailability [22].

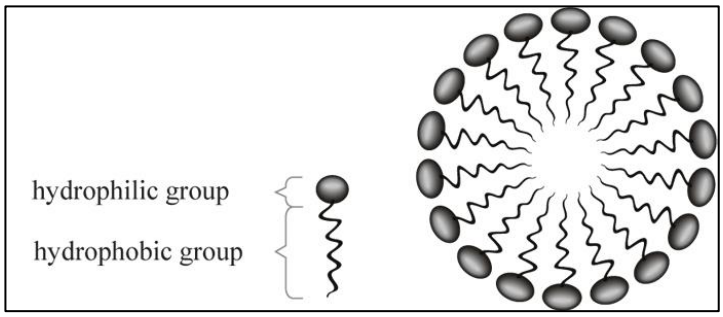

Figure 6.6: Schematic Structure of Micelle

Micelles have a wide range of applications due to their unique properties. Including, drug delivery, biomedical imaging, environmental remediation, cosmetics, etc [23].

B. Lipids:

Lipids are a class of biomolecules that play an important role in supramolecular chemistry. They are composed of a hydrophobic tail and a hydrophilic head, which allows them to spontaneously form structures such as vesicles, bilayers, and micelles in aqueous environments. These structures, known as lipid assemblies, have unique properties that make them of great interest in various fields, including cosmetic and food industries, and in nanotechnology [24]. Lipid assemblies have been used as a model for cell membranes and have been explored as a carrier for drugs and other hydrophobic molecules in targeted drug delivery [25].

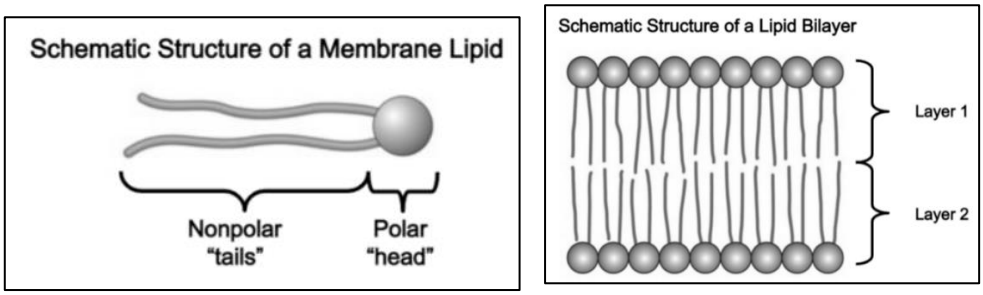

Figure 6.7: Schematic Structure of Lipids

Lipid assemblies have also been explored as a scaffold for the formation of supramolecular assemblies, and as a tool to understand the principles of self-assembly.

C. Liposomes:

Liposomes are a type of supramolecular structure that is composed of a phospholipid bilayer enclosing an aqueous compartment [26]. They are stabilized by non-covalent interactions such as hydrogen bonding and van der Waals forces. Liposomes have been used as a carrier for drugs, allowing for targeted drug delivery and improved bioavailability. Additionally, they have been explored as a means of gene therapy and as a tool for delivering drugs to specific cells or tissues [27].

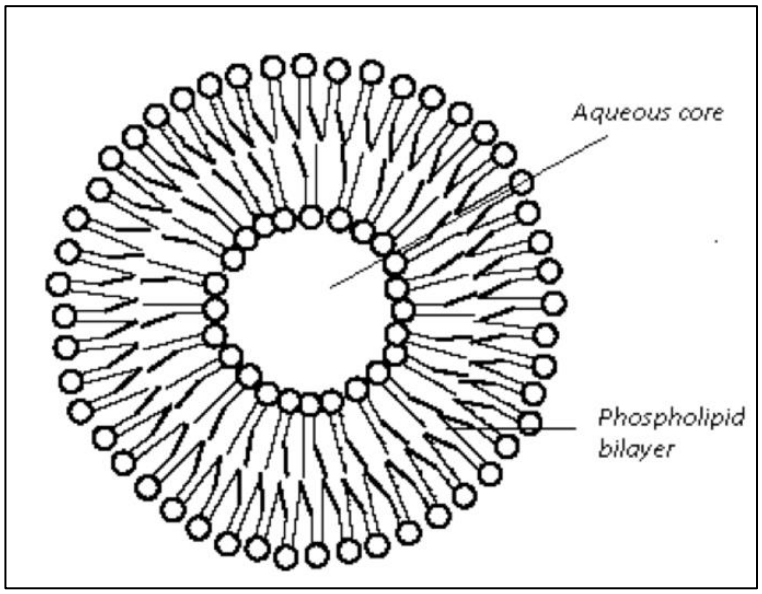

Figure 6.8: Schematic Representation of A Liposome

Liposomes have been used to create new materials with specific properties, such as liposome-based membranes for separation and filtration. Liposomes have also been found to be useful in the field of 'sensing', as they are able to encapsulate and detect specific molecules [28]. In addition, it is also useful in various fields like healthcare, cosmetics, medical imaging techniques, and the agricultural industry.

6.4 Molecular Recognition (Host-Guest Chemistry):

Molecular recognition is the specific interaction between more than two molecules via non-covalent interactions such as hydrogen bonding, metal coordination, hydrophobic forces, Van der Waals forces, pi-pi interactions, electrostatic, and electromagnetic effects. The molecule that receives an incoming entity is referred to as a host molecule, while the incoming entity itself is known as a guest molecule. The main concept of molecular recognition is lock and key. In this model, the host molecule makes interaction with a guest molecule or ion.

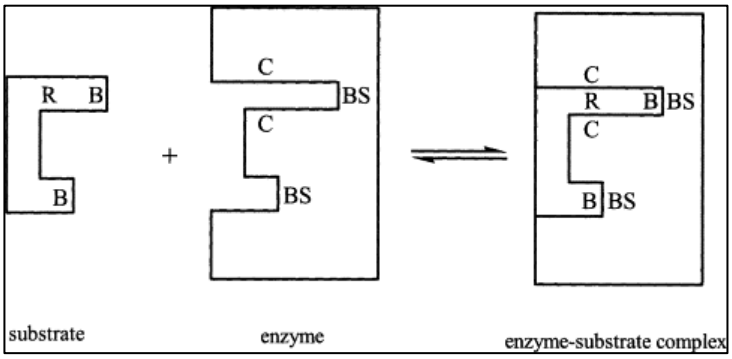

Figure 6.9: Lock and Key Model

Host + Guest= Host Guest Complex; Host = Enzyme; Guest = Substrate

In this complex, the host molecule is bigger in size and also has hollow nature than the guest molecule. Such kinds of interactions are mainly known as the bio-recognition process. Eg., enzyme–inhibitor, antigen-antibody, and DNA- protein interaction.

A. Crown ether:

Crown ethers are the first class of artificial host cyclic compounds which consist of ring groups containing ether (R-O-R). The most common crown ethers are oligomers and ethylene oxide. E.g.; 18-crown-6

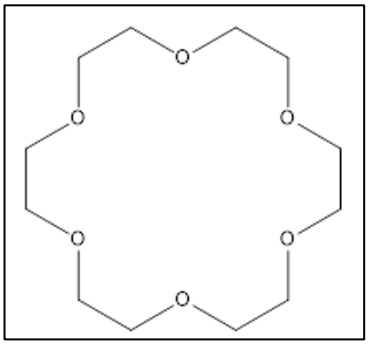

Figure 6.10: Structure Of 18-Crown-6

In the crown ether, the number used in the first is referred to as the number of atoms in the system and the last one says the number of oxygen atoms present in that system. Crown ethers are strongly bound to form complexes with metal ions based on the size of the atom. Crown ethers are soluble in nonpolar solvents because of their hydrophobic character which is mainly useful in phase transfer catalysis [29].

The modification of crown ethers, based on their number of the atom to giving various crown ethers by attaching some functional groups to the edges of the crown ethers, which enrich them with some interesting properties and made them ideal candidates for the fabrication of supramolecular polymers [30].

B. Cyclodextrin:

Cyclodextrin is a naturally occurring cyclic host molecule, which is a family of oligosaccharides of a macrocyclic ring of the glucose subunits joined by 1,4 glycidic bonds constituted by 6-8 glucopyranoside units. Which is prepared by the treatment of starch materials with enzymes. The CD has the molecular recognition capacity, and also enhanced their properties through chemical modification by introducing the –OH groups on the exterior rims. β-CD derivatives are widely used as greener textile auxiliaries for potential applications in the textile industry [31]. E.g.; β cyclodextrin

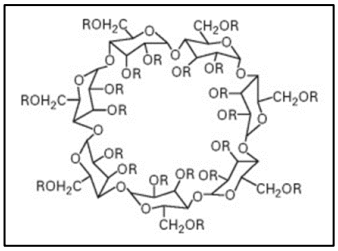

Figure 6.11: Structure Of B Cyclodextrin.

Cyclodextrin sponges are a microporous newly cross-linked 3D network of cyclodextrin that was designed as novel delivery for the lipophilic or hydrophilic active agents. Cyclodextrin's hydrophobic outer cavity and hydrophilic inner cavity enable their ability of novel delivery. Cyclodextrin possesses various applications like they are versatile absorbent for volatile organic compounds abatement [32].

C. Polyamine:

Replacing an oxygen atom in the crown ethers by nitrogen atom-induced cyclic hosts are called macrocyclic polyamines, many synthetic polyamines feature NCH_2CH_2N linkages which contain more than two amino groups most of the alkyl polyamines are natural and some of them are synthesized by the laboratory. Several synthetic polyamines are used in the chemical industry and the research laboratory. They are mainly used as additives to motor oil and as co-reactants (cold hardeners) with epoxy resins. E.g.; Cyclen

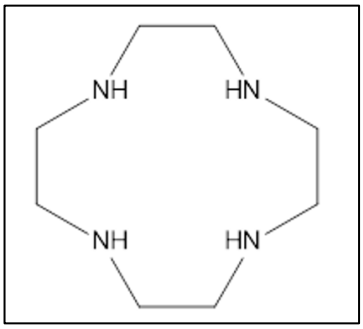

Figure 6.12: Structure Of Cyclen

Polyamines are possible therapeutic agents in biological disorders such as cancer and parasite diseases. They also act as ion–exchange blockers or vectors in gene delivery.

D. Calixarene:

Calixarenes are made from phenol units, which are attached by methylene bridges known as calixarene, and can have different cavity sizes. Each of these has conformation isomers, and the phenolic hydroxyl group is constantly modified. This type of character possesses to made calixarene derivatives with various structural modifications.

This isomeric host has different selectivity in metal ion inclusion in the upper cavity and the lower cavity. The number of phenol inclusion in the calixarene alters the guest molecule size appropriate for effective inclusion.

Calixarenes has attention in the treatment of cancer, it is mainly useful in delivery systems because of its biocompatibility and non-cytotoxicity [33]. And also used in the field of host-guest chemistry and sensing of metal ions.

E. Cyclophane:

Cyclophanes are three-dimensional cyclic hosts made from the linking of aromatic rings between aliphatic units. Cyclophanes are classified as follows, [n] orthocyclophane,[n] metacyclophane,[n] paracyclophane.

The aromatic ring in the cyclophane system is maybe either heterocyclic or carbocyclic. Cyclophane core unit is in many biologically active molecules and is also used in pharmaceutical catalysis [34]. Figure; [6.12**]** paracyclophane

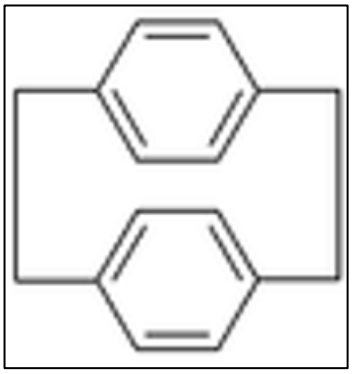

Figure 6.13: Structure of Paracyclophane

The small cyclophanes are the model for the fundamental studies of strain and aromaticity. The short bridges in cyclophanes give free rotations of the ring, and this takes place to thermodynamically disfavoured rotation to each other. This is not in open-chain molecules. This cyclic core was twisted because of the strain on the whole system. This kind of strain only acquires natural cyclophanes, not artificial ones [35].

6.5 Molecular Tree:

A. Dendrimers:

Dendrimers are tree-like macromolecules, which consist of core, branching, and surface units. It is in nanometres to tens of nanometers in size, which is larger than a typically closed molecule (diameter,0.7nm) and smaller than a microsphere(diamatere0.1-10μm). In dendrimers, if we increase the branching units, which will increase the dendrimer generation from zeroth to first, second, and so on.

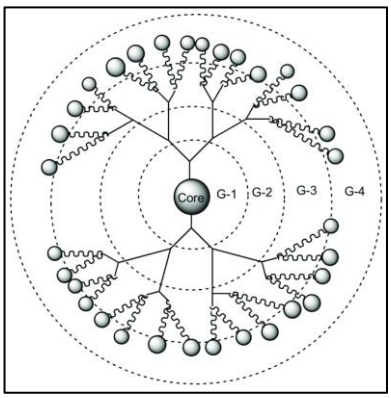

Figure 6.14: Schematic Representation of A Dendrimer Structure [36].

Dendrimers have been widely studied for their potential applications in drug delivery [63], where they can be utilized to transport therapeutic agents directly to diseased cells or tissues. In addition, they have been investigated for their use as imaging agents for diagnosing diseases, as well as in tissue engineering and regenerative medicine, where they can be utilized to deliver growth factors to promote tissue regeneration. Dendrimers have also shown promise as carriers for gene therapy, where they can be used to deliver genes to specific cells, thereby modifying their functions. These and other applications highlight the versatility and potential of dendrimers in the fields of medicine and biology [37].

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ISBN: 978-93-94570-79-5

7. Recent Updates on Methyl Fluorosulfonyl Difluoroacetate Mediated Synthesis of Trifluoromethylated Molecules

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Abstract:

Organofluorine compounds have been widely used in pharmaceutical and agrochemical field. Triflurorомethylated compounds particularly show extensive applications in field of life sciences and material sciences. The trifluoromethyl group is used in biologically important molecules due to its enhanced anti-oxidant ability, improved metabolic stability and increased lipophilicity of the compound. MFSI, which was first reported by Chen and Wu in 1989 is used as an efficient, safe, resistant to moisture absorption and economical reagent for trifluoromethylation in synthesizing variety of trifluoromethyl containing heterocycles having great significance in drugs and many bioactive molecules. Contrary to its widespread applications, this reagent has not been exploited much and thus a comprehensive review of MFSI mediated trifluoromethylations is reported here, which we believe will provide further exposure to the chemists about this underutilized reagent.

Keywords:

7.1 Introduction:

In current years, a huge variety of applications[1-5] have been steadily developed in the sphere of organofluorine chemistry. Amongst the fluorinated compounds, trifluoromethyl-substituted molecules have created significant interest. The trifluoromethyl group is most attractive moiety and mostly used in pharmaceutical[6-8]and agrochemical industries.[9-13]

There are many CF_3 containing drugs available in market [14-21] (Figure 7.1). It is used in biological applications because of its high electron withdrawing ability, increased anti-oxidant ability, enhanced metabolic stability and increased lipophilicity of the target molecule.[22-25] The trifluoromethyl group can promote the drug efficacy by enhancing electrostatic interactions with targets, elevate cellular permeability and amplify the power towards oxidative metabolism of drug.[5,26,27]

Trifluoromethyl group is also widely used in dye industries in which trifluoromethylation of chromophore prevents from fading when exposed to light.[28,29] Trifluoromethylated polymers have upgraded chemical and thermal stability, better solubility and improved mechanical properties.[30] It has applications in developing batteries and cells.[31-33]

Ritter et al[34] proposed that if more complex trifluoromethylated compound is needed it is easier to start with simple molecule containing trifluoromethyl moiety and then build structure around it. Nagib et al[35] proposed the direct trifluoromethylation of arenes and heteroarenes by C-H activation through photo redox catalysis.

There are various reagents, which are used for trifluoromethylation. Rupert−Prakash reagent, CF_3SiMe_3 (trifluoromethyl) trimethylsilane is used for trifluoromethylation of heteroarenes and highly electron deficient arenes.[36] For trifluoromethylation of arenes and heteroarenes, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) is also used[35].

Moreover, $PhSOCF_3$ and $PhSO_2CF_3$ are used as a source of trifluoromethyl anions.[37-39] Alkynyl triflones[40,41], Togni's reagent[42] and many more reagents (Sulfides[43,44], Sulfoximines[45], Sulfonium Salts[46], Sulfinate Salts, Sulfonyl Halides[47-49]) were evolved for the trifluoromethylation in different substrates.[50]

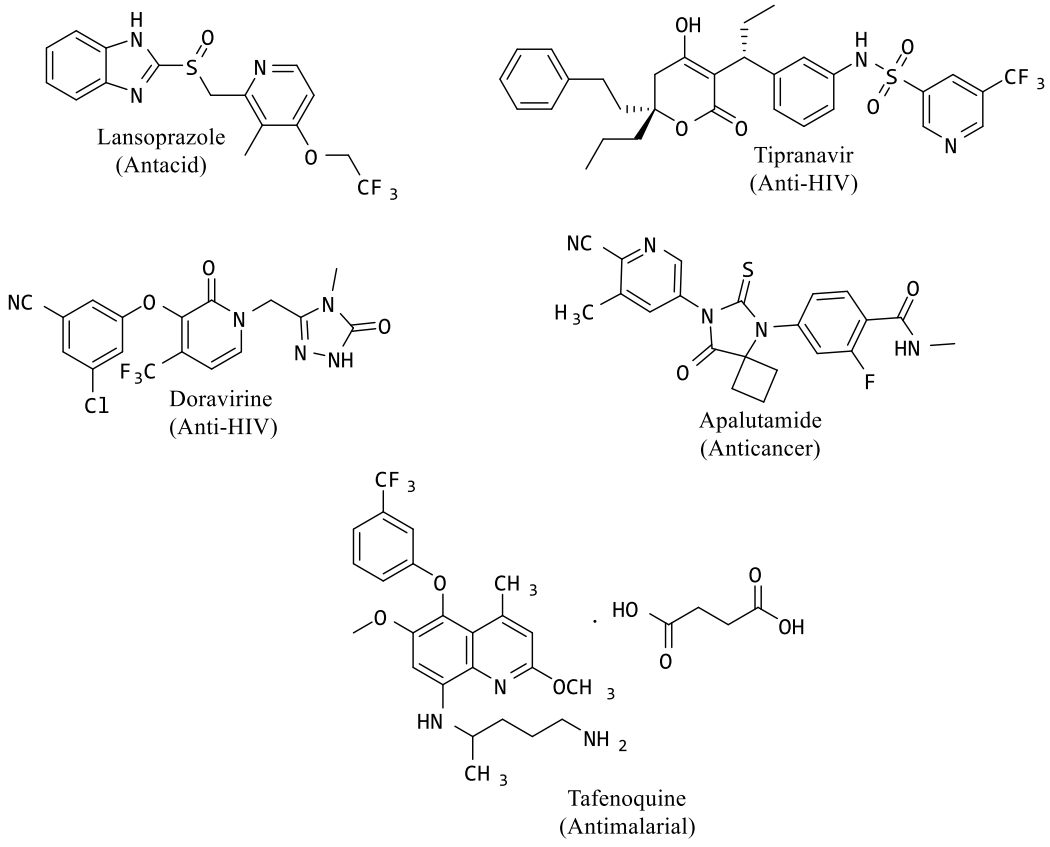


Figure 7.1: CF_3 Containing Drugs

In this chapter, we particularly emphasize on economical and widely used methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSDA or MFSI), reagent. We have focused here on summarizing the literature reports involving the synthetic transformations brought about by MFSI in the last one decade.

7.2 Discovery of trifluoromethylating reagent: Methyl fluorosulfonyldifluoroacetate (MFSI):

Methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSI) reagent also known as Chen's reagent and was first reported by Chen and Wu in 1989[51] as a trifluoromethylating reagent. It has CAS No. 680-15-9 and b.p. 116–118°C.

It is comparatively economical, safe and convenient to use and resistant to moisture absorption.[52] A number of methods have been developed for the trifluoromethylation of different substrates.[53-56] MFSI is used for the synthesis of a wide variety of trifluoromethyl containing heterocycles that is of greater significance in synthesizing drugs and making many bioactive molecules. MFSI is commercially to be held and purchased from the chemical industries but it can also be prepared within the laboratories by using diverse techniques. For example, MFSI can be synthesised *via* reacting 3,3,4,4-tetrafluoro[1,2]oxathiethane-2,2-dioxide with sodium methoxide[57], in two steps from difluoro(fluorosulfonyl)acetic acid[58] or by the addition of methanol to trimethylsilyl fluorosulfonyldifluoroacetate.[59] Finally, the reaction of tetrafluoroethylene with sulfur trioxide gives a useful cyclic compound tetrafluoroethylene β-sulfone.[60,61] Successive reaction with methanol affords MFSI in 85% yield.[62]

MFSI displays the nucleophilic trifluoromethylation reaction and used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides for diverse copper mediated reactions. Chen and Wu showed the order of reactivity of halide to be RI>RBr>RCl where the bromo derivatives being more useful and the chloro derivatives is quite slow. Presence of CuI is crucial for the success of reaction. KI can also be used as an alternative of CuI.[9]

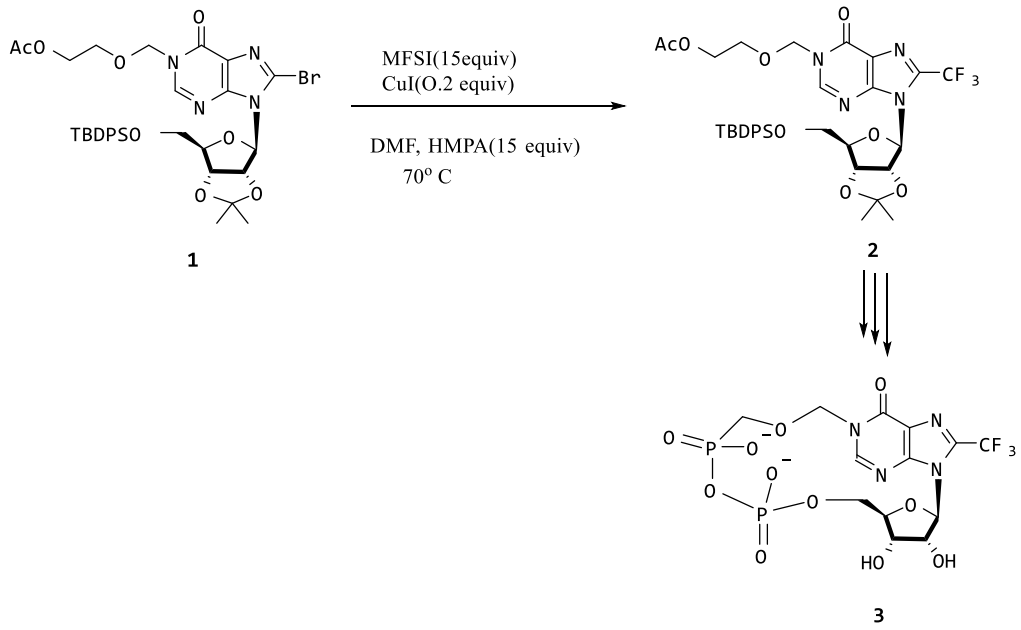
Scope of Methyl Fluorosulfonyldifluoroacetate in Trifluoromethylation reactions

MFSI has been reported in various organic transformations from last so many years and a summary of those reports is being summarised here starting from the year 2010. The triazolylpyridine system are not found in nature in free form but its trifluoromethylated derivatives shows many biological properties like insecticides, antibacterial activity[63], anti-proliferative activity against tumour[64], more cell permeability[65] and many more biological activity[66-70]. Dong et al[71] reported the synthesis of 8- CF_3-cIDPRE **3** (N1 - [(5"-O-Phosphorylethoxy) methyl] -5'-O-phosphoryl -8 - tri-fluoromethylinosine 5", 5"-Cyclic pyrophosphates.

8-CF_3-cIDPRE is agonist and mimics the cADPR (cyclic adenosine 5'-diphosphoribose). 8-CF_3-cIDPRE penetrate the plasma membrane and releases Ca^{2+} which is required in variety of cellular process. Fluorine has strong electron withdrawing property and ability to form hydrogen bonding, it shows metabolic stability and membrane permeability. In this, there is introduction of trifluoromethyl group at 8- position of purine nucleoside, which is important intermediate for synthesis of 8- CF_3-cIDPRE **3**.

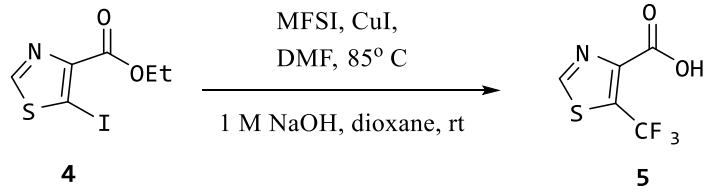
Huang et al[72] also reported the synthesis of trifluoromethylated analogues of cADPR using MFSI. In this, MFSI is used for trifluoromethylation of bromo derivative *viz N*1-[(5``-

Acetoxyethoxy) methyl]-5`- O-TBDPS-2`,3`-O-isopropylidene-8-bromoinosine **1** in the presence of CuI in DMF, HMPA and reaction was stirred for 12hrs at 70° C to form *N*1-[(5``-Acetoxyethoxy) methyl]-5`-O-TBDPS-2`,3`-O-isopropylidene-8-trifluoromethyl inosine **2,** which is an important intermediate and further undergo reaction for synthesis of 8-CF_3-cIDPRE **3** (Scheme 7.1).



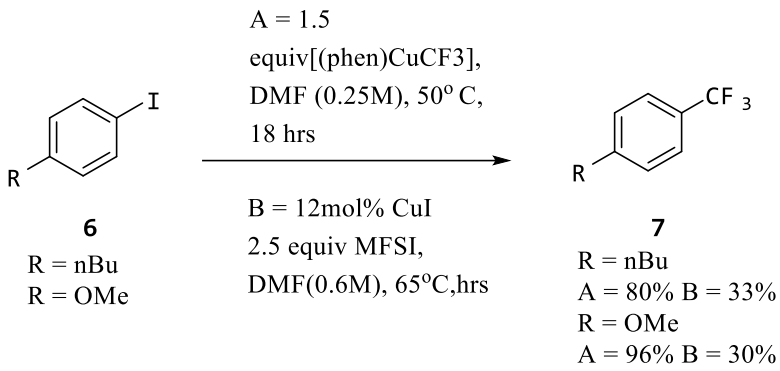
Scheme 7.1: Trifluoromethylation of cyclic adenosine diphosphate ribose.

Hodgetss and his coworker[73] reported that MFSI is used to introduce trifluoromethyl group in thiazole ring **4** to obtain trifluoromethylated product **5**, which is a bioactive molecule. (Scheme 7.2)



Scheme 7.2: Trifluoromethylation of thiazole ring

Boechat et al[74] reported the synthesis of trifluoromethylated derivatives of 1*H*-1,2,4-triazol-3-yl benzenesulfonamide to develop new antimalarial lead compounds with 50%-62% yield. Morimoto et al[75] reported the use of MFSI in copper iodide mediated reactions for the trifluoromethylation of aryl iodides **6** and bromides. The yields of trifluoromethylarene products **7**, which was determined by ^{19}F NMR analysis using 4-$CF_3OC_6H_4OMe$ as internal standard, were much higher (above 80%) under the reaction conditions with 1.5 equiv phen-ligated 1 than with catalytic CuI and 2.5 equiv. $FSO_2CF_2CO_2Me$. (Scheme 7.3).

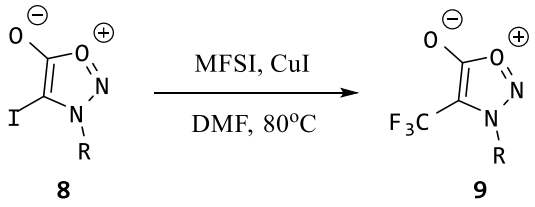


Schemes 7.3: Trifluoromethylation of aryl iodides

Foster et al[76] designed more efficient policy for trifluoromethylation of pyrazoles using MFSI. He reported the trifluoromethylation of 4-iodosyndones **8** to synthesize bioactive 5-trifluoromethylpyrazoles **9** with good yield in the presence of MFSI, CuI and DMF, which was further used as an intermediate to synthesize herbicide fluazolate.

He suggested that when the reaction was accomplished with 4-iodo-*N*-phenylsyndone, the yield of trifluoromethylated product is 79%. When electron-donating substituent like p-methoxyphenyl group is present, the obtained yield is similar (80%).

When the reaction was executed with electron- withdrawing like p-nitro phenyl group, the time taken for trifluoromethylation was increased with comparatively low yield (55%). Non-aromatic group on nitrogen were also accepted under same reaction conditions. (Scheme 7.4).



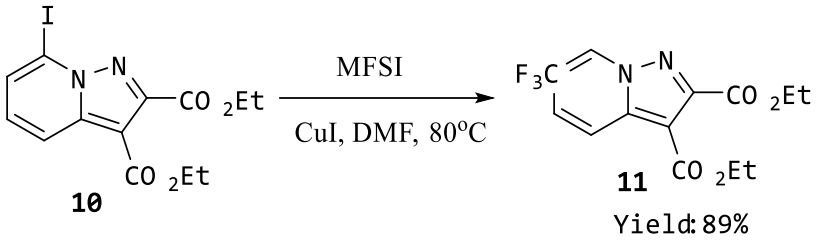
R= Ph

R= Me, Bn, Ph, 4-OMeC_6H_4, 4-$NO_2C_6H_4$

Scheme 7.4: Trifluoromethylation of 4-iodosyndones.

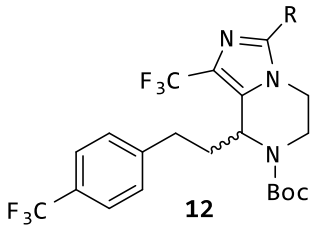
Chong and Bullock[77,79] synthesized 7-Trifluoromethylpyrazolo[1,5-*a*]-pyridinedicarboxylate **11** which is an important intermediate for a potential drug candidate.

MFSI reacted with iodide derivative of pyrazolo[1,5-*a*] pyridine dicarboxylates **10** in the presence of CuI in DMF at 80° C to give trifluoromethylated pyrazolopyridinecarboxylate **11** with 89% yield. (Scheme 7.5)



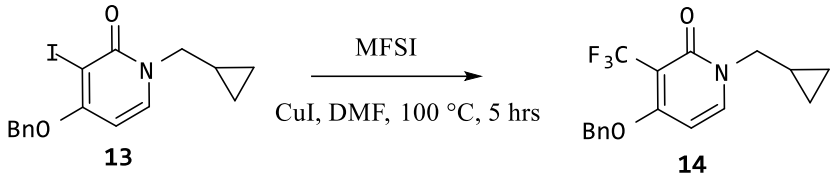
Scheme 7.5: Trifluoromethylation of iodo derivative of pyrazolopyridine dicarboxylates

Sifferlen[79] et al has been reported the incorporation of trifluoromethyl moiety using MFSI in synthesis of bioactive intermediate **12** which was further used in synthesis of 5,6,7,8-tetrahydroimidazo[1,5-*a*] pyrazines which is an orexin receptor antagonist.



Cid et al[80] discovered a novel bioactive derivative of phenylpiperidine substituted pyridones which act as an allosteric modulator of glutamate receptor.

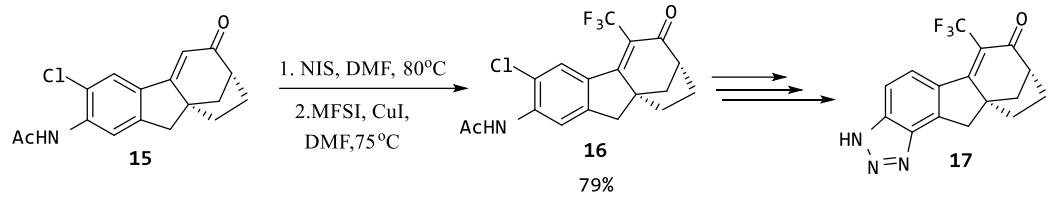
MFSI used for trifluoromethylation of 3-iodopyridones i.e., 4-Benzyloxy-1-cyclopropylmethyl-3-iodo-1*H*-pyridin-2-one **13** to synthesize 3-trifluoromethylpyridone i.e., 4-Benzylox-1-cyclopropylmethyl-3-trifluoromethyl-1*H*-pyridin-2-one **14** which is a key intermediate to form the bioactive molecules. (Scheme 6).



Scheme 6. Trifluoromethylation of 3-iodopyridones

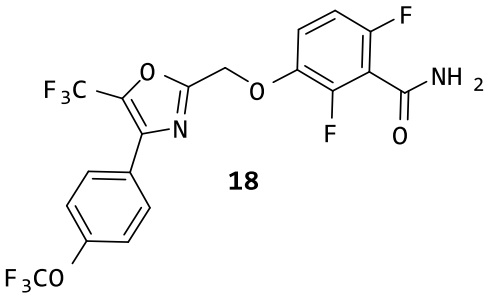
Madess et al[81] discovered derivatives of tetrahydrofluoroene which act as beta agonist for estrogen receptors used in therapy of postmenopausal women for treating the symptoms related with decreased oestrogen level.

Compound **15** undergo iodination followed by trifluoromethylation using MFSI, CuI in DMF to synthesize the compound **16** with high yield which on further transformation give desirable bioactive molecule i.e., tetrahydrofluoroene **17** (Schemes 7.7)

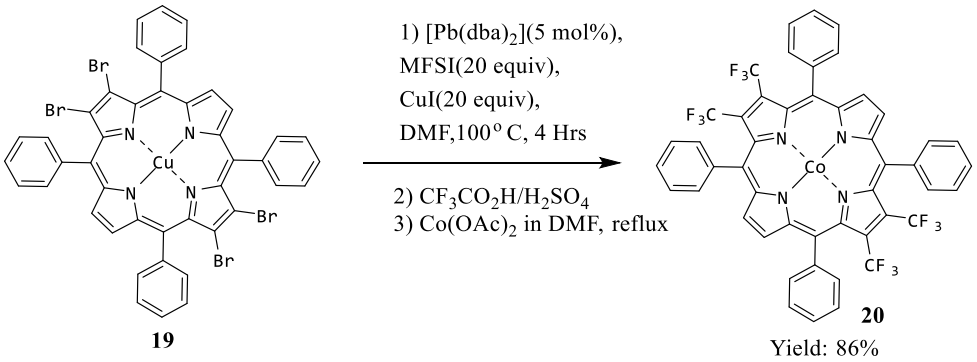


Schemes 7.7: Trifluoromethylation of intermediate in the synthesis of tetrahydrofluoroene

Stokes and coworkers[82] suggested the synthesis of bioactive intermediate **18** by the trifluoromethylation of its oxazolyl iodide intermediate using MFSI.



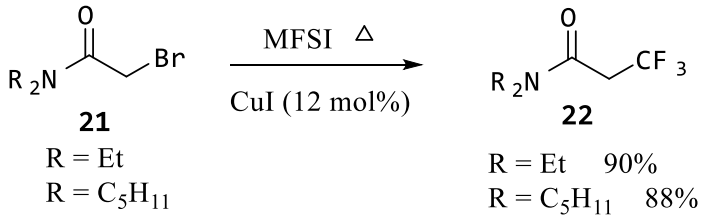
Zhao et al[83] reported that cobalt (II) β-tetrakis- (trifluoromethyl)-meso-tetraphenylporphyrin ($CoTPP(CF_3)_4$) exhibited excellent catalytic selectivity as well as conversion of benzylamines to imines through oxidative coupling with the product yield of 52–89% . He prepared $[Co\{TPP(CF_3)_4\}]$ **19** by the trifluoromethylation of $[Cu(TPPBr_4)]$ **20** in good yield using MFSI and subsequent insertion of Co^{II}. (Schemes 8)



Schemes 7.8: Synthesis of $[Co\{TPP(CF_3)_4\}]$

Zhang et al [84] reported the wide use of MFSI for various copper mediated reactions in a review published in 2014. MFSI was used for trifluoromethylation of aryl halides, alkyl halides and alkenyl halides and trifluoromethylthiolation of aryl halides. Alonso et al [85] reported in their review that MFSI was used as trifluoromethylation of various substrate in presence of CuI.

(a) trifluoromethylation of bromomethyl amide **21** to synthesize parallel trifluoromethyl derivatives **22** with excellent yield. (Schemes 7.9)

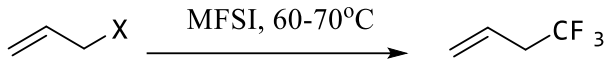


21
R = Et
R = C_5H_{11}

22
R = Et 90%
R = C_5H_{11} 88%

Schemes 7.9: Trifluoromethylation of bromomethyl amide

(b) trifluoromethylation of allyl halide **23** to give trifluoromethylated derivative **24** in high yield. (Schemes 7.10)

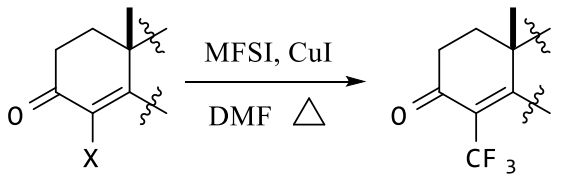


23
X = Br, I

24
Yield :68-70%

Schemes 7.10: Trifluoromethylation of allyl halide

(c) trifluoromethylation of iodo- steroidal molecule **25** to give trifluoromethyl steroids **26** with good yield. Trifluoromethylated flavonoid and antitumor trifluoromethylated flavonoid derivatives were also prepared using this methodology[86] (Schemes 11).



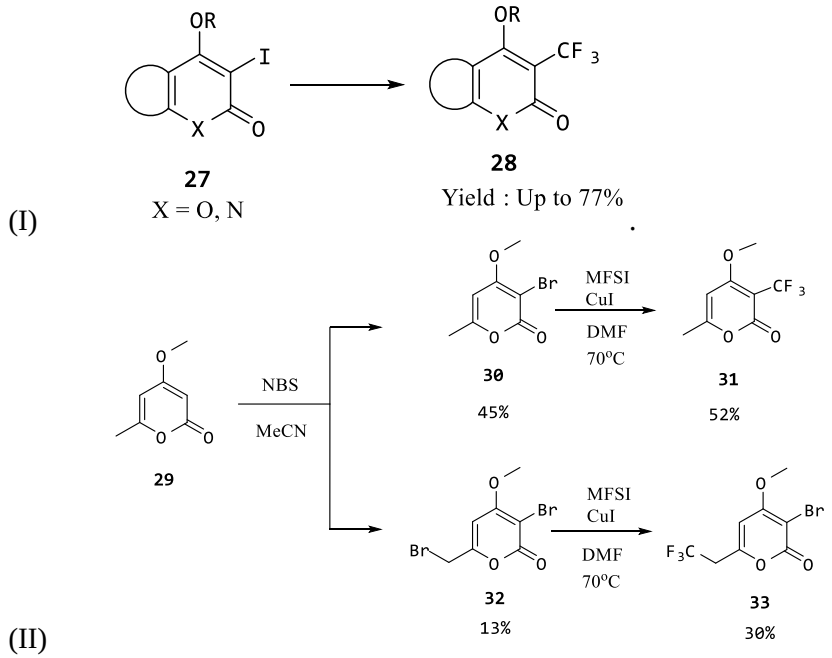
25
X = Br, I

26
Yield : 70-91%

Schemes 7.11: Trifluoromethylation of iodo-steroids

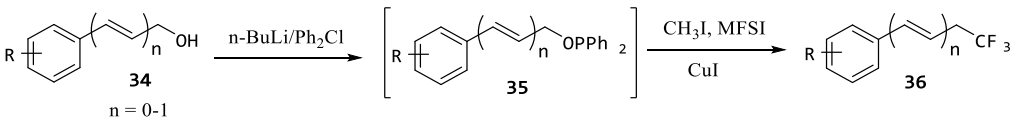
Clarke et al[87] developed the trifuoromethylated series of 4-alkoxy -2-pyrones, pyridones and quinolone using MFSI. These compounds have special biological properties.

They reported that when 1.2 equivalents of MFSI with 1.2 equivalents of copper iodide in DMF were used, good yields were obtained. As shown in scheme 7.12 (I), trifluoromethylation of iodinated starting material **27** gave **28**.



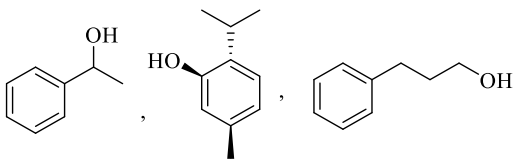
Scheme 7.12: Trifluoromethylation of pyrones, pyridones and quinolones

whereas mono **30** and di brominated **32** products were obtained by the bromination of 4-methoxy -6-methyl -2- pyrones **29**. The bromo derivative further underwent trifluoromethylation to yield product **31** and **33**. [Scheme 7.12(II)]. Li et al[88] suggested an efficient method for the trifluoromethylation of benzyl alcohol or allyl alcohol **34** to obtain various trifluoromethylated compound **36**. Derivatives of **35** were formed by reacting compound **34** (benzyl or allyl alcohol) with *n*-BuLi, Ph_2Cl. Intermediate **35** undergo trifluoromethylation in the presence of methyl iodide and MFSI in the presence of copper iodide when stirred at 80° for 15 hrs to obtain compound **36**. A variety of compounds were prepared from this method. (Scheme 7.13). Electronic density of alcohols affects the yield of reactions. Electron-donating groups such as methoxy and methyl group gave good yield whereas halide-substituted alcohols gave the moderate yield and low yields were observed with secondary alcohols because of steric hindrance.



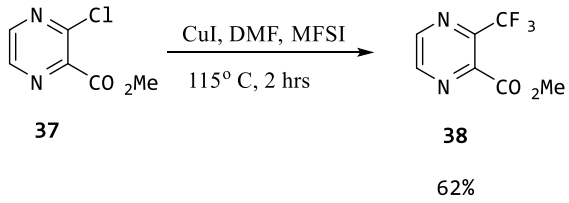
R= p-CF_3, -OMe, p-Me, p-Br, o-Cl, p-Cl,

n= 0,1



Scheme 7.13: Trifluoromethylation of benzyl alcohol or allyl alcohol

Oda et al[89] suggested the application of MFSI for the trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate **37** in the presence of CuI in DMF, toluene and converted into methyl 3-(trifluoromethyl) pyrazine-2-carboxylate **38** which is a key intermediate to synthesize pyraziflumid and many other derivatives. Pyraziflumid shows excellent fungicidal activity partiparticularly against gray mold, Brown rust and powdery mildew. (Scheme 7.14). Sharma et al[90] described the successful nucleophilic trifluoromethylation of differently substituted α-iodinated oxoketene dithioacetals **39** *via* using MFSI in presence of CuI and DMF which provided α-trifuoromethylated oxoketene dithioacetals **40** with good to outstanding yield. Those synthons were further utilized for the synthesis of biologically important diversely substituted trifluoromethylated pyrazoles. (Scheme 7.15).

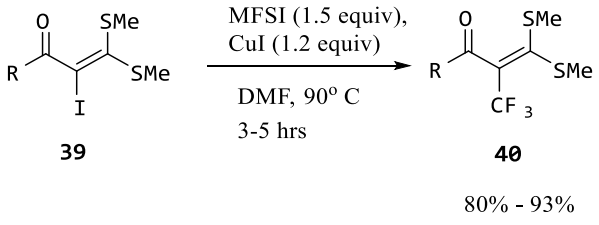


37 **38**

62%

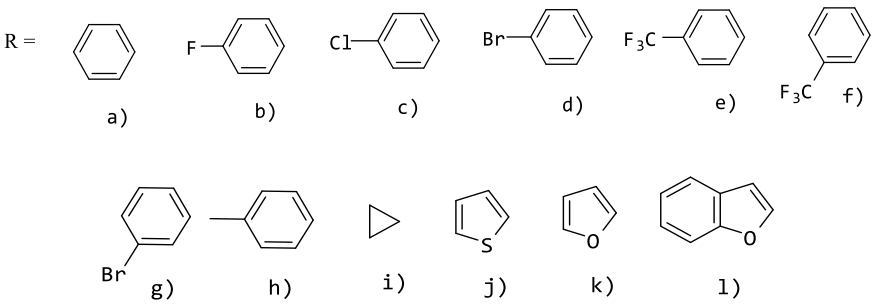
Scheme 7.14. Trifluoromethylation of methyl 3-chloropyrazine-2-carboxylate

Electron withdrawing group present at the *m*- and *p*- position in the α-iodinated oxoketene dithioacetals (b-g) contributed good yield of α-trifuoromethylated oxoketene dithioacetals. Though, electron releasing group in substrarte with *p*-CH_3 gave decent yield. On the other hand, with *o*-CH_3 in α-iodo oxoketene dithioacetals at -*o* or -*p* positions were confirmed unproductive due to incapability towards nucleophilic substitution. High yield was obtained with cyclopropyl substituted substrate. Heteroaromatic substituted α-iodo oxoketene dithioacetals (j – l) produced good to excellent yield.



39 **40**

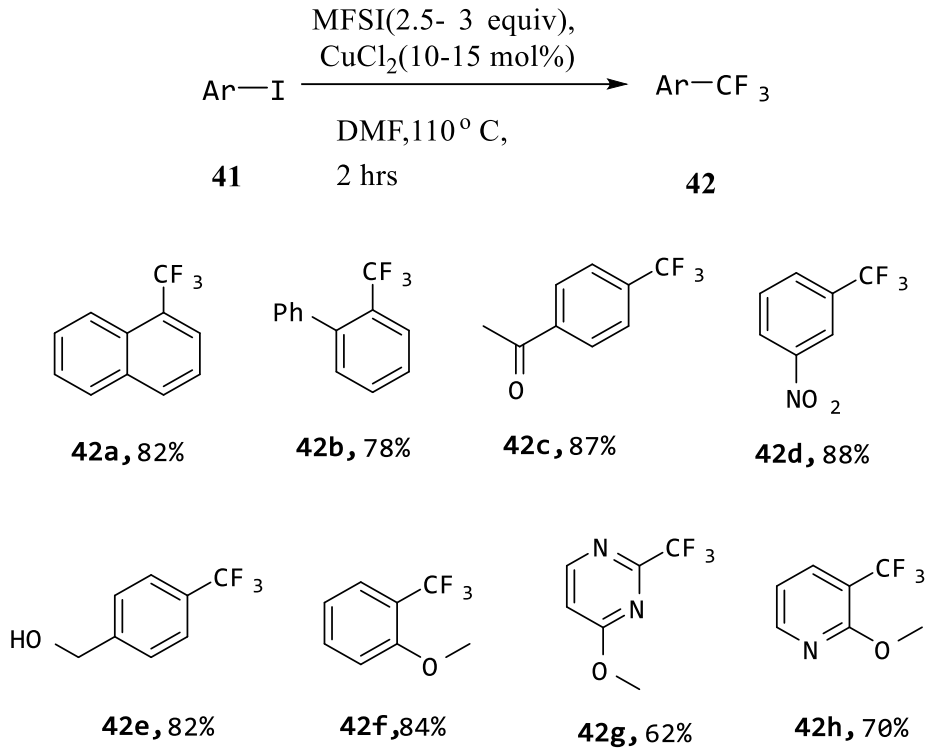
80% - 93%



Scheme 7.15: Trifluoromethylation α - iodinated oxoketene dithioacetals

Zhao and coworkers[91] proposed the nucleophilic trifluoromethylation of various aryl and heteroaryl iodides **4** using MFSI, and carried in the presence of $CuCl_2$ with excellent yield. In their review, they started with the trifluoromethylation of 1- iodonapthalene.

After the successful trifluoromethylation of iodonapthalene, they further synthesized a number of structurally diverse trifluoromethylated (hetero) aryl derivatives **42(a-h)** in the presence of $CuCl_2$ as catalyst at 110°C when stirred for 2 hrs. Effect of others salts of Cu on the yield, were also studied. (Scheme 7.16)

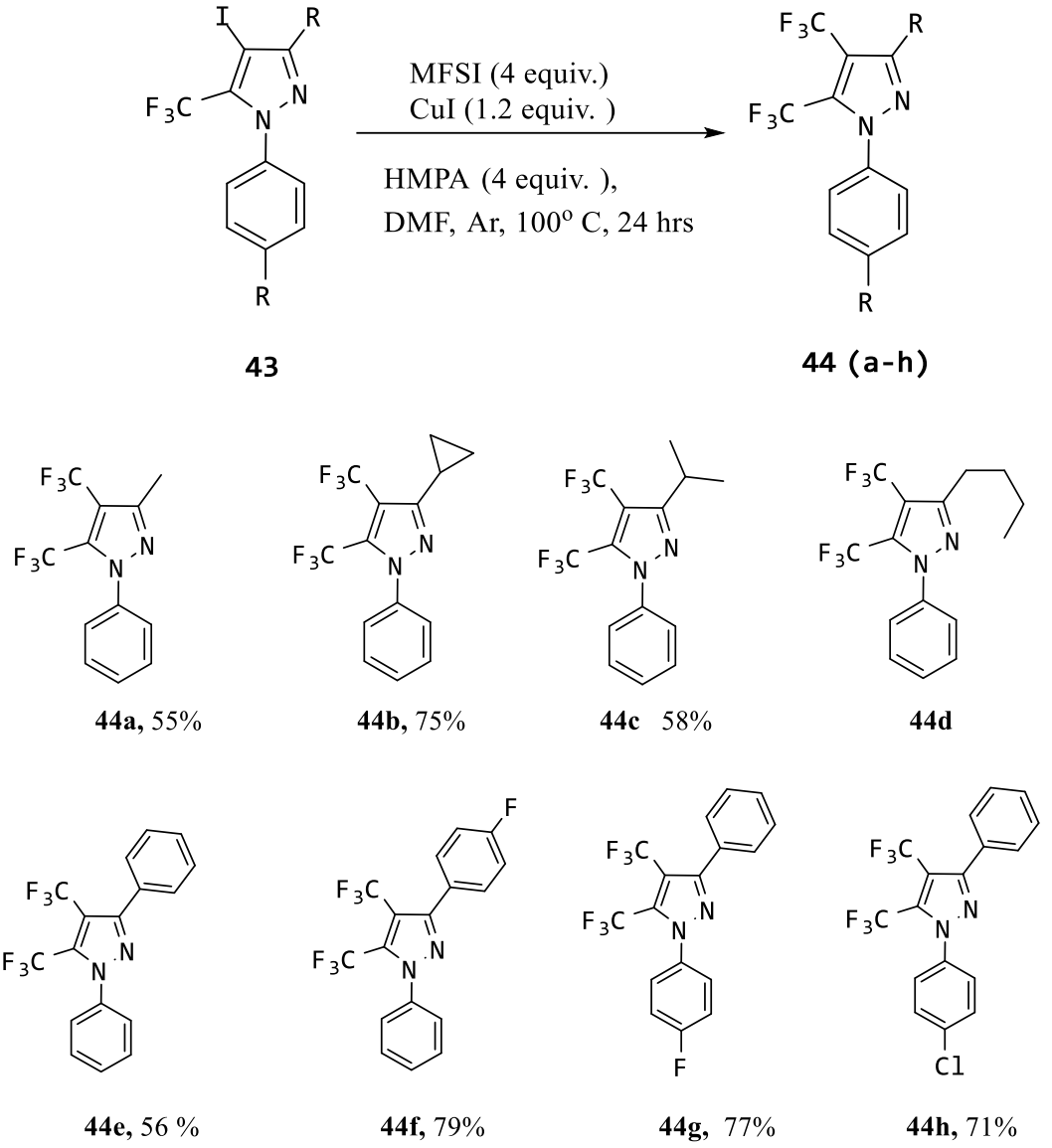


Scheme 7.16: Trifluoromethylation of aryl and heteroaryl iodides

Junges et al[92] reported the trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles **43** in CuI, MFSI and HMPA under anhydrous DMF for 24 hrs at 80°C to obtained a chain of 1-aryl-3-alkyl(aryl)-4,5-bis(trifluoromethyl)-1*H*-pyrazoles **44(a-h)** in good yield which showcased the insecticidal property. (Scheme 7.17).

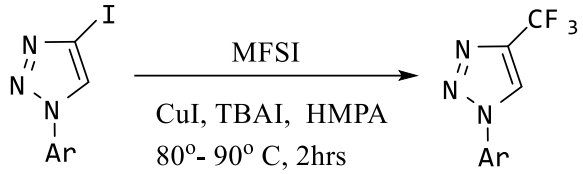
Recently Xie and Hu[93] posted an article on huge application of MFSI in area of organic chemistry wherein they mentioned about the discovery, applications and reactions of Chen's reagent.

MFSI used normally to acquired trifluoro methylated and difluoro alkylated compounds. Over a decade, a substantial amount of research has been performed to use MFSI as a difluorocarbene precursor and radical difluoro alkylating agent in presence of visible light.



Scheme 7.17: Trifluoromethylation of 1-aryl-3-alkyl(aryl)-5-trifluoromethyl-4-iodo-1*H*-pyrazoles

Panja et al[94-98] reported the common method for trifluoromethylation of 1-aryl-4-iodo-1*H*-1, 2, 3-triazole **45** which were carried out in TBAI (Tetrabutylammonium iodide), CuI and MFSI, stirred at 80-90°C for 2 hrs. to obtain 1-aryl-4-(trifluoromethyl)-1*H*-1, 2, 3- triazole **46** in moderate yield. (Scheme 7.18). The reaction was not dependent on the electron density of substituent in aryl ring and it was chemoselective when carried out with bromo and chloro derivatives. Consequently, this is a useful method for synthesis of many 1-aryl-4-trifluoromethyltriazoles[99-101] from the respective iodo-precursor. TBAI act as useful reagent as it is solubilizing the Cu and make it available for the reaction.



45 **46**

Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Cl-C_6H_{44}-F-C_6H_4, 4-CH_3-C_6H_4, C_6H_5, 3,5-$(CF_3)_2$-C_6H_3
4-$COCH_3$-C_6H_4, 4-$CO_2CH_2CH_3$-C_6H_4, 4-CN-C_6H_4, 4-OCF_3-C_6H_4

Scheme 7.18: Trifluoromethylation of 1- aryl 4-iodo-1, 2, 3-triazoles

7.3 Conclusion:

Since MFSI was discovered in 1989 as a trifluoromethlating reagent, it has found wide application for the trifluoromethylation of aromatic, herteroaromatic and alkenic compounds. A huge number of CF_3 containing biologically important and structurally diverse molecules have been synthesized by using this excellent reagent. Instead, it shows significant advantages over other trifluoromethlating reagent like CF_3CO_2Na and Ruppert Prakash reagent ($TMSCF_3$). Ruppert Prakash reagent is widely used as a trifluromethlating reagent but it is very expensive. MFSI reagent is commercially available, pretty cheaper and persuadable for trifluoromethylation of halogenated compounds. Scientists are doing more research on this reagent in organic synthesis. However, it has been somewhat underutilised by chemical community. We demand for extra attention to this crucial reagent. This reagent will continue to find more uses in the field of life sciences and material science.

7.4 References:

1. Kirsch, P. *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**.
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List of Abbreviations:

CF_3 - Trifluoromethyl

CF_3SiMe_3 - Ruppert-Prakash reagent

CF_3SO_2Cl - Trifluoromethane sulfonyl

$PhSOCF_3$ - Trifluoromethyl sulfoxide

$PhSO_2CF_3$ - Trifluoromethyl sulfone

MFSI - Methyl fluorosulfonyldifluoroacetate

CuI - Copper iodide

KI - Potassium iodide

DMF - Dimethylformamide

HMPA - Hexamethylphosphoramide

NaOH - Sodium Hydroxide

NIS - Nickel sulfide

$[Pb(dba)_2]$ - Bis(dibenzylideneacetone) Palladium

CF_3CO_2H - Trifluoroacetic acid

$Co(OAc)_2$ - Cobalt(II) acetate

NBS - N- Bromosuccinimide

MeCN - Methyl cyanide

n-BuLi - n Butyllithium

CF_3CO_2Na - Sodium trifluoroacetate

ISBN: 978-93-94570-79-5

8. Medicinal Chemistry

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Abstract:

Medicinal chemistry involves designing and developing of pharmaceutical drugs. Medicinal chemistry deals with the identification, synthesis, and development of medicinally active compounds. Quantitative structure –activity relationship (QSAR) and quantitative structure property relationship (QSPR) studies are important in silico methods in rational drug design. The goal of this medicinal chemistry is to produce pharmacologically active drugs. QSAR and QSPR Methods are having the goal to optimize the existing leads in order to improve their medicinal property and physicochemical properties. These methods also gives the information about biological activities of untested and yet unavailable compounds. QSAR study is good prediction tool for investigating drug activity and binding capacity on specific receptors.

Keywords: *QSAR, SAR, Drug discovery strategies, conventional synthesis, combinatorial synthesis. And computer aided drug design.*

8.1 Introduction:

Medicinal or pharmaceutical chemistry is the branch of chemistry involved basically with designing and developing pharmaceutical drugs. It involves the identification, synthesis and development of new chemical entities suitable for therapeutic purpose. It also includes the study of existing drugs, their biological properties and their quantitative structure-activity relationships. It concerns the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at the molecular level. It also includes study, identification, and synthesis of the metabolic product of both synthetic and naturally occurring drugs and related compounds.

Medicinal chemistry is interdisciplinary science which covers the biochemistry, pharmacology, molecular biology, immunology, toxicology, pharmacology on one side. on other side it covers chemistry based disciplines such as physical chemistry, crystallography, spectroscopy, and computer based information technologies.

It is the branch of chemistry concerned with the design, development and synthesis of pharmaceutical drugs. Medicinal chemistry is also involves the designing and developing of pharmaceutical drugs. It also includes the study of existing drugs, their biological properties, and their Quantitative structural activity relationship (QSAR).

Medicinal chemistry involves the isolation, characterization, synthesis, mechanism of action of compounds that can be used as medicines in the treatment of diseases. It is the linkage between structure and biological activity of compounds.

Medicinal chemistry covers three critical steps.

A. Discovery step
B. Optimization step
C. Development step

A. Discovery step:

It deals with the therapeutic target that is enzyme, transport group, receptor etc. and the identification and production of new active substances interacting with the selected target. Such compounds are usually called lead compounds. The sources of Lead compounds are

- From natural products.
- Chemical libraries.
- Computational medicinal chemistry.
- Green chemistry

Importance of lead molecules:

- Lead compounds are having potential to treat particular disease.
- It is chemical compound or natural product which is having biological activity against disease.
- Lead identification and optimization plays an important role in drug discovery process.

B. Optimization step:

It deals with improvement of the lead structure. The optimization process takes primarily into account the increase in potency, selectivity and toxicity. Its characteristics provide analysis of structural activity relationships to produce understanding of the molecular mode of action such as pharmacokinetic parameters that is absorption, distribution, oral bioavailability of lead compounds.

C. Development step:

This step involves the identification of candidates, synthesis, characterization, validation, screening, and assays for therapeutic efficacy. Once compound has shown its significances in these investigations, it will initiate the process of drug development earlier to clinical trials. It involves the improvement of pharmacokinetic properties and fine tuning of

pharmaceutic properties of the active substances in order to render them suitable for clinical use. This chemical formulation process consist in the preparation of better absorbed compounds, of sustained release formulations, of water soluble derivatives or in the elimination properties related to patience compliance (causticity, irritation, painful injections, undesirable organoleptic properties).

Structural activity relationship: The analysis of biological effects of chemical upon its molecular structure. Molecular structure and biological activity are correlated by observing the results of systemic structural modifications**.** Structural activity relationship is qualitative not quantitative relationship.

8.2 QSAR:

It is method that gives the information about activity, reactivity, specificity, properties and characterization of an unknown set of molecules which is based upon the analysis of structures of molecules to their respective activity and property. It is the mathematical relationship between the biological activity and physicochemical parameters. QSAR try to identify and quantify the physicochemical properties of a drug and to check whether any of these properties has an effect on biological activity or not. Quantitative structure activity relationship (QSAR) is one of the widely used techniques in ligand based drug designing method.

A quantitative structure activity relationship related to quantitative chemical structure to a biological activity. QSAR plays an important role in drug discovery process because their application can save time and human resources. For the prediction of QSAR model several parameters are important. On One side some different statistical methods are used to check the linear and non linear behavior of data set. On another side selection techniques are used to reduce the model complexity. QSAR model can be useful in the discovery of new compounds with improved potency. The molecules which show interesting activity will be synthesized.

Table 8.1: Structural activity relationship v/s quantitative structure activity relationship.

Structural activity relationship	Quantitative structure activity relationship
Relationship between chemical or 3D of molecule and its biological activity.	Gives that idea that there is simple mathematical relationship between biological activity of drug and physicochemical properties.
It can help to insert new chemical groups into the biomedical compound and test the results.	QSAR attempt to finds consistent relationship between biological activity and molecular properties. So that these rules can be helped to evaluate the activity of new compounds.
It is done by X-rays and NMR techniques.	It is done by procedure known as linear regression analysis by the least square method**.**

Structural activity relationship	Quantitative structure activity relationship
Structure activity relationship is technique to find qualitative relationship between chemical structure and biological activity.	QSAR models are theoretical models that relate a quantitative measure of chemical structure to a biological property.

Importance of QSAR and drug design:

- To modify the chemical structure of the lead compound to retain the desirable biological activity while minimizing unwanted pharmacological, physical and chemical properties.
- QSAR studies can be applied to design, identify and synthesize new drugs or molecules to optimize absorption, distribution, metabolism, excretion and toxicity profile of identified molecules from various sources to cure the diseases.
- A major goal of Quantitative Structure Activity Relationship (QSAR) studies is to find a mathematical relationship between the activity under investigation, and one or more descriptive physicochemical parameters and descriptors related to the structure of the molecule.

QSAR parameters:

The parameters used in QSAR are measure of the potential contribution of its group to particular biological activity of the parent drugs.

- Lipophillic parameters: partition coefficient,
- Electronic parameters: Hammet constant, dipole moment.
- Steric parameters: Molar refractivity, verloop steric parameter.
- Polarizability parameters: molar volume, parachor.
- Miscellaneous parameters: Topological parameter.

Combinatorial chemistry:

The Combinatorial Chemistry is a scientific method in which a large number of chemical entities are synthesized by condensing a small number of chemical compounds together in all combinations defined by a small set of chemical reactions.

Combinatorial technologies produce new compounds in practically with unlimited number. Combinatorial chemistry is which collects the techniques for the synthesis of multiple compounds at same time. It is one of the important new technology developed by researchers in the pharmaceutical industry to reduce the time and cost associated with producing effective and competitive new drugs. It is technique by which large no. of different but structurally similar molecules are produced rapidly and submitted to pharmacological assay. This reaction uses same reaction conditions with same reaction vessels to produce large number of analogues.

8.3 Drug Discovery:

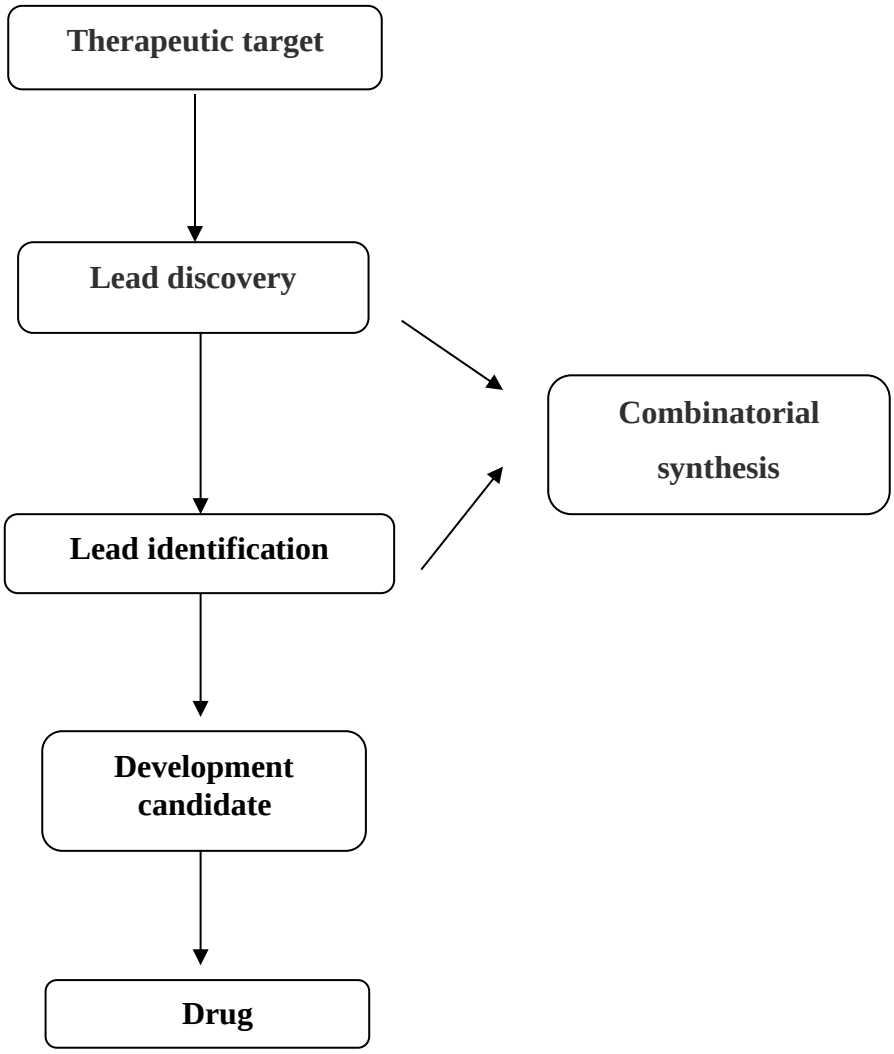

Figure 8.1: Drug Discovery

Strategies:

Conventional synthesis	Combinatorial synthesis
Only one compound can be synthesized at a time.	A range of compounds are synthesized at a time
Requires more time	Requires less time
More expensive	Less expensive
Slower lead generation	Faster lead generation

Role of combinatorial chemistry in drug discovery:

- By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.
- It provides immobilization strategies which allows high throughput and multiple parallel approaches to drug discovery.

Advantages of combinatorial chemistry:

- Mixed combinatorial synthesis produces chemical pool.
- More opportunities to produce lead compounds.
- From combinatorial chemistry the identification, isolation, purification and synthesis is very easy.
- Combinatorial approach can give million of compounds in same time as it will take to generate one compound by traditional method synthesis.

Techniques used in combinatorial chemistry:

A. Solid phase synthesis.

- Solid support method.
- Parallel synthesis.
  - a. Manual
  - b. Automated
- Mixed combinational synthesis.
- Mixed & split combinatorial synthesis.

B. Solution phase technique.

A. Solid phase synthesis:

In this synthesis, reactant is bound to insoluble resin bead, reagents are added to the solution in excess. The resulting products are isolated by using simple filtration which traps the bead while the excess reagent is washed.

Requirements:

a. Solid support.
b. Protective groups.
c. An anchor or linker.

Parallel synthesis:

It is process which is used to produce a single reaction product is produced in each reaction vessel. Parallel synthesis, individual peptides are synthesized in separate reaction vessels.

Mixed combinatorial synthesis.

- To use a standard synthetic method to produce a large range of different analogues where each reaction vessel or tube contains a mixture of products.
- The identities of the structures in each vessel are not known with certainty.
- By using mixed combinatorial synthesis lead molecule can be identified.
- It involved in the synthesizing large numbers of compounds quickly each mixture is tested for activity as the mixture.
- Inactive mixtures are stored in combinatorial libraries.
- Active mixtures are studied and are used to identify active component.

Mixed and split combinatorial synthesis:

The split –mix combinatorial synthesis is the rapid synthesis of larger libraries of compounds. On each polymer bead type of compound can be prepared. The split and combine approach is one of the classic strategies in combinatorial chemistry.

B. Solution phase technique:

It is the process in which allows reaction to accommodate solid support. It leads to the formation of mixture of product. This helps to find the development of new mixture.

Disadvantages:

- Difficult to remove unwanted material from reaction mixtures.
- Purification step is necessary at each step for each product.
- Other practical problems.

Table 8.2: Difference between solid phase and solution phase technique:

Sr. No	Parameter	Solid phase technique	Solution phase technique
1	Reagent	Excess	Optimum unless purification done.
2	Purification	Easy	Can be difficult.
3	Automation	Easy	Difficult.
4	Reaction	Suitable for new substance.	Suitable any organic reaction.
5	Scale-up	Expensive	Easy and inexpensive.
6	Dependence of reaction development	Mainly on -support -linkers	Time

Computer Aided Drug Design:

Drug design with the help of computer is very useful. It represents the computational methods and resources that are used to facilitate the drug design an discovery of new therapeutic solutions. It may be used at any of the following stages of drug discovery:

- Hit identification using virtual screening (structure- or ligand based design)
- Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc).
- Lead optimization, optimization of other pharmaceutical properties while maintaining affinity.

8.4 Conclusion:

In the medicinal chemistry, drugs are discovered by screening test of compounds, synthesized in laboratory or obtained from natural sources. Then Studies are conducted to get information on the mechanism of drugs action. QSAR is basically used to study the biological activities of drugs. It is also used to build models which can predict the physical and chemical properties and activities of organic compounds. A computational method give the information about drug structure with physical and biochemical properties of the drug and produces the efficacy of the drug. The computational methods used to model drug chemistry. It allows the observation in three –dimensions of a drug interaction with the protein or drug. Drug interaction with enzymes or receptors which leads to the structural features that are required in discovery and designing of new medicinally active drugs.

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Kripa-Drishti Publications
A-503 Poorva Heights, Pashan-Sus Road, Near Sai Chowk,
Pune – 411021, Maharashtra, India.
Mob: +91 8007068686
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Web: https://www.kdpublications.in

ISBN: 978-93-94570-79-5

Chapter 5
Print ISBN: 978-81-961090-8-0, eBook ISBN: 978-81-961090-9-7

Covid-19 Infection among Pregnant Women: An Overview of Diagnosis, Treatment and Clinical Management

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DOI: 10.9734/bpi/pramr/v6/4228B

ABSTRACT

Coronavirus disease or more popularly called COVID-19 is known to be caused by a novel coronavirus 2. COVID-19 has been identified to be originated in Wuhan, Hubei, China. This pandemic started in December 2019, and since then it has spread across the world within a short period. In the current scenario, no specific anti-viral drug is recommended for COVID-19 management. Vulnerable populations, such as pregnant women infected with COVID-19, must be identified and followed up on in order to effectively manage morbidity and mortality. In India, very few case reports on COVID-19-infected pregnant women have been published, and no proven exclusive treatment protocol exists. This article summarizes a review of COVID-19 infection in pregnant women, including signs and symptoms, etiopathogenesis, risk factors, diagnosis, and possible management. This overview may be helpful for medical professionals in terms of the practical approach and limitations of the drugs used in the current management, and it takes into account the selection of drugs with special attention paid to side effects in order to improve maternal health, pregnancy, and birth outcomes.

Keywords: Covid-19; pregnant women; pathogenesis; management.

1. INTRODUCTION

Coronavirus disease, also known as COVID-19, is caused by novel coronavirus 2 and is characterized by a specific syndrome with extreme acute respiratory

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distress as the most prominent feature. In general, initial infection is characterized by mild to severe respiratory symptoms and can progress to respiratory failure) later can be fatal due to multi-organ failure. COVID-19 was discovered in Wuhan, Hubei, China. This pandemic began in December 2019, and it has rapidly spread throughout the world since then [1]. India currently has the highest number of confirmed cases of COVID-19 infection in Asia and the third-highest number worldwide [2]. The World Health Organization has discussed the global effects of the epidemiological situation, with over 32.7 million COVID-19 cases and 991,000 deaths recorded by the end of September 2020; total deaths are predicted to surpass one million in the future. South-East Asia is the second most affected region, accounting for 21 %and 11 %of total cases and deaths, respectively. It has been recorded that countries such as India, Indonesia, and Bangladesh continue with the greatest numbers [3].

Indian Government launched a mobile application named Aarogya Setu, which was developed to reach the app users about the best practices, risks, and relevant advisories related to COVID-19 containment. “Arogya setu” app data indicate about10,374,932 confirmed cases, 9,997,272 recovered and 150,114 deaths were reported as of January 06, 2021. Totally 167.6 million users of the Aarogya Setu mobile application helped to update the country's health status [4]. The ministry of health and family welfare of GoI reported 227,546 active COVID-19 cases, 9,997,272 discharged, and 150,114 deaths till 06 January 2021. Indian council of medical research reports that the total Testing Status of SARS-CoV-2 was 9,31,408 which were cumulative total samples tested up to November 03, 2020 [5]. There is no specific anti-viral drug for COVID-19 outbreak management in the current scenario [6]. The elderly (> 65 years) persons, people with impaired immune systems, and perhaps pregnant women have been reported to be susceptible to the virus [7, 8, 9].

As per earlier reports, women are categorized vulnerable to respiratory infections, especially during pregnancy.

However, pregnant co-morbidity patients may have an increased risk of serious illness, consistent with the general population of similar co-morbidity patients. High-risk groups need to be monitored accordingly by clinicians. Around (85%) of women will experience mild illness, (10%) more severe illness, and (5%) more critical illness [10]. At present, very few case reports on COVID-19 pregnant women have been published in India and there is no proven exclusive treatment protocol for its management. Vulnerable populations such as pregnant women affected by COVID-19 infection are very important to recognize and follow up and the cases should be handled effectively concerning morbidity and mortality.

However, in India, a protocol for the management of pregnant women affected by COVID-19 has been prepared by the Indian Council of Medical Research. Yet the normal protocol and procedure need the hour to learn and adapt. Here we summarize a review of signs and symptoms, etiopathogenesis, risk factors, diagnosis, and possible management of pregnant women infected with COVID-19.

2. SIGNS AND SYMPTOMS

Fever, dyspnea, cough, and lymphopenia are predominant features of COVID-19 in pregnancy, similar to non-pregnant patients. 18% of patients reported breath shortness. In some cases, due to increased maternal oxygen requirements from increased metabolism, gestational anemia, and fetal oxygen consumption, which are common in pregnancy, this may be difficult to discern from physiological dyspnea [11]. Initially in China reports specified seven COVID-19-affected pregnant women showed symptoms viz. cough, fever, diarrhea, and shortness of breath [12].

As described above, the symptoms can differ, and women with a variety of clinical manifestations ranging from mild symptoms and signs to serious disease, including pneumonia with or without acute respiratory distress syndrome (ARDS), renal failure, and multi-organ dysfunction can require immediate to advanced critical care support. As a consequence, those affected are generally described as having moderate, serious, or critical illnesses [13]. In one of the studies, critically ill pregnant women affected by COVID-19 needed oxygen and were reported to have cardiomyopathy [14]. To evident such cases, more data is required to require to optimize incidence of the incidence of cardiomyopathy secondary to postnatal or in pregnant covid patients.

There are signs of very high fever associated with coughing, trouble breathing, diarrhea, pneumonia, headache, excess sputum, and hemoptysis in infected people with symptoms. Some people with infections are asymptomatic and, since they ignore health conditions, are labeled as highly infectious. Conditions such as respiratory arrest, heart attack, RNA anemia, and ground-glass opacity were fatal events [15, 16 17].

3. ETIOLOGY

SARS-CoV-2 of order Nidovirales, belonging to the family Coronaviridae is causative of Coronavirus disease-19. These are non-segmented, enveloped RNA viruses that include the coronaviruses of SARS-CoV and MERS-CoV [18].

Vulnerable groups are susceptible to COVID-19 especially pregnant women/lactating mothers. Current knowledge and clinical management of pregnant women with COVID-19 are mainly based on information from the general population. Despite the growing number of pregnant women with COVID-19, data on the clinical characteristics and disease severity of pregnant patients are still limited. Considering the particularity of immune status and physiological features in pregnant women, there is an urgent need to investigate the differences in the clinical characteristics and severity of COVID-19 between pregnant and nonpregnant women and the potential impact of COVID-19 infection on the clinical outcomes of the fetus and neonate [19].

4. PATHOGENESIS OF COVID-19

COVID-19 contains a single-stranded RNA genome with 4 genes; nucleocapsid, membrane, envelope, and spike protein [20]. The pulmonary area is the main target of the virus. Coronavirus binds via receptor-binding domains to the host receptor, named ACE2 [21]. For the release of RNA in a host cell, conformational changes occur by spike protein which activates the viral envelope to bind with a receptor of a host cell. Viral replication happens when RNA enters the host cell later proteinase enzymes divide them into small particles. Later translated using mRNA and stored in the endoplasmic reticulum and Golgi apparatus through which they are released as vesicles into endothelial, alveoli, and blood cells [22].

5. ROLE OF LYMPHOCYTES IN COVID-19

The immune system plays an important role to fight against viruses and other microorganisms. Especially lymphocytes (T and B cells), natural killer cells are essential [23].

Compared with non-pregnant women, the total white cell count was significantly increased at all pregnancies and also post-partum. In pregnancy, the absolute number and percentage of T lymphocytes were slightly elevated while almost no changes in B cells were found. No significant changes were found in the percentage of suppressor/cytotoxic (CD8+), helper/inducer (CD4+) T lymphocytes, nor of CD4+/CD8+ ratio at any stage of pregnancy and puerperium [24].

However pregnant COVID-19 patients showed significantly lower numbers of blood lymphocytes and higher numbers of neutrophils, as well as higher levels of C-reactive protein and total bilirubin.

Signature features of COVID-19-related severe illness include the presence of elevated levels of pro-inflammatory cytokines, coagulopathy, and lymphopenia. However, no deaths were reported, dissociating lymphopenia in the patients from mortality. Thus, the question of whether a pregnancy is an immunological contributor to severe or controlled COVID-19 disease should be extensively debated [25].

6. ROLE OF D- DIMER AND THROMBOEMBOLISM

It is assumed that the mechanism by which COVID-19 infection causes multi-organ dysfunction involves inflammatory cytokines release which triggers tissue factor development and activates thrombin. Increased thrombin and D-dimer (> 1µg /mL) are linked with an increased risk of death.

It was presumed COVID-19 affected pregnant women were less likely to have serious morbidity/die, however, reports indicate a subset can develop multi-organ failure that leads to death. During common infections generally, pregnant women

show evidence of elevated intravascular inflammation and increased thrombin along with prothrombin which might exaggerate thrombosis risk [26].

7. THE INFLAMMATORY RESPONSE TO COVID-19

COVID-19 patients are in extreme need of intensive care as per previous reports since different inflammatory mediators are involved to provoke response [27, 28] In another study, IL-6 numbers appear to increase with time in COVID-19 patients and are comparatively higher in non-survivors than in survivors [29]. Critical patients addressed a substantially higher percentage of peripheral blood inflammatory monocytes in CD14+CD16 + compared to patients with moderately ill [30].

Cytokine storm is contributed by the release of cytokine along with IP-10, MCP, and MIP1 alpha. The cytokine storm also has body-wide ripple effects. Elevated levels of TNF with cytokines can result in circulatory failure and myocardial damage led by septic shock [31,32].

7.1 During Viral Infection

During viral infection inflammatory process is associated with high plasma levels of cytokines, as cytokines storm, including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα. This might play an important role in pregnancy as IL-2 has been implicated to be upregulated in pre-eclampsia, miscarriage, and IL-7/IL-7R signaling pathway in fetal miscarriage, due to the upregulation in the ratio of Th17/Treg cells.

Another relevant aspect is the possible implication of polymorphisms in COVID-19 diseases, as is well-documented for other viral infections. Also, cytokines polymorphisms, such as TNF-α 308G/A (rs1800629) polymorphism is associated with recurrent miscarriage.

TNF-α and TNF-α receptors play an important role in the development of the fetus, being present in the ovary, endometrium, placenta, and fetus, and the amniotic fluid in different concentrations. This increase in TNF-α during pregnancy may implicate different health outcomes depending on the gestational period, leading to tissue necrosis in the placenta and hypoxia [33].

8. ROLE OF ACE2 RECEPTOR IN THE PATHOGENESIS OF COVID-19 INFECTION IN PREGNANT WOMEN

Mechanism of vascular injury up-regulation of the ACE 2 receptor during pregnancy can increase the risk of coronavirus 2 infections with severe acute respiratory syndrome. ACE 2 virus affinity contributes to decreased regulation and may increase Angiotensin II levels compared to Angiotensin(1-7), which favors vasoconstriction and may exacerbate vascular dysfunction in preeclampsia cases as shown in Fig. 1.

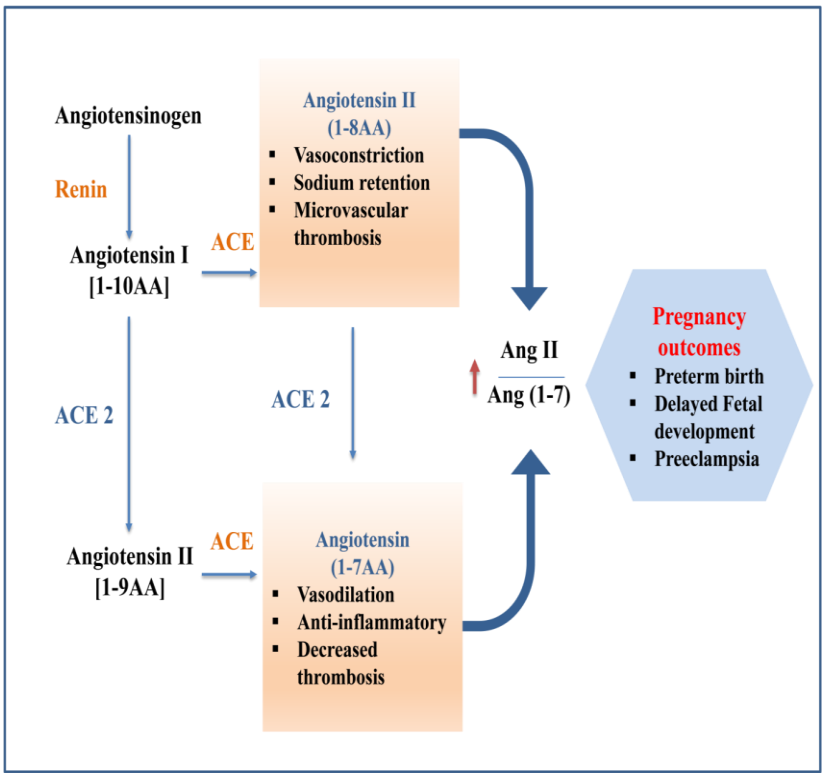

Fig. 1. Role of angiotensin in pregnant women

'Adopted from Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, et al. Differential Downregulation of ACE2 by the Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63. J Virol. 2010;84(2):1198–205; with permission'

ACE2 converts angiotensin (Ang) II to Ang-(1-7), and Ang I to Ang-(1-9), then back to Ang-(1-7), allowing blood pressure to be controlled. ACE2 in syncytiotrophoblasts is believed to help vasodilate the maternal vasculature by regulating the release of Ang 1-7 into the bloodstream [34]. The placentas, uterus, and kidneys were all found to be significant sources of ACE2 activity in one analysis, bolstering the theory that transient ACE2 overexpression and increased activity throughout pregnancy may modulate hemodynamics within the uteroplacental structure [35].

During gestation, ACE2 and Ang-(1-7) can serve as autocrine/paracrine regulators for early pregnancy angiogenesis, apoptosis, and development, as well as late pregnancy uteroplacental blood flow events, with late pregnancy models demonstrating augmented ACE2 and decreased uterine perfusion pressure models illustrating substantial ACE2 depletion [36]. The ACE2 receptor

is demonstrated predominantly during the first months of pregnancy by placental syncytiotrophoblast cells. Early ACE2 expression, which has been linked to placental immaturity, makes the first trimester the most possible time for SARS-CoV-2 infection [34].

For viral entry, a serine protease called TMPRSS2 is also necessary [37, 38], and placental expression is still a topic of debate. mRNA expression in the human placentas is reported to be low [39] but present in some studies, while it is not reported in others [40]. Because TMPRSS2 and ACE2 expression are linked in the first few months of pregnancy, this period is more vulnerable to SARS-CoV-2 infection. Li et al. confirmed this high level of ACE2 expression in maternal-fetal interface cells, such as decidua stromal cells and perivascular cells, as well as placental cytotrophoblast and syncytiotrophoblast [40]. In comparison, a recent study showed that in the third trimester, co-transcription of ACE2 and TMPRSS2 (transmembrane proteases) in the placenta was marginal, and chorio-amniotic membranes lacked expression of SARS-CoV-2 receptors, implying that the placenta was an unexpected pathway for vertical transmission [41]. However, the authors did not rule out the possibility that SARS-CoV-2 could infect the placenta by a different route and via interactions with other proteins, such as Basigin (also known as CD147 or EMMPRIN), a transmembrane glycoprotein that belongs to the immunoglobulin superfamily and is highly expressed in the placenta and chorioamniotic membranes [42]. Dexamethasone-induced reductions in placental expression of ACE2 and Ang-(1-7) have been related to intrauterine growth restriction and possibly disease programming in adulthood [43].

During the normal gestation period, there is an increase in the ACE2 enzyme in Renin-Angiotensin-Aldosterone System this could be a risk factor for covid infection in pregnant women [44]. Furthermore, hypotensive pregnant women sustained by the refractory response of Angiotensin II result in vasodilatation systemically [45, 46]. 3.5% of pregnancies are associated with preeclampsia due to a gestational hypertensive state [47]. Clinically, multisystem involvement and, typically, proteinuria are characterized; this equilibrium is lost, with an exaggerated reaction to blood pressure from Ang II. Decreased maternal plasma Ang-(1-7) levels have also been associated with Preeclampsia [46]. Since not only does SARS-CoV-2 bind to ACE2, it also induces its downregulation, Covid infection during pregnancy may potentiate the RAAS abnormalities, ie, dysregulation of ACE2, including coagulation abnormalities endothelial cell dysfunction (immune cell-mediated) was also identified recently [48, 49].

9. ROLE OF MATERNAL IMMUNE RESPONSE IN COVID-19

Aghaeepour and colleagues recently proposed the term "immune clock" to describe the precise timing of immunological activities in peripheral blood that took place during a full-term pregnancy. They discovered that endogenous STAT5ab signaling was strongly and gradually increased throughout pregnancy in a variety of T cell subsets, including CD25+FoxP3+ Treg cells, naive and

memory CD4+ and CD8+ T cells, and T cells. The immune system of the mother is well-equipped to fight against the invasion of foreign infections. While some adaptive immune responses are down-regulated during pregnancy, such as the reduction of T and B cells, innate immunity cells like NK cells and monocytes respond more strongly to viral assaults. Additionally, the upper respiratory tract often swells during pregnancy due to high estrogen and progesterone level [50].

There is a lot of proof that systemic viral infections in pregnant women can have an impact. Pregnancy-related SARS infection has been linked to a high incidence of spontaneous abortion, early birth, and intrauterine growth restriction, according to earlier investigations. However, there is no proof that a mother might have contracted SARS and then passed it on to her child. Therefore, viruses' direct impact on mothers may contribute to these pregnancy difficulties.

We cannot overlook the possible risk of infected pregnant women and the fetus, notwithstanding the scant available information. A cytokine storm, which is characterized by elevated plasma concentrations of interleukin 2 (IL-2), interleukin 7, interleukin 10, granulocyte-colony stimulating factor, interferon—inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and tumor necrosis factor (TNF-), may occur in severe cases of COVID-19 infection and may be brought on by ADE. Given that the first and third trimesters of pregnancy are known to be pro-inflammatory states, the cytokine storm brought on by SARS-CoV-2 may cause these women to experience a more severe inflammatory state.

Additionally, the development of the fetal brain can be impacted by maternal inflammation brought on by a viral infection during pregnancy. This can result in a variety of neuronal dysfunctions and behavioral abnormalities that are identified later in postnatal life [51].

10. PREGNANCY REGISTRIES

To gather data on how COVID-19 affects pregnancy and newborns, registries are being created by different international officials [52].

11. PREVALENCE OF CONGENITAL INFECTION

In several cases of third-trimester maternal infection within 14 days of delivery, the possible vertical transmission was identified, indicating congenital infection is possible but rare (< 3 to 4 percent of maternal infections). It is assumed that most neonatal infections arise from respiratory droplets that are exposed to mothers/caregivers after delivery [53, 54,55].

11.1 The Risk for Congenital Infection

One downside to the diagnosis of maternal-fetal transmission is that the acceptance criteria are not fulfilled by conclusive proof of congenital infection. We agree, in general, with the criteria proposed by Shah et al. Maternal symptoms and epidemiological exposure, maternal test outcomes, neonatal clinical status at birth, and neonatal test results are taken into account in the system.

11.1.1 Intrauterine fetal death/stillbirth congenital infection

Diagnosed by fetal or placental tissue polymerase chain reaction (RT-PCR) or electron microscopy to detect viral particles in tissue or culture to detect viral development in fetal or placental tissue. RT-PCR virus identification from the fetal surface or the fetal side of the placenta will be identified as a potential infection. If the virus was only identified by RT-PCR from the maternal side of the placenta in a surface swab and RT-PCR and no virus detection from fetal or placental tissue was carried out, then it is unlikely to consider that there is infection.

11.1.2 Congenital infection in live babies

Congenital infection in live babies depends on the presence or absence of clinical features of SARS-CoV-2 infection in newborns and mothers. Congenital infection is confirmed in symptomatic cases if the virus is detected by RT-PCR in umbilical cord blood or neonatal blood collected within the first 12 hours of birth or amniotic fluid collected before membrane rupture. Neonatal infection is confirmed in asymptomatic cases if the RT-PCR virus is detected in cord blood or neonatal blood collected within 12 hours of birth. There are also criteria for likely, possible, unlikely, or non-infectious.

11.1.3 Neonatal infection may be acquired intrapartum

Intrapartum infection is reported for symptomatic newborns of infected mothers if the SARS-CoV-2 RT-PCR of the nasopharyngeal swab is both positive at birth (after cleaning the infant) and at 24 to 48 hours of age, and an alternative cause of the symptoms is excluded. There are also requirements for probable, possible, impossible, or non-infectious.

11.1.4 Neonatal infection may be acquired postpartum

This is established by the clinical characteristics of COVID-19 at about 48 hours of age (regardless of parent/caregiver SARS-CoV-2) and verified if the respiratory sample SARS-CoV-2 RT-PCR at birth is negative, but the nasopharyngeal/rectal swab SARS-CoV-2 RT-PCR is positive at 24 to 48 hours of age [56].

11.2 Diagnosis

The current gold standard to detect COVID-19 infections/ suspected specimens by Real-time reverse transcriptase Polymerase Chain Reaction with 70% specificity [57].Chest imaging and re-testing help confirm infection if initially, the negative swab persists even if clinically has symptoms. In the early stages of pregnancy, the peripheral count of WBCs/lymphocytes is reduced C-reactive protein may be increased. There may be mild thrombocytopenia, elevated liver enzyme levels, and creatine phosphokinase in some patients.

Without contrast, computed tomography (CT) scan of the chest is essential to confirm pneumonia or to rule out pneumonia as it avoids radiation exposure to the fetus. Compared to the RT-RT-PCR test, chest CT revealed greater diagnosis (71% vs 98% respectively) as per the recent study. In the vast majority of recorded COVID-19 infection pregnancies, radiological symptoms of viral pneumonia were present [58].

Given its high specificity for COVID-19, RT-PCR testing can be used as an independent diagnostic tool; however, some studies say it has limited sensitivity. While COVID-19 chest CT sensitivities vary by sample, many of these recorded sensitivities are higher than those for RT-PCR research. Many trials, however, have exaggerated CT's vulnerability and used approaches that are fraught with confounding factors and skewed patient populations [59, 60].

A study by Fang Y and et.al concluded that the sensitivity of chest CT was greater than that of RT-PCR in Covid-19 subjects and Endorsed the use of chest CT to test for COVID-19 infection that has clinical and epidemiologic features that are consistent with COVID-19 infection, particularly when RT-PCR findings are negative [61]. On the other hand, in a metanalysis covering the broad prevalence range, RT-PCR sensitivity was reported to be 94% and specificity of 37% [62], which is contrary to the study done by Fang Y and et al. [63]. The sensitivity and specificity of RT-PCR and chest CT for COVID-19, as seen in the literature are controversial and the subject matter for debate. However, CT scans alone are unable to diagnose viral pneumonia and have lower sensitivity than RT-PCR. COVID-19 scanning was found to be more sensitive when RT-PCR and CT scans were used in combination [64, 65].

Suppose the SARS-COV-2 nucleic acid is not observed in samples taken at least 24 hours apart on two consecutive occasions, it is possible to rule out COVID-19. If RT-PCR is not available serology is used as a diagnostic tool. Before starting antimicrobial therapy, blood cultures that ideally cause pneumonia/sepsis are essential to be considered [66].

Some laboratory abnormalities associated with COVID-19 in pregnant women, such as thrombocytopenia, elevated liver enzyme levels, and hemolysis, are typical characteristics caused by extreme preeclampsia and HELLP syndrome. In COVID-19, prolonged prothrombin time; elevated levels of D-dimer, procalcitonin, and C-reactive protein (CRP); and low levels of fibrinogen can also be observed

(note that the reference ranges for D-dimer, CRP, and fibrinogen levels in pregnant women are higher [67, 68].

Neurological symptoms of COVID-19, as well as results of preeclampsia with extreme features/eclampsia, can be headaches, acute cerebrovascular disorder, and seizures. In COVID-19 and as a complication of obstetric disorders, acute kidney injury can occur (e.g. preeclampsia with extreme features, abruptio placentae, shock). Such diagnoses should also be considered and COVID-19 can coexist with them [69,70,71].

12. TESTING STRATEGIES IN INDIA

Newborns are at risk of COVID-19 infection by asymptomatic pregnant women In this regard, the ICMR proposed on 20th April 2020 that SARS-CoV-2 be screened in all pregnant women living in clusters/containment areas or large migration meetings/evacuation centers from hotspot districts in India and functioning or likely to be delivered in 5 days. Which greatly increased the rate of testing and also the number of obstetric patient referrals with confirmed COVID-19.

ICMR recommends testing reported cases for only symptomatic patients (symptoms of influenza-like disease) and asymptomatic immediate or high-risk contacts in its recent strategy [72,73]. It also endorses that emergency procedures, such as delivery, should not be delayed due to a lack of testing and that the same criteria should be adopted when sending samples for testing. The inpatient research approach was also revised accordingly where all patients were initially sent oropharyngeal swabs for (RT-RT-PCR) every 48 hours, this was modified to send them only on a case-by-case basis when repeat swabs were sent before discharging them from the hospital for critically ill or immune-compromised patients. Sampling, packaging, and transport of all specimens collected to comply with the MoHFW guidelines [74].

As per respiratory infection severity, admission criteria chosen for pregnant women depend on mild or moderate/severe signs. In Table 1, the admission criteria are used in detail. The modified severity scale of the CURB (Confusion, Urea, Respiratory rate, Blood pressure) will help us determine the severity and standardized guidelines can assess the need for critical treatment (adapted from the American Thoracic Society and Infectious Diseases Society of America) as shown in Table 2 [75].

13. MANAGEMENT OF PREGNANT WOMEN WITH COVID-19

There are several challenges in the management of COVID-19-infected pregnant women starting from screening, during labor and delivery along to protection of the healthcare unit [76]. The clinical management of pregnant women is shown in Fig. 2.

Table 1. Admission criteria for pregnant women during Covid-19 pandemic

Hospital	**Intensive care unit**	
	Major criteria	**Minor criteria**
▪ If there is Persistent fever more than 38° C even after treating with paracetamol ▪ Chest X-ray demonstrating pneumonia ▪ Pregnant women with co morbidities [[chronic hypertension, COPD, pregestational diabetes, immunosuppression or immunocompromised like HIV infected patients with >350 CD4+ cells, organ transplantations, patients receiving corticosteroids like prednisolone for more than 2 weeks and or neutropenia] should be considered for stringent evaluation by infectious disease specialist. ▪ CURB severity scale with total score 0 [each item gives a score of one point], where, C: Confusion (Acute in nature) U: Urea levels more than 19 mg/dL R: ≥30 bpm B: Systolic blood pressure ≤ 90mm Hg or diastolic blood pressure ≤ 60 mm Hg.	▪ Need for invasive mechanical ventilation ▪ Shock with the need for vasopressors	▪ Respiratory rate ≥ bmp ▪ PaO_2/Fio_2 ratio < 250 ▪ Multilobular infiltrates ▪ Confusion/disorientation ▪ Uremia [BUN > 20 mg/dL] ▪ Leukopenia $< 4000 cells/mm^3$ ▪ Thrombocytopenia < 100000 platelets/ mm^3 ▪ Hypothermia/central $< 36\ ^0C$ ▪ Hypotension in need of aggressive fluid resuscitation.

'Adopted from López M, Gonce A, Meler E, Plaza A, Hernández S, Cobo T, et al. Coronavirus Disease 2019 in Pregnancy : A Clinical Management Protocol and Considerations for Practice. 2020;519–28; S. Karger AG Publishers with permission'

Table 2. Classification of Covid-19 case based on the severity of respiratory infection

Mild infection	Moderate infection	Severe infection
Includes local symptoms like Sore throat, Cough, rhinorrhea or anosmia along with or without non-specific symptoms such as fever or myalgia and a CURB score of 0.	Mild pneumonia [Chest x-ray confirmed pneumonia] with no serious signs, with basal SO2 > 90%, no need for vasopressor or ventilator support, with CURB score up to 1. The patient should be admitted to the isolation ward [ideally in negative pressure set-up] along with constant monitoring of vital signs, supported with consultation with the specialists such as maternal-fetal, anesthesiologist and infectious diseases.	**Severe Pneumonia:** If there is one or more than one organ failure, basal SO2 < 90%, respiratory rate ≥ 30 bpm, or there is need for vasopressors **Respiratory distress:** Certain clinical findings such as [dyspnea, chest retraction] or with radiological evidence of bilateral infiltrates along with oxygen deficiency [SO_2/fraction of inspired oxygen (FiO_2) ratio ≤ 315 or PaO_2 FiO_2 ratio ≤ 300 Mild: PaO_2 FiO_2 ratio 200-300 Moderate: 100-200 Severe : ≤ 100 Sepsis: The Sepsis-Related Organ Failure Assessment [SOFA] can be used to evaluate sepsis severity [consider if the score is >2] and also quick SOFA with two of the three following criteria: Glasgow ≤ 13, systolic blood pressure ≤ 100 mm Hg, or respiratory rate ≥ 22 bpm. Septic Shock: Arterial hypotension that

Mild infection	Moderate infection	Severe infection
		persists after resuscitation volume and that requires vasopressors to maintain a mean arterial pressure ≥ 65 mmHg and lactate ≥ 2 mmol/L [18 mg/dL] in absence of hypovolemia.

'Adopted from López M, Gonce A, Meler E, Plaza A, Hernández S, Cobo T, et al. Coronavirus Disease 2019 in Pregnancy : A Clinical Management Protocol and Considerations for Practice. 2020;519–28; S. Karger AG Publishers with permission'

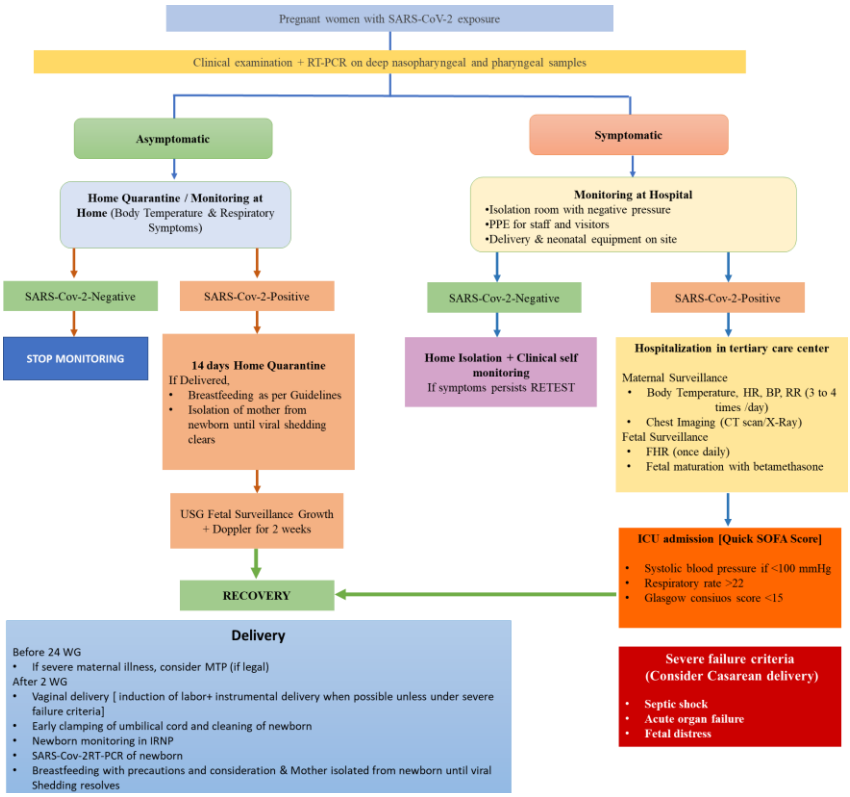

Fig. 2. COVID-19 Management during Pregnancy

'Adopted from Tripathi S, Gogia A, Kakar A. COVID‐19 in pregnancy: A review. J Family Med Prim Care 2020; 9:4536‐40; with permission'

14. TREATMENT APPROACHES WITH LIMITATIONS OF DRUG THERAPIES

The list of drugs used in the management of COVID-19 infection in pregnancy is shown in Table 3.

14.1 Plasma Therapy

In addition to drugs such as Remdesivir, Lopinavir / Ritonavir, steroids, convalescent plasma has been used effectively in a few pregnant women; it should be conducted as part of a clinical trial, if possible, which will assess protection and efficacy. Two studies have conducted the impact of plasma in COVID-19 patients at the University of Pennsylvania in the United States and are available to pregnant women who meet inclusion criteria [77, 78].

Table 3. Treatment approaches for COVID-19 with their limitations

Drug Class	Drug	Mechanism of Action	Dosage	Limitations/ Contradiction	References
Antiviral	Remdesvir	Inhibition of viral replication- Viral RNA-dependent RNA polymerase blockage	5mg/ml vial [reconstituted]. Single i.v. 200 mg loading dose, followed by 100 mg daily infusion for 9 days	Elevation of liver enzymes [particularly transaminase] [80]	Mulangu et al. 2019. [88]
Antiretroviral	Lopinavir/ Ritonavir	Inhibition of viral replication and release fro host cells: ▪ Lopinavir inhibits viral enzyme 3-chemotrypsin like protease [3CLpro] ▪ Ritonavir increases the half-life of lopinavir by inhibiting cytochrome P450 3A	400 mg/100 mg tablets, one tablet *bid.* For up to 14 days or 200 mg/50 mg tablets, together every 12 hours with α-IFN 5 million IU in 2 ml of nebulized physiologic solution regardless of meals	Low placental transmission to fetus No teratogenicity was found [81]	Chu et al. 2020 [89] Koss et al. 2014 [90] Liang et al. 2020 [91]

Drug Class	Drug	Mechanism of Action	Dosage	Limitations/ Contradiction	References
Antiprotozoal Antirheumatic	Chloroquine	Inhibition of host TNF-α & IL-6 production	500 mg or 250 mg tablets: 500 mg oral every 12 to 24 hr for 5 to 10 days; or 1 gm oral for the first day of the treatment and then 500 mg daily for 4 to 7 days depending up on clinical response.	Risk of congenital anomalies [82]	Sanders et al. 2020. [92] Berghella, 2020. [93] Klumpp, 1965. [94]
Antimalarial Antiprotozoal Antirheumatic	Hydroxychloroquine	▪ Inhibition of viral host cell penetration, viral replication, and mitigation of host inflammatory response ▪ Inhibition of	200 mg tablets: 400 mg oral every 12 hours for one day followed by 200 mg every 12 hours for 4 days or 400 mg daily for 5 days or 200	Risk of congenital anomalies [82]	Sanders et al, 2020. [92] Berghella, 2020. [93] Klumpp, 1965. [94]

Drug Class	Drug	Mechanism of Action	Dosage	Limitations/ Contradiction	References
		terminal ACE-2 glicosilation ▪ Increases endosomal pH.	mg every 8 hours for 10 days.		
Anticoagulant	Heparin	▪ Inhibition of viral host cell penetration ▪ Prevention of endovascular thrombosis ▪ Inhibition of Factor Xa	4000 IU S.C. daily [also during post-partum if still positive]	Osteoporosis and heparin-induced thrombocytopenia [82]	Berghella, 2020. [93] Di Renzo et al. 2020. [95]
Corticosteroids	Betamethasone & Prednisolone	▪ Mitigation of host inflammatory response. Inhibition of host IL-1, IL-2, IL-6, IL-12, INF-γ & TNF-α production	12 mg i.m. two injection 24 hr apart as prophylaxis for fetal lung maturation.	Classified as C/D approved drugs by FDA	Poon et al. 2020. [96] Kakoulidis et al. 2020. [97]
Antibiotic	Azithromycin	▪ Inhibition of viral host cell penetration. ▪ Inhibition of terminal ACE-2 glicosilation. ▪ Endosomal pH elevation Inhibits the 50 S	500 mg/day for 3-5 days depending on clinical response.	Class B drug Contradiction: Combination with Chloroquine causes QT prolongation	[98]

Drug Class	Drug	Mechanism of Action	Dosage	Limitations/ Contradiction	References
		subunit of bacterial ribosome		with greater risk of Cardiac effects [59]	
Antibiotic	Ceftriaxone	Produces bactericidal effects by interfering with the synthesis of peptidoglycan layer	1gm i.m. or 1-2 gm i.v. daily depending up on clinical response	Class B drug approved by FDA [86]	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/050796s000_PRNTLBL.pdf [99]
	Convalescent plasma	▪ Direct neutralization of virus ▪ Mitigation of host inflammatory response &immunoodulation of a hypercoagulable state Anti-idiotypic antibodies blocking autoreactive antibodies.	Lack of data on pregnancy	Lack of data on pregnancy	Van Grienswen et al. 2016. [100]
Monoclonal Antibody	Tocilizumab	▪ Mitigation of host inflammatory response Blocks the membrane bound	400 mg IV for 1-2 doses , Second dose after 8-12 hr if required	Not assigned by FDA	Weber-Schoendorfer et al. 2016. [101]

Drug Class	Drug	Mechanism of Action	Dosage	Limitations/ Contradiction	References
		IL-6 receptor	(infuse in 60 minutes)		
Immunomodulator	Interferon -I	▪ Inhibition of viral replication ▪ Mitigation of host inflammatory response ▪ Hinders the cellular metabolism Inhibits host Il-1b & TNF-α production.	Limited data available [variable dose]	Limited data available	Yazdani et al. 2012. [102] Romero et al. 2015. [103]

'Adopted fromFavilli A, MatteiGentili M, Raspa F, Giardina I, Parazzini F, Vitagliano A, et al. Effectiveness and safety of available treatments for COVID-19 during pregnancy: a critical review. J Matern Neonatal Med [Internet]. 2020;0(0):1–14; with permission'

14.2 Micronutrients

Micronutrients especially vitamin B12, Zinc, and serum 25(OH)D play important role in pregnant women. Yalcin et al. 2020, [79] conducted a study on 44 Covid positive pregnant women and observed that these micronutrient levels were less compared to normal values. Hence, this deficiency may become vulnerable to COVID-19 infection. During a pandemic, micronutrient supplementation may be helpful during pregnancy.

14.3 Remdesivir

One of the cases reported about third-trimester pregnancy affected with COVID-19 required intensive care support along with Remdesivir treatment. However, elevated transaminases as a side effect were noticed but it was unclear whether transaminitis was due to Remdesivir or due to Covid infection [80].

14.4 Lopinavir/ ritonavir (LPV/r)

These drugs were considered safe during pregnancy based on earlier reports of LPV/r exposure to HIV pregnancy cases; however, it has been reported that lopinavir has low placental transfer to the fetus yet human teratogenicity was not found [81].

14.5 Hydroxychloroquine

Huybrechts K F et al reports quantified the risk of congenital malformations/birth defects related to early pregnancy administered with hydroxychloroquine and its potential use as prophylaxis were notable [82].

14.6 Heparin

This is a heavy molecular anticoagulant chosen as safe during pregnancy and lactation since it does not cross the blood-brain barrier. in the case of long-term effects, 2 main potential side effects need to be considered: osteoporosis and heparin-induced thrombocytopenia [83].

14.7 Azithromycin

Azithromycin works by inhibiting protein biosynthesis and bacteriostatic drug. Common side effects are nausea, vomiting, diarrhea, abdominal pain, and, less frequently, a change in the electrical activity of the heart in particular by prolonging the QT interval. The addition of Azithromycin to the protocol with chloroquine is not recommended as their combination may cause QT prolongation, with a greater risk of adverse cardiac effects. Azithromycin is classified as class B by FDA and is commonly used in pregnancy and breastfeeding [84].

Recently NIH U. S. National Library of Medicine posted a clinical trial (Phase 3) of Hydroxychloroquine and azithromycin treatment of pregnant COVID-19 patients with mild symptoms with expected outcome measures such as the percentage of patients with a negative RT-PCR test result to COVID-19 nasopharyngeal swab at the 7th day of treatment by hydroxychloroquine and azithromycin and measure maternal and neonatal outcomes [85].

14.8 Ceftriaxone

FDA approved this antibiotic under Category B safe for use in pregnancy and breastfeeding. This has side effects viz. diarrhea, pancreatitis, nausea or vomiting, etc. [86].

14.9 Ivermectin

Ivermectin is an anthelmintic agent. The antiviral function of ivermectin has recently been discovered. Ivermectin has been used in current clinical trials at doses of 200 to 1200 mcg/kg for 3-7days, showing a positive response to reduce viral load and symptomatic relief.

However, Ivermectin was shown to be teratogenic in preclinical studies using pregnant experimental animals. However, there were no appropriate and well-controlled trials available for pregnant women. Since protection in pregnancy has not been developed, Ivermectin should not be used during pregnancy. The data also suggests that the drug is excreted at low concentrations in human milk. Treatment of lactating mothers should be undertaken only if the possibility of delayed mother-to-mother treatment exceeds the potential risk for neonates [87].

15. MANAGEMENT OF NEONATES DELIVERED WITH COVID-19

There are indications for obstetric surgery or when a pregnant woman is in critical condition from new coronavirus pneumonia. Timely termination of pregnancy won't increase the risk of neonatal asphyxia and premature delivery, but it will be helpful for the treatment and recovery of maternal pneumonia. Postpartum hemorrhage can occur less frequently when taking depressants. Neonates exposed to new coronavirus pneumonia during pregnancy were not found to have the infection [104].

16. COVID-19 VACCINATION: IS IT PRIORITIZED FOR PREGNANT WOMEN?

India started the COVID-19 vaccination drive on 16th January 2021. To start with, 30 million healthcare staff and frontline workers would be vaccinated. Till now, DCGI approved ‘Covishield’ and ‘Covaxin’ for emergency use in India. However, for instance as per WHO reports no relevant/insufficient data to recommend the vaccination of pregnant women.

Although several vaccine efficacies and safety studies were conducted with pregnant and lactating women during the H1N1 pandemic, the COVID-19 vaccine trials have excluded these groups, and therefore, critical perinatal safety information remains largely unknown [105].

With the development of multiple effective vaccines, reducing the global morbidity and mortality of COVID-19 will depend on the distribution and acceptance of COVID-19 vaccination. Estimates of global vaccine acceptance among pregnant women and mothers of young children are yet unknown. Acceptance of COVID-19 vaccination among pregnant women and mothers of children younger than 18 years old, as well as potential predictors, were assessed through an online survey, in one of the research. Vaccine acceptance was generally highest in India, the Philippines, and all sampled countries in Latin America; it was lowest in Russia, the United States, and Australia. The strongest predictors of vaccine acceptance included confidence in vaccine safety or effectiveness, worrying about COVID-19, belief in the importance of vaccines to their own country, compliance to mask guidelines, trust of public health agencies/health science, as well as attitudes towards routine vaccines. COVID-19 vaccine acceptance and its predictors among women vary globally. Vaccination campaigns for women and children should be specific for each country to attain the largest impact [106].

17. CONCLUSION

December 2019 has been remembered as a pandemic month due to the spread of COVID-19 globally. Given the novelty of COVID-19, data on the effect of COVID-19 on pregnancy and the newborn are so far limited to a few small case reports and case series; however, early reports and lessons from SARS, MERS, and other infections give an insight that pregnant women could have severe clinical course. The lack of early diagnosis, and specific treatment conditions lead clinicians to choose earlier drugs having their efficacy against similar viruses or *in-vitro* tests due to emerging situations. The vulnerable group especially COVID-19-infected pregnant women and their complications have been ignored during a pandemic scenario. The exclusion of pregnant women in a clinical trial is well known despite in search for the treatment of COVID-19 for non-vulnerable groups and the criteria are not justified as many of the treatments are used with low safety measures. Inclusion may be needed to identify better treatment options for this population [107]. Due to a paucity of inconsistent data regarding the impact of COVID-19 on pregnant women, caution should be undertaken to further investigate and monitor possible effects on pregnant women. A current overview may be useful for healthcare providers for the practical approach and limitation of drugs used in the current management and considers the choice of drugs with special attention given to adverse effects to improvise maternal health, pregnancy, and birth outcomes. The basis of treatment for all pregnant women with COVID-19 is the standard intervention to treat any significant respiratory infection and should be applied vigorously in a team-based care model.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
Monaldi Archives for Chest Disease, 91:1785: page number, 2021.

Peer-Review History: During review of this manuscript, double blind peer-review policy has been followed. Author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the peer-reviewers. As per the comments of the peer-reviewers and depending on the quality of the revised manuscript, the Book editor approved the revised manuscript for final publication.

ISBN: 978-81-19149-00-1

1. Pharmacy Information for Consumers

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Abstract:

A leaflet called the Consumer Medicines Information (CMI) provides guidance on how to use prescription medications safely and effectively, as well as some over-the-counter medications and biological products. Making it easier to personalize information to meet individual requirements. The most successful technique of conveying pharmacological information is verbal counseling, with written and verbal communication functioning together to further increase patient awareness regarding medical illness, importance of therapy, administration steps and severity of illness if not treated well.

Keywords:

Pharmacy Information, Consumers, PILs, Consumer Medicines Information.

1.1 Introduction:

Pharmacy is the science and practice of discovering, manufacturing, dispensing, reviewing and monitoring medications, aiming to ensure the safety, efficacy and affordable use of medicines by the Healthcare professionals/public [1]. In addition to dispensing and distributing medications, Clinical Pharmacists play a important role in public health care system by helping patients to manage their current illness by usage of medications more effectively and encouraging healthy lifestyles modifications. Patients have a wide range of information regarding treatment options. The Pharmacists/ practitioner's responsibility in this situation is to give the patient accurate, reliable information in a way the patient can understand. The pharmacist could be required to explain the advantages and disadvantages of the treatment as well as the effects of not taking medications [2].

According to the study reports significant ratios between 30% and 50% of people with chronic diseases don't follow the directions on their prescriptions. several factors are believed to have an impact on a patient's decision to follow a prescribed regimen. They include the nature of the disease and the methods used to treat it, the patient's attitudes towards their condition and any medications they may be taking, and the effectiveness of the communication among them and the healthcare provider [3].

Patients / Consumers need to have access to information that is relevant to the type and quality of treatment they get in hospitals. They get a deeper understanding of their symptoms, the diagnosis, the recommended treatments, and the prognosis for their illness.

A fundamental foundation for successful decision-making is the dissemination of accurate, fact-based information regarding alternatives and expected outcomes. The provision of clear, evidence-based information about options and likely outcomes is an essential basis for proper drug use, safety, and storage [4].

The Consumer Medicines Information (CMI) is a leaflet that contains information on the safe and effective use of prescribed drugs, as well as some non-prescription medicines and biological products.Drug information may be patient specific, academic (for educational purposes), or population based (to aid in the decision-making process for evaluating medication use for groups of patients)[5].

1.2 Importance of Pharmacy Information for Consumers:

For medicine purchases, over-the-counter interaction between the patient and a healthcare professional may be limited or unavailable. In this case, written information has an increased importance for safe use of the medicine [5].

One of the key management technique for preventing the progression of chronic diseases (Hypertension, Diabetes Mellitus, COPD, Hyperlipdaemia, Epilepsy etc.) is patient education. Educating the patients about their present illness, reasons for that, what is the need of therapy and preventive care.

The patients' inappropriate medication use has been linked in major part to a lack of information. In order to adhere with the medicine, patients must fully understand their therapy. Patients' knowledge, compliance, and awareness of the potential side effects were found to be improved by giving them Patient Information Leaflets [6].

Just 49% of the patients in actual practice received medication education upon discharge, therefore having accurate information is important for patients to choose the right medications (Indication, Dosage, Frequency) as advised by their doctor. Medication adherence is increased by education and awareness of drug usage, making it possible to treat patients with a variety of diseases and achieve treatment goals.

It may be difficult or impossible for patients to communicate with healthcare providers over the counter while buying medications. For the proper use of the medication in this situation, written advice is more crucial than ever [7].

A Consumers Medication Information (CMI) is intended to provide with precise information regarding the safety of medication and the ideal method of administration. The drug manufacturer creates the CMI and is required to adhere to legal requirements.

For the benefit of patients, written patient information is routinely utilized to supplement doctor-patient contact. Moreover, it helps to highlight the directions and cautions while bridging the communication gap between patients and doctors. Printed information can capture patients' attention, encouraging them to take their medications as prescribed and changing their lifestyle [8].

A. The goal of treatment for elderly people is to enhance quality of life as well as increase life expectancy. The right therapy must be chosen in order to achieve this.
B. Around 70% of older people have blood pressure levels that are higher than 140/90 mmHg, indicating a significant incidence of Hypertension. Furthermore, they have a relatively high risk of cardiovascular problems.
    a. Large-scale clinical trials have established the use of calcium channel blockers and low-dose thiazide diuretics as safe and efficient therapies for elderly hypertension patients. The effectiveness of β-blockers in lowering blood pressure and minimizing clinical effects is lower. (Hansson et al., 1999b) [9].
    b. In type I diabetes, the presence of Hypertension:
        - There will be a need for pharmacological combinations to manage blood pressure effectively. Thiazides, beta-blockers, calcium channel blockers, and α-blockers can all be used in combination with ACE inhibitors to treat other conditions as first-line therapy.
    c. In type II diabetes, the presence of Hypertension:
        - Indapamide and Perindopril to diabetic patients. Blood pressure was further reduced, and unfavorable renal outcomes were significantly reduced (by 21%). (Patel et al., 2007) [10].

As a result, this population would benefit the most from blood pressure treatment in absolute terms. Moreover, antihypertensive medication may lower the incidence of dementia and heart failure.

In comparison to young individuals, elderly patients may need lower dosages of all medications. The majority of adverse medication responses in elderly patients are widely recognized to be dose-related and potentially preventable. So, it is appropriate to begin with the lowest dose of a particular medicine and then gradually increase, as needed.

For elderly people who struggle to grasp most of the information given during medication counseling, written instructions, such as medicine cards, medication charts, or any printed material in a plastic sheet or laminated sheet, also helps in increasing adherence [11].

1.2.1 The Following Instructions Relate to The Use of Dry-Powder Inhalers in Pediatrics/Parents.

A. Request that the child exhale naturally and as far as they can. Once they have started to breathe in, administer (give) the amount as instructed by your pharmacist or nurse. • Put

the mouthpiece of the inhaler firmly between the lips, making sure there is a strong seal around the mouthpiece. In order to inhale the medication puff, the child should keep breathing in fully.

B. Remove the inhaler from their mouth. During 5 to 10 seconds, or whatever long they can comfortably handle, they should keep their mouths shut and hold their breath. Then, they can breathe properly.
C. If the child has to take more than one puff, they should wait about a minute to breathe properly before providing the next.
D. Brush their teeth or thoroughly rinse their mouth with water [12].

1.2.2 Use of Nebulizers:

A nebulizer is a machine that creates a mist or vapor from liquid medications so that you may breathe it in (inhale). If your child suffers from a respiratory disorder like asthma or pneumonia, they might need to use a nebulizer.

Nebulizers come in a variety of forms. Your child will breathe in via a mouthpiece. Some use a mask that covers child's lips and nose. Child's age will determine the type of nebulizer they use.

A. Before Using the Nebulizer, Follow These Instructions:

- Since nebulizers differ, read the manufacturer's instructions for the appropriate use.
- Before using medicine see your child's prescriptions. Verify that it is in good condition and has not expired.
- Use soap and water to wash your hands.
- Position the nebulizer's components on a solid, level surface.
- Join the reservoir and nebulizer together with the tubing.
- Use the liquid medication as directed by your child's doctor after measuring it. Fill the reservoir with the medication.
- Fit the mask or mouthpiece.
- Check to see if a spray comes out of the nebulizer by turning it on. Then switch it off.

Infection might result from using a nebulizer that does not fit well or is not cleaned thoroughly.

- Eye discomfort.
- Excessive or insufficient medication delivery.
- An irritated mouth.

If your kid starts coughing or if the medication foams or bubbles, make sure to stop the machine immediately.

i. Encourage your Child to sit up straight and comfortably.
ii. If necessary, aid your kid in unwinding. You can do this by consoling your child while holding them or by occupying them with a peaceful activity.

iii. Choose one of these:
   - Cover your child's mouth and nose if he or she uses a mask to take the medication. It need to be tight enough to prevent gaps around the nose or mouth. There shouldn't be any holes around the nose or cheeks where the medication may escape. It should fit rather tightly.
   - If your kid uses a mouthpiece to take the medication, put it in his or her mouth and have them tightly seal it with their lips.

iv. Switch the nebulizer on.

v. After the medication starts to mist out, encourage your kid to breathe deeply and slowly in and out.

vi. Encourage Child to keep inhaling slowly and deeply until there is no longer any medication in the nebulizer and no mist is visible. Takes ten to fifteen minutes.

vii. If your child is old enough to do so and the medication contains a corticosteroid, have him or her rinse and spit with water. If your child is too small to rinse their mouth, wipe their tongue and inside cheeks with a damp towel. Wash your face as well if you're wearing a mask.

B. Nebulizer Maintenance/ Cleaning the Nebulizer:

All of the nebulizer's components need to be maintained clean. The nebulizer's inside might develop germs if it isn't cleaned thoroughly. Your Child may become ill if they breath the microorganisms. For nebulizer maintenance, according to the manufacturer's guidelines. You should adhere to these rules for the majority of nebulizers:

- Wash the reservoir, mask, and mouthpiece by: Rinsing them following every usage. Use distilled or sterilized water. Washing them once or twice a week with warm water and soap.
- Avoid washing the tubing.
- Lay the components out on a clean towel to dry entirely after rinsing or washing them. Reconnect the parts once they dried, then turn the nebulizer on without any medication in it. By doing this, air will be blown through the apparatus to aid in its drying.
- Keep the nebulizer clean and clear of dust.
- At least once a week, check the filter. If the filter appears to be dusty, replace it [13].

1.3 Use of Insulin:

1.3.1 Before Get Started:

- Cleanse your hands.
- Ensure that the insulin is transparent and colorless. If it's hazy or you notice particles, don't use it; instead, toss it away.
- Should not be used or diluted with any other insulin or solution. It won't function as planned, and you can lose control of your blood sugar.
- Avoid sharing syringes, insulin pens, and needles with others.
- NEVER re-use needles. Use a fresh syringe every time.

1.3.2 Get Ready the Dosage:

Remove the protective cap if you are using a brand-new vial. Avoid removing the stopper.

A. Clean up the top:
- Using an alcohol swab, clean the vial's top.
- Pull air into the syringe that is equivalent to your daily dose of insulin to inject into the vial.

B. Place the needle:
- To inject air into the vial, insert the needle through the rubber cap and press the plunger.

C. Prepare the dose:
- Turn both of them upside down while keeping the syringe in the vial. With one hand, firmly grasp the syringe and vial. Ensure that the needle's tip is inserted into the insulin. Pull the plunger with your free hand to dispense the proper dosage into the syringe.

1.3.3 Remove Air Bubbles:

Check for Bubbles: Before removing the needle from the vial, be sure there are no air bubbles in the syringe. If the medication contains bubbles, tap the side of the syringe while holding it straight up until the bubbles rise to the top.

- **Eject the Air:** Using the plunger, expel the air bubbles and then slowly re-inject insulin to adjust the dosage.
- **Take the Needle Out:** Take the needle out of the vial. Keep the needle away from any surfaces. Now that you are prepared to inject

1.3.4 Choose an Injection Site:

Choose where to inject: either the upper arm, thigh, or abdominal. Each injection must be administered at a distinct spot within the injection region.

Rub alcohol should be used to clean the area of skin where you will inject. If the region is not totally dry when you inject the alcohol, it may hurt. Wait a few seconds for the alcohol to evaporate, or pat the area dry with a clean cotton ball.

Pinch a Skin Fold: Hold the skin in a pinch. As instructed by your healthcare provider, insert the needle. To administer insulin, slowly insert the syringe's plunger all the way, being careful to inject every last bit of the medication. Give the needle 10 seconds in the skin.

Lightly Pressurize: Draw the needle straight out and apply gentle pressure to the injection site for a few seconds. Avoid rubbing the region. Dispose of Materials Carefully: Put the needle and syringe in the trash according to the advice of your doctor.

A. Storage Guidelines:

- Refrigerate unused vials between 36 and 46 degrees Fahrenheit (2 and 8 degrees Celsius).
- Insulin vials that are currently being used (opened) should be kept cold or at a temperature below 86 °F (30 °C).
- Avoid freezing Insulins.
- Keep insulin preparations away from intense light and heat.
- Throw away any vials that have been frozen or overheated.
- Even if there is still insulin in the vials you are using, it should be discarded after 28 days [14].

1.4 Conclusion:

Written patient information is frequently used to enhance doctor-patient interactions for the benefit of patients. Also, it aids in bridging the communication gap between patients and doctors by highlighting the instructions and warnings. Printed materials can grab patients' attention, motivating them to follow prescription instructions and adopt a healthier lifestyle. Interviewing patients about their drug histories and medical conditions was thought to be an effective and beneficial use of a pharmacist's time.

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ISBN: 978-81-19149-00-1

2. Evolution of Teleconsultation and E-Pharmacy

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Abstract:

Teleconsultation and internet pharmacy have advanced significantly in recent years. With the use of the internet, face-to-face or virtual teleconsultations have developed from listening to radio conversations and making direct phone calls to health professionals. Also, individuals looking for prescriptions with the convenience of home delivery have a wide range of possibilities thanks to the internet. Teleconsultation has grown in popularity recently all around the world, particularly in light of the COVID-19 epidemic. There are now many benefits to teleconsultation and online pharmacies, but there are also certain problems that are being resolved daily and showing a quick rise. Future medication delivery may make use of online pharmacies and teleconsultations, which may also examine the possibility of offering cognitive services in addition to medical care. In order to retain a younger, more technologically advanced generation of potential parents and carers, brick-and-mortar pharmacies should consider the value they provide to the transaction.

Keywords:

E-Pharmacy, Evolution, Teleconsultation, Internet Pharmacy, Online Pharmacies.

2.1 Teleconsultation:

Teleconsultations, as defined by the World Health Organization (WHO), are "interactions that take place between a physician and a patient with the goal of delivering diagnostic or therapeutic advice using electronic means." Or Teleconsultation is also known as simultaneous or asynchronous consultation that avoids functional and geographic distance

via the use of communication and information technologies. A quick and easy approach to get in touch with your healthcare providers has always been through teleconsultation. Most people have access to a network or video links, as like watsapp or google zoom, that they can use at some time to speak with a healthcare expert. That is not a novel idea in India, where it has long been popular. Unfortunately, due to a dearth of effective teleconsultation platforms and patient data that is compatible, at the level of consultation that India needs, it is not a viable approach.

2.2 E-Pharmacy:

Consumers may buy medications through e-Pharmacies, which are online stores that let them do so without having to go to a physical pharmacy. As a result, there is now greater demand for the system all over the world and it is more convenient for the buyer to use. The expansion of this online market is also related to the increase in the use of e-prescriptions in hospitals. Or online pharmacies, often known as Internet pharmacies or mail-order pharmacies, operate via the Internet and dispatch their clients' orders via the postal service or other delivery services.

2.3 Evolution of E-Pharmacy:

The main business model that pharmacies used across the world has changed slightly over the past few decades. The patient sought the advice of their physicians, who wrote prescriptions. The pharmacist who delivered these pills would then get this prescription. Patients now have more options and control over how they manage their health thanks to the growth of online pharmacies. In the United States, the first online pharmacy that sold exclusively prescription drugs originally launched for business in the late 1990s.

The pharmaceutical supply chain has become more complex as the roles of the participants in the e-pharmacy industry have grown over time. Leading e-pharmacies now provide end-to-end client solutions that improve pharmaceutical companies' understanding of their supply chains and jeopardise the conventional functions of pharmacies as primary care providers and sellers of medications. During the past several years, e-pharmacies have gained popularity in India and currently make up between 2% and 3% of all medicine sales (1). Many purchases in this market have been made with the goal of enhancing reach, technology, and customer experience. In the following five years, it is anticipated that the e-pharmacy sector would represent 10%–12% of total revenue (2).

Online pharmacies, sometimes known as e-pharmacies, have significantly evolved in recent years. These are some significant junctures. Early on, e-pharmacies served largely as online versions of traditional pharmacies. They offered home delivery and online purchases, but the range of goods was constrained. Independent online pharmacies began to appear in the middle of the 2000s, including Netmeds, 1mg, and PharmEasy. These platforms offered a larger variety of medications and healthcare items, competitive price, and more ease. In 2015, the Indian government started to regulate online pharmacies. As a result of an amendment to the Medicines and Cosmetics Act, e-pharmacies are now subject to licencing requirements and must follow stringent regulations for the storage, packing, and delivery of medications.

Pharmacy: Health Care

Figure 2.1: Evolution of E-Pharmacy

The e-pharmacy business has undergone substantial consolidation recently, with bigger firms buying up smaller ones. Nowadays, e-pharmacies provide more than only the sale of medications. They provide diagnostic testing, home healthcare services, and medical consultations online. They are also utilizing technology to tailor healthcare and enhance patient outcomes, including AI and machine learning. E-pharmacies in India have attracted considerable funding from investors in recent years, with the sector's overall investment expected to reach $700 million by 2020 (3). Because of this, there has been development and consolidation as bigger businesses buy out smaller ones. For instance, Netmeds was acquired by Reliance Retail in 2020, and Amazon bought a share in Med Plus. Indian e-pharmacies are gradually offering more services than merely selling medications. They provide diagnostic testing, home healthcare services, and medical consultations online. They are also utilizing technology to tailor healthcare and enhance patient outcomes, including AI and machine learning. For millions of people, particularly those in distant and disadvantaged areas, this has made healthcare more inexpensive and approachable.

The biggest government-funded healthcare insurance scheme in the world, Ayushman Bharat, was also launched by the Indian government (GoI). It presently operates more than 255,000 popular service centers for telemedicine, e-pharmacies, and e-diagnosis and plans to spend over $200 billion on medical infrastructure by 2024(5). In spite of these efforts, only acute illnesses like the common cold or short-term illnesses are covered by pharmaceuticals for 92% of the rural population. In 2019(6), the Indian e-pharmacy sector was predicted to be worth US$0.5 billion, with Net Meds, PharmEasy, Midlife, and 1mg dominating the industry (3). With a predicted CAGR of 44% from 2019 to 2025, it will reach US$4.5 billion. By 2025, it is anticipated to account for around 10%–12% of pharmaceutical revenues, up from the current 2%–3% levels in 2019 (4). With the

coronavirus outbreak, e-pharmacies have become more popular since people are avoiding pointless encounters and engaging in social isolation. Consumer Value Store (CVS), an important American retail chain partnered with UPS that is United Parcel Service move ahead to offer delivery of prescription pharmaceuticals using drones to Florida municipalities in response to COVID-19. Publix Pharmacy and ScriptDrop collaborated to offer home delivery services, with an emphasis on serving older persons. As the number of delivery requests increases, leading UK online pharmacy Echo is adding more staff. From the last week of March 2020 and the last week of June 2020, there was a 60% rise in nominations for prescriptions written by the NHS (National Health Service). Globally, the number of orders placed at e-pharmacies has increased.

Major Indian online pharmacies have reportedly reported a spike in orders of 50% to 100% (13) during the lockdown. While e-pharmacies have increased their employment efforts internationally, Indian players are having difficulties as a result of the supply chain's fragmented character. Because there are no major retail or distribution chains in India, there are issues with ineffective procedures and poor technical infrastructure.

2.3.1 Advantages of E-Pharmacy:

E-Pharmacy makes it incredibly simple to acquire prescription medications. This technique is a very simple and quick way to get medicine, especially for persons who live far from a conventional pharmacy, the elderly, the crippled, and those who work extremely hard. A typical pharmacy is significantly more expensive to visit than online pharmacies are, and delivery is also lot less expensive. Online medicine purchases also result in financial savings. Online medicine purchases, according to studies, can result in overall financial savings of up to one third.

Confidentiality and privacy are additional benefits provided by e-pharmacy. For people who find it difficult to interact with doctors and pharmacists in person, this technique is very helpful. Also, ordering drugs is possible without restrictions on any unique circumstances, such as sexuality or adolescence, which can be embarrassing.

Patients can greatly benefit from e-Pharmacy, which offers a considerably greater selection of alternatives than a conventional pharmacy. There are many more medicine possibilities accessible in regular drug stores, but it is impossible to find every drug in a real pharmacy in a specific location.

2.3.2 Disadvantages of E-Pharmacy:

The absence of face-to-face communication is one of the drawbacks of e-pharmacy. Finding a qualified pharmacist to ask questions about the medications they are taking is quite challenging for people. Because of this, patients might not be able to get their medication on that exact day. A prescription is not always necessary when ordering medications from internet pharmacies. Patients might not heal in such a situation, but rather become considerably sicker. As a result, pharmacists must surely ask for a prescription while dispensing medications. It is incredibly challenging to stop some illicit internet pharmacies from selling over-the-counter medications while endangering people's health.

2.4 Evolution of Teleconsultation:

Telehealth, telemedicine, and teleconsultation are terms used to describe the delivery of healthcare services using telecommunications technology. Teleconsultation has grown in popularity recently all around the world, particularly in light of the COVID-19 epidemic. In affluent countries as opposed to developing ones, teleconsultation has been accepted more widely and fast. In the United States, where telemedicine has been expanding since the early 2000s, the COVID-19 outbreak strengthened its adoption. In Europe, telemedicine has been used for a long, particularly in remote areas with poor access to healthcare.

The healthcare industry is growing swiftly to increase patient accessibility and reduce total healthcare expenditures. Healthcare professionals may now communicate with their patients thanks to recent technological advancements, which removes any barriers to patient access to care. Many methods of obtaining healthcare are now feasible thanks to teleconsultation. It is expected to fundamentally alter how clinical practice is conducted. A virtual visit allows distant patients to receive professional care at their convenience without having to be present in person at the doctor's office. In addition to allowing doctors to assist their current patients online, it also helps them expand their reach by interacting with newer patients in the same or other geographic areas. Elderly patients and those who are close to death benefit greatly from patient monitoring at home. By lowering the cost of readmissions, particularly for patients with chronic illnesses like diabetes and hypertension, it improves the patient route. Online second views are also more easily accessible to patients. One doctor is needed for every 1,456 people in India, well below the WHO guideline of one doctor for every 1000 people. The significant need for and potential of teleconsultation in India is due to this, as well as the fact that the density of doctors is much larger in urban than in rural regions. Teleconsultation has the potential to enhance health outcomes by enabling patients to recover more quickly and maintain their health, albeit it may not always be practical.

Hospitals and technology platforms throughout the world have noticed a sizable rise in teleconsultation, with health systems reporting a particularly large rise after COVID-19. Across the world, digital primary care interactions have climbed 5-95% since January 2020 (7). Teleconsultation has been more common in India as well, especially during the COVID-19 epidemic. India has a sizable population, and many people reside in isolated regions with little access to medical care. Telemedicine has received support from the Indian government as a means of expanding access to medical treatment. The Indian government published teleconsultation rules in March 2020, enabling licenced physicians to offer telemedicine services throughout the nation. These regulations were updated in September 2020 to broaden the range of permissible teleconsultation services. After the release of these regulations, a number of private businesses have also entered India's telemedicine sector, offering patients teleconsultation services via mobile applications and web platforms. The necessity for in-person trips to hospitals or clinics has decreased as a result of these platforms, which have made it simpler for patients to consult with doctors remotely. According to Practo, five crore Indians accessed digital medical services from March 2020 and May 2020. The typical user contacts a medical practitioner online two times in one month, according to Practo's data, which led to a 67% reduction in in-person visits (8). General medicine, obstetrics, and dermatology make up three disciplines that account for 51% of all teleconsultations. 80% of telemedicine users are first-time users, while 44% of users are from non-metropolitan areas.

Leading healthcare organisations in India have been performing 200–500 teleconsultations every day during the COVID-19 pandemic, with a small number of well-known doctors providing 8–10 consultations each day.

Major teleconsultation platforms have seen a 500% increase in online consultations after COVID-19. Globally, teleconsultation use has been increasing, and this trend is anticipated to continue as technology develops and more people become accustomed to utilising telecommunications to obtain healthcare services. In India, the government's promotion of telemedicine and the growth of private teleconsultation platforms suggest that the use of teleconsultation will continue to grow in the coming years.

2.4.1 Advantages of Teleconsultation:

Every patient finds visiting a hospital or doctor's office uncomfortable. By preserving convenience and dedication, this method fosters dialogue between patients and healthcare personnel. Also, by using telemedicine, medical data and photos may be securely and privately sent from one location to another. People may thus have faith in this system and feel at ease asking for assistance from it.

Consistent medical treatment is inaccessible in many rural areas, distant locations, and post-disaster settings. To deliver emergency treatment in such locations or circumstances, telemedicine can be used. With the use of computer, tablet, or phone technologies, telemedicine has made patient monitoring easier and has therefore cut down on outpatient visits.

Doctors are now able to check prescriptions or manage medication supervision. The homebound patients can also call an ambulance to get medical attention without going to the clinic. As a result, health care expenses have decreased.

Telemedicine prevents the spread of infectious illnesses between patients and medical workers, saving lives in emergency circumstances when there isn't enough time to get the patient to a hospital.

2.4.2 Disadvantages of Teleconsultation:

If a service is provided by an unskilled professional, virtual clinical therapy reduces personal connection between healthcare workers and patients and raises the chance of clinical errors. Additionally, a malfunctioning technological system might allow the leakage of private medical data.

Due to server issues or slow internet speeds, virtual communication in telemedicine may take longer than expected. Moreover, this system is unable to deliver rapid care, which including antibiotics. To avoid unauthorized and unlawful service providers in this industry, telemedicine systems need strict legal regulations. Moreover, low-quality health informatics data, such as X-ray or other pictures, clinical progress reports, etc., run the risk of inaccurate clinical treatment.

2.5 Conclusion:

Teleconsultation and E-pharmacies have nevertheless number of difficulties, including as opposition from conventional brick-and-mortar pharmacies, regulatory obstacles, internet issues, server problems and worries about the safety and veracity of drugs purchased online. Yet, the industry is prepared for continuing expansion and transformation in the upcoming years with the backing of the government, investors, and consumers. In general, e-pharmacies and teleconsultation have advanced significantly from their beginnings and it has come a long way. In the future, we may anticipate more people using teleconsultations and online pharmacies than traditional doctors, and this trend will continue to expand as new technologies develop.

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ISBN: 978-81-19149-00-1

3. Clinical Services, Reviewing Medications for Safety and Efficacy, and Providing Drug Information

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Abstract:

The main objective of health services is to provide safe, high-quality medical treatment. Medication error can arise during any stage of the pharmaceutical process, including storing, prescription, transcription, production, distribution, administration, and tracking. Each of these medicine system elements, with their numerous parts, is prone to failure, directly affecting patients. The clinical pharmacist's role includes managing pharmaceutical care, so the pharmacist is capable and willing to influence medication safety at the specific patient level. The pharmacist is uniquely positioned to evaluate the effectiveness of medication processes and to undertake redesign initiatives to reduce potentially harmful drug-related consequences. Here, it explains the methods for ensuring the safety of medications and offers a framework for establishing a foundation for medication safety programmes inside healthcare facilities. One of the basic professional obligations of all pharmacists is to provide drug information (DI). To raise the standard of patient care, increase patient treatment results, and secure the responsible use of resources, suggestions for particular medication-use practices should be carefully considered and supported by data. Here, the particular function of pharmacists and clinical pharmacy services in ensuring the safety of medications is addressed.

Keywords:

Drug safety, ADR-adverse drug reaction, DI-Drug Information, CP-Clinical Pharmacist, Medication Review, High-risk medications, OTC medications- non-prescription drugs,

emergency medications, Antimicrobial stewardship program, ADR reporting, TDM-therapeutic drug monitoring.

3.1 Clinical Service:

Clinical pharmacy includes a number of activities that support the secure, efficient, and cost-effective use of medications for specific individuals. A number of services that have been demonstrated to lower hospital readmission rates and improve patient care and treatment can be provided by the pharmacist involvement on both inpatient and outpatient teams [1].

A. These includes:

- Access to medications
- Assuring drug availability,
- providing medication information, and determining whether a prescription is suitable
- Increasing drug compliance promoting health and wellbeing services;
- providing drug administration services
- Medication dosage titration and adjustment,
- Medication reconciliation
- Patient Education
- Medication Chart Review
- Development of disease management pathways
- Patient monitoring
- Promotion of medication adherence, and post discharge follow-up [2] etc.

B. Community Pharmacist services includes:

- Dispensing of medications,
- Self-care assistance
- Drug use evaluation
- Distribution of patient information leaflets,
- Smoking/alcohol cessation programmes ensure rational drug use,
- Promotion of healthy lifestyles
- Psychosocial support,
- Promote health status by working as part of a multidisciplinary team of healthcare professionals [2].

3.2 Clinical Pharmacist's Services Include:

- Clinical pharmacists are in charge of conducting a patient interview. that covers the patient's social and family history, medical and medication history, and history of allergies.
- **Medication History Interview:** To assess the patient's understanding of medications, indications of drug abuse, approval of treatment, and recording of allergies and adverse

drug reactions, as well as the use of OTC medications, nutritional supplements, and alternative medicine. A thorough medication history of the subject is necessary.

- Reviewing medications for safety and efficacy
- Providing Drug and Poison Information
- Patient Satisfaction Survey and Audit
- Preparation of Hospital Formulary
- Preparation of Patient Information leaflets for various diseases like Diabetes Mellitus, Hypertension
- Adverse Drug Reaction identification and reporting
- Ensuring patient medication adherence
- **Patient Counselling:** clinical pharmacist may provide details on the patient's current clinical state or progress and instruct him/her on how to use medications safely and effectively, which will enhance the benefit and efficacy of his/her therapy which leads to improved quality of life. The clinical pharmacist has an essential role in managing and educating patients about asthma, spirometry management, and proper inhaler utilization as well 11.

3.3 Reviewing Medications for Safety and Efficacy:

Clinical pharmacy services are aimed at specific patients rather than the system as a whole, and are crucial safety measures of current and future individualized patient care, particularly in high risk patients and groups 3. Clinical pharmacists take an active role in hospital visits with physicians and provide advice or recommendations as necessary. To ensure that the medicines are being used correctly, pharmacies double check the prescription that doctors write.

They check to see if the medication has an indication, if it is the right medication, quantity, length, dosage, time, etc. If there is a deviation from these, they take the required steps, notify the doctor, and record their actions. The fact that every doctor agreed with the outcomes of the intervention shows that the pharmacist's involvement in the research had a verified effect on therapy.

Clinical pharmacists can share their expertise with patients in the areas of medication evaluation, treatment suggestions for drug-related issues, and motivation to take medications as prescribed. Among other things, they collect medical and medication related data, look for medication errors like prescription, dispensing, and administering errors, find drug interactions, monitor adverse drug reactions (ADR), suggest recommend specific dosage regimens, and provide patient counselling. The primary criteria in the medicine safety are prevention decrease in the number of interactions and adverse drug reactions (ADRs)1.

To guarantee the safety and effectiveness of the medicine, they also provide guidance on how to use, eye drops inhalers, insulin pens, nasal sprays, and other healthcare products. The involvement of a clinical pharmacist in ward/ICU visits helps to create treatments that are affordable, that are cost effective treatment for the patients. Clinical pharmacists also perform dosage estimations, emergency formulations, and drug dilutions. They can take part in clinical studies in addition to building databases for every medication.

Clinical pharmacy services collaborate to enhance the pharmacological aspects of patient care by establishing and maintaining a medical practice with a patient care service with the help of medical and nursing personnel2.This enables the development of a schedule that maximizes curative impact while minimizing toxicity, as well as the best selection of pharmacologic agents.

3.4 Role and Responsibilities of Clinical Pharmacist On Drug Therapy Review:

Clinical pharmacists conduct drug therapy reviews to identify and address medication-related issues such as drug-drug and drug-food interactions, drug duplication, improper dosage (frequency, strength), possible complications, absence of necessary lab monitoring requirements, potential adverse drug reactions (ADRs), irrational drug selection, and medication therapy. Actions involving the identification, evaluation, comprehension, and avoidance of side effects or other medication-related issues are given significant consideration for patient safety.

It is recorded and assessed when adverse drug reactions occur[2]. Clinical pharmacists are responsible for making sure that the delivery, stabilization, storing, compatibility, and refilling of medications are done properly. When required, they make it easier to switch from parenteral to oral dosage types. Another crucial duty is providing warning notes to patients who have ADR or who are taking medicines that require additional attention or notice (epilepsy, cardiac problems, drug allergies, or using warfarin, aspirin, insulin etc.).

3.5 Role of Clinical Pharmacist in an Endocrinology:

The clinical pharmacist in an endocrinology section focusing mainly on hyperthyroidism and adrenal incidentalomas and also gave recommendations on how to use insulin pens appropriately, give insulin shots, follow dietary limits, alter lifestyle habits, and the value of routine check-ups, among other things[1.] The effectiveness of clinical pharmacist instruction workshops and patient care services (pill boxes, diary records, and follow-up calls) has been demonstrated in significantly reducing mean FBS and HbA1c[3].

3.6 Role of Clinical Pharmacist in Neonatal and Paediatric Department:

Due to their undeveloped pharmacokinetics and pharmacodynamics alterations, children are the most vulnerable segment of the population and most likely to experience drug-related issues When a medication error occurs, paediatric patients are at a far greater risk of dying than adults are[11].Clinical pharmacists give assistance with dosage form adjustment, and dose measurement in the neonatology and paediatric departments[1].

A clinical pharmacist can reduce medication errors in a variety of ways, including by reviewing physician prescription orders and, if needed, recommending an alternative order, estimating doses based on weight, age, surface area, renal impairment, and hepatic impairment, reviewing daily process reports, identifying administration errors, and verifying medications as patients are discharged from the hospital and changing the route of medications to ensure patient adherence[11].

3.7 Role and Responsibilities of Clinical Pharmacist in The Management of High-Risk Patients.

High risk patients include who are in older age, comorbidities, renal failure patients, and people taking high-risk medicines etc. Cardiovascular medicines, anticoagulants, non-steroidal anti-inflammatory drugs, hypoglycemic, and antibiotics are among the high-risk medicines[12]. Clinical Pharmacist (CP) can identify high-risk patients as well as possible adverse effects and drug drug interactions. In the case of stroke, CP may suspect bleeding so they keep track of patients taking warfarin's INR range after consulting with a doctor, and they make suitable suggestions for changing the warfarin dosage [1]. Pharmacists in clinical settings should concentrate on adjusting drug dosages for patients with renal failure. Increased morbidity and death as well as higher care costs will occur if the dosage is not changed. It is strongly advised in these circumstances to estimate creatinine clearance previous to placing a drug purchase and to use a trust worthy dosage guidance. thus guaranteeing the safety of individuals with renal failure.

3.8 Clinical Pharmacist's Contributions in Antimicrobial Stewardship Program:

Stewardship programmes can help decrease over-prescription and broad-spectrum use of antibiotics, enhance population-wide therapeutic results, delay the development of antibiotic resistance, and save money on medical expenses [13]. Participation of pharmacists in stewardship initiatives has been shown to enhance therapeutic results, lower adverse events, and decrease antimicrobial/antibiotic resistance [6].

3.9 Role of Clinical Pharmacist in Therapeutic Drug Monitoring:

A division of clinical pharmacology and clinical pharmacy known as therapeutic drug monitoring service is dedicated to measuring drug amounts in patients' blood, such as serum, plasma, and sputum. The primary objective is to optimize the dose schedule in order to keep blood drug concentrations within a therapeutic range or window, which can deliver sufficient and safe drug treatment. The term "therapeutic range" has traditionally been used to refer to the range of dosages that result in a therapeutic reaction without having any negative side effects. The therapeutic window is a ratio that combines maximal beneficial quantities with minimal toxic concentrations. As concentrations above reference values are typically linked to an increase in side effects, while concentrations below reference values would result in ineffectiveness or an unsatisfactory response. The main goal of clinical pharmacist is to maintain plasma drug concentrations within a predetermined range to optimize treatment outcomes [14].

3.10 Role and Responsibilities of Clinical Pharmacist in an Emergency Department:

The role of the pharmacist in the emergency unit is unquestionably crucial for patient safety and medication effectiveness. Analgesia and sedation, anticoagulation, cardiovascular crises, emergency preparation, endocrine emergencies, infectious illnesses, neurology, respiratory care, shock, drug misuse, toxicology, and trauma are among the conditions that

call for emergency medicines and treatments 9. The emergency pharmacist program's main objectives are to reduce expenses and the likelihood of adverse consequences. To enhance drug safety and give staff pharmaceutical knowledge, the creative emergency pharmacist programme collaborates with the diverse staff in an Emergency Department.

Examples:

- Intranasal analgesia is used in the emergency room to treat severe pain.
- Antithrombotic treatment is used to treat VTE illness.
- Thrombolytic therapy is used to treat lung emboli.
- Adult patients with supraventricular tachycardia are managed.
- Vancomycin and beta-lactam correlation with nephrotoxicity;
- dosage of trimethoprim-sulfamethoxazole to treat methicillin-resistant epidermis and skin structure infections etc[9.]

3.11 ADR Reporting:

An adverse drug reaction (ADR) is defined as "a unpleasant and unexpected reaction that develops at doses administered to a patient for prevention, diagnostic, or treatment" [11]. Prompt **ADR reporting** is crucial in ensuring drug safety by the pharmacist[4.]

A. Event to Be Reported Are:

Reporting serious adverse drug reactions:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Reporting non-serious, known or unknown, frequent or rare adverse drug reactions due to Medicines, Vaccines and Herbal products.

B. Where to report:

A properly completed Potential Adverse Drug Reaction Notification Form will be sent to the National Coordination Center (**NCC**) or the nearby Adverse Drug Reaction Monitoring Center (**AMC**) [7.]

Pharmacists are essential in both hospital and outpatient care environments because they are specialists in drugs and protectors of the safe and efficient use of medications. To accomplish the greatest standards of medication safety, they strive not just to detect, record, and monitor adverse drug reactions (ADRs), but also to avoid future ADRs from occurring and to optimize pharmacotherapy [4].

3.12 Providing Drug Information:

Pharmacists are expected to offer accurate, unbiased information on all aspects of medication use, including medication strength, drug formulation availability, brand, and cost. For example, in people with compromised renal or hepatic function, they offer guidance on how to choose the dose of medications empirically. Since they have a better understand of the drugs, CP can easily identify and warn patients about lookalike and sound alike medicines. They may participate in programmes for patient instruction, medical camps, pharmaceutical development, and therapeutic drug management[1]. While employed in the paediatric section, they advise parents on medication and immunizations. The medicine profile, indication, and dosage, adverse drug events, patient care, drug interactions, drug use during pregnancy and lactation, poisons, and information on drug preservation are just a few of the inquiries that a clinical pharmacist may be able to respond to[1.]

The following factors of medications may be discussed with the patient by the pharmacists in their guidance or instruction.

- The drug's brand and generic designations;
- The dose and dosage of respective medications
- The drug's advantages and indications, and also anticipated action
- crucial to store medications properly.
- How should you take medication?
- When should you consume your medicine, and for how long?
- Information on a medicine that has been withdrawn from the market or a new prescription.
- Measures to be observed when using the drug
- Serious drug reactions and common occurrence.
- What should you do if a dose is missed?
- Avoiding specific medications and/or foods.

Patient counselling has a number of advantages, including improved therapeutic outcomes, a decline in medication errors, and an increase in patient satisfaction. Instructing patients is crucial when managing chronic illnesses. Patient education regarding medication is crucial for some diseases, such as epilepsy, diabetes, hypertension, dyslipidemia etc. (1).

3.13 Providing Information on High-Alert Medications:

Medication that has a high chance of harming patients if administered incorrectly is commonly referred to as a high-alert drug. As a result, the safety administration relies heavily on giving information to both patients and medical personnel[3].

Pharmacist goal is to Identifying high-risk and problem-prone medications, standardize high-alert drug handling procedures and improve medication education programmes by including them in the yearly core skills of all staff members who handle high-alert medications[15].

A. A few instances of high-alert medications:

- Chemotherapy
- Opioids
- Anticoagulants
- Neuromuscular blocking agents
- Insulins
- Concentrated electrolytes

3.14 Conclusion:

The minimal standard by which a pharmacist examines each and every prescription for a patient's medicine is to ensure that the right dosage of the right drug is delivered to the patient at the right time by the appropriate route[10].

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ISBN: 978-81-19149-00-1

4. Pharmacy's Role in Modern Health Continuum

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Abstract:

The term "continuum of care" is now used in the healthcare sector to describe how medical professionals follow a patient from preventative care through medical emergencies, rehabilitation, and maintenance, which includes acute care hospitals, ambulatory care, or long-term care institutions, depending on the patient. It is vital for patients and carers alike because it increases patient satisfaction, lowers costs, and promotes better health.

In the healthcare continuum, Pharmacist plays vital role through various services such as modifying of prescription, extending the prescription, technical service, planning of treatment, efficacy monitoring, education and counselling, collaborative care etc. In modern days, technology plays major role, as it eases the process by maintaining electronic health records, health analytics, internet-based devices, cloud database etc. along with it has various drawbacks such as data theft, authority of data, how it's used and how it is used by other professionals.

4.1 Introduction:

The term "continuum of care" is now used in the healthcare sector to describe how medical professionals follow a patient from preventative care through medical emergencies, rehabilitation, and maintenance. It may involve using acute care hospitals, ambulatory care, or long-term care institutions, depending on the patient. Better outcomes for the patient are a result of the integrated approach to medical care. The phrase "continuum of care" is neither a novel concept, nor does it necessarily refer to medical care. Usually, it is referred as solutions to homelessness. The phrase continuum of care has been used to describe a range of services for expectant mothers, including prenatal care, birthing, and parenting. [1]

The treatment continuum is vital for patients and carers alike because it increases patient satisfaction, lowers costs, and promotes better health. This is particularly important for patients who are more dependent on medical services, such as the elderly, those with severe medical illnesses, those who are mentally ill, and those who have chronic diseases. Coordination, cooperation, and information sharing between different healthcare providers in various clinics, between the HMO and the hospital, between wards and facilities inside the hospital, and in the transition from hospitalisation to discharge and vice versa, are all examples of continuum of care in the transition from one unit to another.[2] The primary care workforce is made up of a varied group of medical specialists, including allopathic and osteopathic doctors, nurse practitioners, physician assistants, and registered nurses providing direct patient care.

In the delivery of patient care services within the primary care setting, pharmacists are one of the health professionals with expanding responsibility. The most important contribution pharmacists may make in primary care to improve patient outcomes is by providing pharmacological care. Managing drug treatment and coordinating the "continuum of drug therapy" were all part of providing pharmaceutical care, which required pharmacists to form a relationship with patients and be accountable for drug therapy results with other healthcare providers. [3]

Every person who takes medication stands the possibility of experiencing actual or potential drug therapy issues. When these issues go unnoticed and untreated, they significantly increase the risk of morbidity and mortality and place a considerable financial burden on the health care system. As experts in drug therapy, pharmacists offer drug therapy management services that are based on collaboration with the patient (or his or her caretaker), doctors, and other healthcare professionals. These services are designed to help patients identify and address current or future drug therapy issues, encourage safe and effective medication usage, and make it possible for patients to have successful, focused therapy outcomes. [6]

4.2 Role of Pharmacy:

Having obtained the necessary training in medicine, a pharmacist manages a pharmacy and may assist the patient with minor disorders and ensure they receive the finest treatment. A licenced pharmacy's primary duty is to lower health care costs by preventing medical errors and lowering the likelihood of morbidity.

A. Prescription Support:

- Pharmacist assist in maintaining the continuum by modifying prescriptions and providing alternate medications.
- They dispense the appropriate medications and responds to your inquiries concerning the prescriptions.

B. Extension of Prescription: Pharmacist helps in therapy continuum by extending the prescription for a period, when prescription is about to expire and appointment is further away.

C. Technical Help: Pharmacist provide education regarding the use of various medicines, medical devices, etc. which help them keep track of the condition and continuum of the treatment. [4]

D. Auditing of Prescription: They are crucial in assisting in the prevention of prescription errors and the identification of drug interactions. Thus, helps in better adherence and continuum of therapy. [5]

E. Care Plans: In collaboration with the patient and other members of the healthcare team as needed, the pharmacist develops a plan that outlines objectives and steps that will be taken in order to meet the patient's individual health goals through the most effective use of medication.

F. Monitoring Compliance and Evaluating Effectiveness: Regular follow-ups by the pharmacist allow for the evaluation of the patient's compliance with and reaction to drug therapy, as well as the early identification of any negative effects or drug misuse or abuse. [6]

G. Pharmacist Provided Medication Management: It has been demonstrated that medication management by pharmacists enhances patient outcomes for those with chronic conditions, including drug adherence.

H. Education and Behavioral Counselling: Other forms of pharmacist treatments that have been demonstrated to enhance outcomes may also include counselling from pharmacists as a significant component.

I. Collaborative Team-Based Care:

- Collaborative medication therapy management is one method for fostering collaborative care (CDTM).
- It has been demonstrated that collaborative team-based treatment with a pharmacist improves therapeutic outcomes, especially for chronic illnesses like diabetes. [7]

J. Digital Follow-Up: In this position, pharmacists can assist patients in selecting the best digital health product, set it up, and instruct them on its use, self-management, result interpretation, and data entry into electronic health records (EHRs). [8]

4.3 Different Entities in Healthcare Continuum:

The care continuum concept refers to the delivery of a wide variety of healthcare services by the healthcare system, including acute, ambulatory, extended, home, and even wellness care.

One major advantage is that it emphasizes preventative treatment and actively manages symptoms so that patients may stay out of pain and suffering, emergency situations, and unnecessary doctor appointments.

Setting up an efficient Care Continuum model for the patient is a challenging task. With the use of technology, this problem may be solved and a positive patient experience can be produced at a reasonable cost.

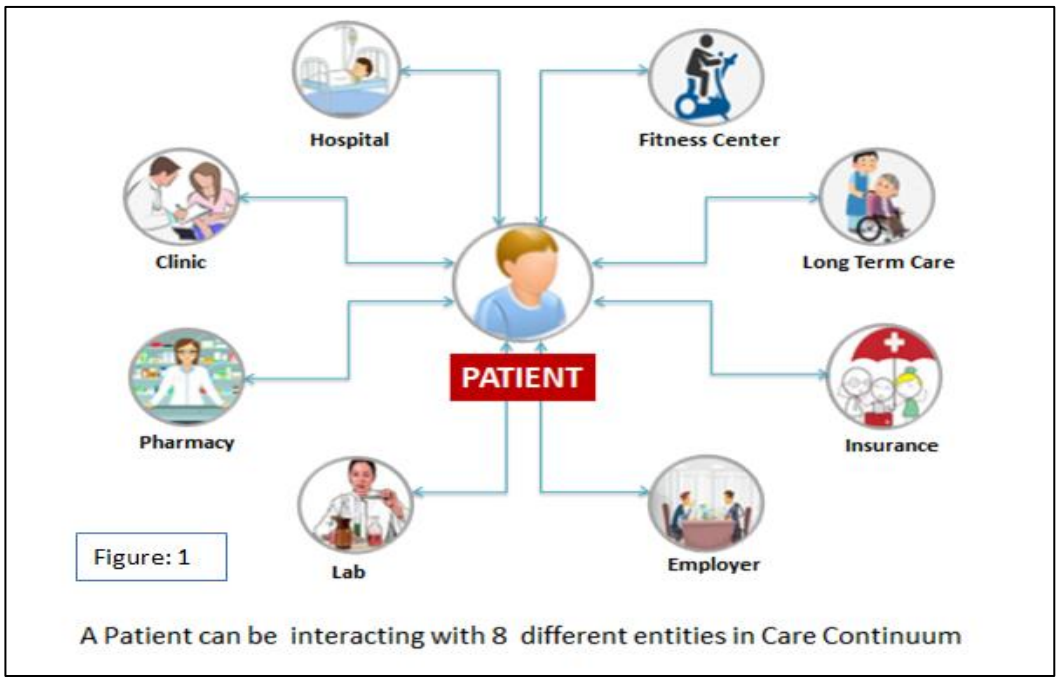

Figure 4.1: The Various Components of a Care Continuum Model. [9].

4.4 Technology in Healthcare Continuum:

Throughout the past two decades, the Care Continuum therapy has benefited from the use of numerous technologies to varying degrees. Nevertheless, by incorporating these technologies into a comprehensive approach to produce high-value results, Care Continuum may be made even more successful.

The following technologies would serve as the foundation for creating such a system:

- **Electronic Medical Record (EMR):** EMR is a digital platform where data and information about a patient's present and previous health condition are recorded, saved, and displayed in a single longitudinal perspective that is available to patients, payers, and decision-makers.
- **Healthcare Analytics:** Big Data analysis can be utilized to increase operational effectiveness, provide better patient care, and identify cures for diseases. Analytics may be used to improve the health of a person or a population.
- **Adoption of Cloud Infrastructure:** In order to reduce the cost of data storage and improve the ability to exchange healthcare data with departments and other entities, healthcare companies have switched from using data centers to cloud-based storage.

- **Internet of Things (IoT) based Healthcare Devices:** Real-time data accessibility and information exchange are being improved through connected gadgets.
- **Automated Healthcare Administration:** Hospital billing, financial applications, and inventory management, among other important administrative tasks in healthcare, have been automated. [9].

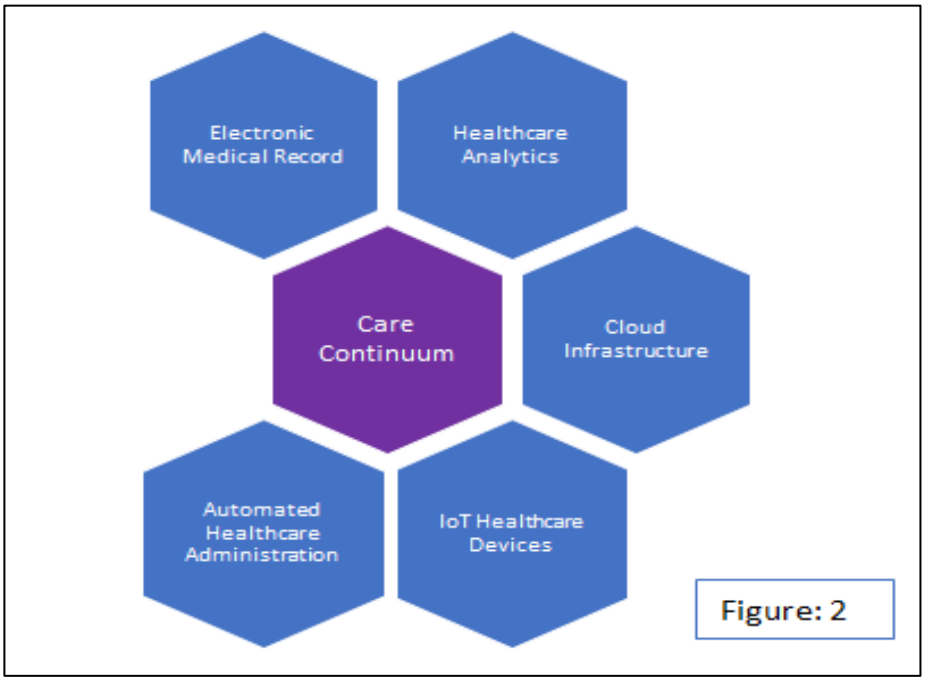

Figure 4.2: Some of The Technological Foundations for Creating Such a System [9]

4.5 Challenges & Risks of Technology Enabled Care Continuum:

- **The Weakest Connection:** Several parties are involved in the care continuum, from well-equipped hospitals to the neighborhood general practitioner office located in a market square. How can we standardize information security, dependability, and availability across all parties? The chain is only as strong as its weakest link.
- **Data Protection:** Healthcare providers' attention has been drawn by a number of high-profile data breaches. Institutions react by restricting access to medical data. So how do we communicate information along the treatment continuum?
- **Owning the data:** Who ultimately owns the data about your health? A hospital? Who is in charge? Yourself? Who then has the authority to share this information? Who has the authority to grant or deny access to your information to insurers, policymakers, and healthcare providers?
- **Data Reliability:** New information about your health may be created or recorded by anybody involved in the care continuum. How are the recordings authorized and verified? Block chain technology, for example, has the potential to help with some of these problems.

- **Clinical Processes:** Hospitals have a good understanding of and experience with implementing clinical workflows. How would the other participants in the care continuum "flow"? Who sets the requirements? [9].

4.6 Conclusion:

The majority of nations' current health care systems are not designed to maximize the actions of all health professionals and are becoming more expensive without corresponding improvements in quality or accessibility. We propose that government initiatives of person-centered care, continuing care, mental health, and chronic illness management will gain significantly more momentum if steps are taken to better incorporate pharmacists into the healthcare system. Through increasing opportunities to access the healthcare system through community-based pharmacists, expediting the creation of creative team-based care models, and improving the coordination of drug treatment management across the health system, improvements in access and quality will be made.

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ISBN: 978-81-19149-00-1

9. Evolution of Teleconsultation and E-Pharmacy

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Abstract:

Telemedicine is a communication methodology which connects physicians with patients and enables them to provide good health care and to exchange information related to health care. The past 35 to 40years have seen a fast progress in this field of telemedicine which previously used to use postal services and has now progressed to using high technology equipments. The technology of telemedicine includes or requires certain essential componenets for its smooth functioning like a trained and educated personnel who is dedicated, loyal and interested in the job, latest and advanced audio-visual technology at hand for the smooth functioning of the communication system. There are several barriers which also need to be overcome while conducting or organizing a session of Telemedicine. The entire process is expensive and session charges are exhorbitant because the dvanced technology needed to conduct the session is demanding. Also legal and ethical aspects need to be considered for conducing the telemedicine sessions. The privacy of the patients and confidentiality of the entire session is of atmost importance and needs to be taken care of. The applications of telemedicine are many so are its advanages however care should be tken to guard the legal and ethical issues involved in the same so that barriers can be oversome and the target of providing telemedicine to all can be met.

Keywords:

Real-time telemedicine, Store and carry forward telemedicine, training of personnel, barriers of telemedicine, legal aspects of telemedicine.

9.1 Introduction:

At the beginning of the 21st Century the biggest challenge the human kind faced was making the health care facilities available and accessible to all. The ever-growing world population, constant threat of resurrection of eradicated diseases, ever increasing newer diseases being discovered, fast happening socio economic changes prove to be hurdles in this pathway of making health care facilities reach all. Until now it was mandatory that the health care provider as well as the health care receiver both be present in the same place to avail the aforesaid facilities. However, with the fast advent of technology, rapid digitization improved financial condition, improved GDP of several developing countries and faster diffusing of sophisticated technological know-how amongst the commoners the vision of the World Health Organization (WHO) of Health for All soon seems to be coming into reality. The utilization of knowledge of telecommunications along with combined knowledge of health care is also the vision of governmental bodies of all countries.

Telemedicine has been defined as the use of information and communication technologies to monitor and treat patients in lieu of a physical in-patient visit. With the help of telemedicine, the delivery of good health care as well as the exchange of information about health care can be inter changed, geographical barriers which until now proved to be a hurdle can be overcome and along with the treatment of the disease, diagnosis and prevention of it, continuous education of health care providers, research and evaluation and care of customers/ patients can be ensured. With the help of telecare, we can arrange provision for distance public health care along with nursing and community support to individual patients.

Although the progress of the field of telemedicine looks to have happened steadily in past 30 to 35 years the history of the field is old with roots in the mid-19th century. It was during this period that the postal and telegraphic services began giving the facility to provide personal health care to far off distances patients from physicians who were experts in the diagnosis, and in providing cure of diseases. With the help of telegraphy which utilizes wires for passing off of signals medical care is being provided to the patients. During the period of American Civil War, the knowledge and facility of telegraphy and telemedicine was found to be useful for communicating casualty list, placing order for medical supplies and for seeking consultation in planning the provision of health care. Telephone superseded the use of telegraph for the communication in further times. There have been examples and evidences of using telephone for communications other than the routine voice communication. Transmitting amplified sound from the stethoscope, transmitting electrocardiograms (ECGs) and Electroencephalograms (EEGs) are some to name a few. At the same time the use of Radio for broadcasting medical advice and health care tips specially to soldiers at war and to seafarers began. The use of radio and radio signals was also made for in flight passengers especially on a long-distance air journey by communicating and seeking assistance from on call health experts on ground.

With ground-breaking efforts of telecommunication and computer engineers, investments made in high tech ventures and the modernization of digital communication techniques there has been remarkable progress and development in the field of telemedicine. Today telemedicine has provided us a sophisticated platform to hear the experiences, opinions, interests and perceptions of the experts in these field from all across the globe.

The advantages of telemedicine especially for the people in remote and rural areas have improved their access to modern sophisticated health services.

A. The Practice of Telemedicine Can Be Divided into Two Categories:

- **Real-time telemedicine**
- **Store and carry forward telemedicine**

Real-time telemedicine involves an interaction between two parties i.e. the one giving the consultation and the other seeking advice occurring synchronously. Real-time consultation can either be done telephonically or through video conferencing. This type of consultation requires investment in terms and software and hardware for the process and at the same time ensures winning of patient trust and patient satisfaction.

This however is an expensive and challenging method as it involves fixing of a specific time convenient for both the parties, not only that it could involve more than one medical expert one who is a remote physician and the other who is a local expert treating the patient.

On the other hand, store and forward is an asynchronous communication in which the medical query is conveyed to the expert by the referrer to which the expert responds at his convenient time. Such type of communication can be done as a follow up after real time medicine or in less severe cases. It proves to be economical, convenient but complex.

9.2 Essential Components of Telemedicine:

Appropriate equipment and a fool proof strong communication medium are the primary requirements of successful telemedicine.

9.2.1 The Three Main Essential Components Are:

A. The Personnel:

For the telemedicine to be successful individuals or people with appropriate skills and knowledge are required to be present during the sessions of telemedicine at both ends. These personnel should also be appropriately qualified. They should be able to handle the patient enquiry, make them feel comfortable with the process and they should prove to be a reliable link between the patient and the clinician providing the consultation.

At the end of the consulting side to the personnel present should be reliable and appropriate. The personnel also should be able to handle the equipment required for the telemedicine procedure carefully and confidently. The telemedicine system would fail to work if appropriate staff is unavailable or the link connecting the patient to the physician is not working. The personnel or concerned staff should also be capable to organize the schedule plan the appointments enable links for usage and be prepared for emergencies if any.

B. The Technology:

The technology involved and required during the execution of the session of telemedicine should function efficiently the entire integration of components involved in the telemedicine process should be closely monitored at the same time easy to use and maintain. The use of reliable fully functional well integrated system for communication and proper use of technology will ensure smooth functioning of the telemedicine link and there will be full usage of the equipment with proper and reliable results.

C. Liberal measure of Perseverance:

The personnel or individual involved in the process of telemedicine practice should be committed, dedicated, loyal with keen interest in the whole process of telemedicine. The quality of perseverance is essential for overcoming the inertia in the process and in demonstrating the usefulness of the process and its results. The entire success of this process is dependent on the quality and ability of the personnel to be persevering towards the process

and mentor the process and implement it successfully at the same time have the capability and competence to identify, overcome and deal with flaws and problems. Absence or lack of any one of the above can lead to the failure of this methodology.

For the telemedicine link to work successfully and efficiently we first need to decide the type of information that is going to be exchanged or transferred through the link, accordingly the network to be chosen for the exchange and the choice of equipment for the same can be chosen. We also need to decide on or have knowledge about the quantity of information that is going to get transferred through the link and choose accordingly.

9.3 Types of Information to Be Transmitted:

The data or information that is being generated or transferred depends on the type of clinical situation that is going to be discussed. Sometimes the discussion is over the hematological or biochemical reports received from the pathological laboratory, over the blood work done on the patient which needs to be evaluated and based on the same the line of treatment for the same needs to be decided by the physician. Other times if the session is being conducted by a psychiatrist at such times to analyze understand and evaluate the mental wellness of a patient they physician may insist on video teleconferencing so that along with audio the video facility with help the physician to understand the posture, gestures and other minute behavioral and physical changes in the patient due to psychological disturbances. However before setting up a link for telemedicine its need, requirement and use should be fully justified. The unit used to describe the transfer of medical information is Byte. Kbyte and Mbyte. Many a times when the information is bulky it could be compressed to make the file size lesser and then be decompressed at the receiver's end however this could prove to be unacceptable medico legally. Also, the time taken to transmit information from one point to another needs to be considered as it is a critical aspect of the procedure. Along with these points to be considered we also need to consider the cost involved in the process of obtaining and transferring data and too data in bulk quantity.

9.3.1 Information Capture:

The information obtained during the telemedicine session is in different forms like documents, videos, audio clips, still images and other electronic media records. The documents usually are in the form of record papers, biochemical and other test reports which can be scanned or nowadays the copy of the reports are also available digitally these digital copies or the scanned copies can be shared with the consulting physician for evaluation and opinion.

If time is at hand the hard copies of the reports could also be posted to the physician in advance and then the consulting link can be scheduled. This postal transmission of information proves to be effective and economical when the data to be communicated is large or in bulk. Soft copies or what are addressed as electronic media records are fast replacing the hard copies of reports and documents the main advantage they give is instant accessibility to the information and also the ease to convey the information to the concerned health staff for their medical opinion.

A. Still Images:

The still images could be of two types one of unspecified quality or the other type with a particular image quality which is as per the demand of a diagnostic concern. For certain diagnosis an image taken from a low-cost low-resolution camera is also acceptable as the requirement of clarity for diagnostic purposes is minimal whereas there could be such health conditions where the diagnosis is crucial high-resolution images with greater clarity and detailing are required.

Such type of imaging requires high resolution equipment which not only give high quality diagnostic images but also obviously are expensive and high maintenance. Such modern high resolution expensive machines have the facility to give digital outputs and transmit the image directly between transmission sites provided both the receiver and the sender are equipped with specialized equipment's to serve the purpose.

B. Audio: information transferred through voice to the physician over a telephone or radio was the simplest form of remote diagnosis. Along with telephone however we need to take into consideration that telephonic conversation process can involve issues like background noise, miscommunication and loss of quality of the voice or communication during the process. The audio output could also be connected to a PC where the audio portion can be saved for later to be reused.

C. Video: This form of communication for consultation could be in real time video for where the video images are transferred between the two sites i.e., between patient and doctor. In this also the quality of the video matters, higher the quality, higher the cost of transmission and higher the cost of equipment required to carry out the process. This however definitely is a straightforward solution to transmitting information from the patient to the doctor and back. Further development of technology in video conferencing like plug-in devices, delivery of videos on smaller screens, improvised audio quality has led to the success of this method of telecommunication.

9.4 Information Display:

The choice of method to display information entirely depends on the methodology implemented to originally capture the information. Audio information captured will be transmitted and displayed in form of sound whereas to display video information several options are available like on TV sets, PC monitors, high resolution screens.

9.5 Training:

Along with high quality machines and technology required for recording and displaying of audios and videos during the process of telecommunication the major prerequisite for the success of the methodology is the presence of trained staff for personnel. Personnel trained in telemedicine communication to handle the sophisticated equipment having capability to take care and operate these machines and handle the telemedicine programme is extremely essential for the success of the telemedicine programme plan.

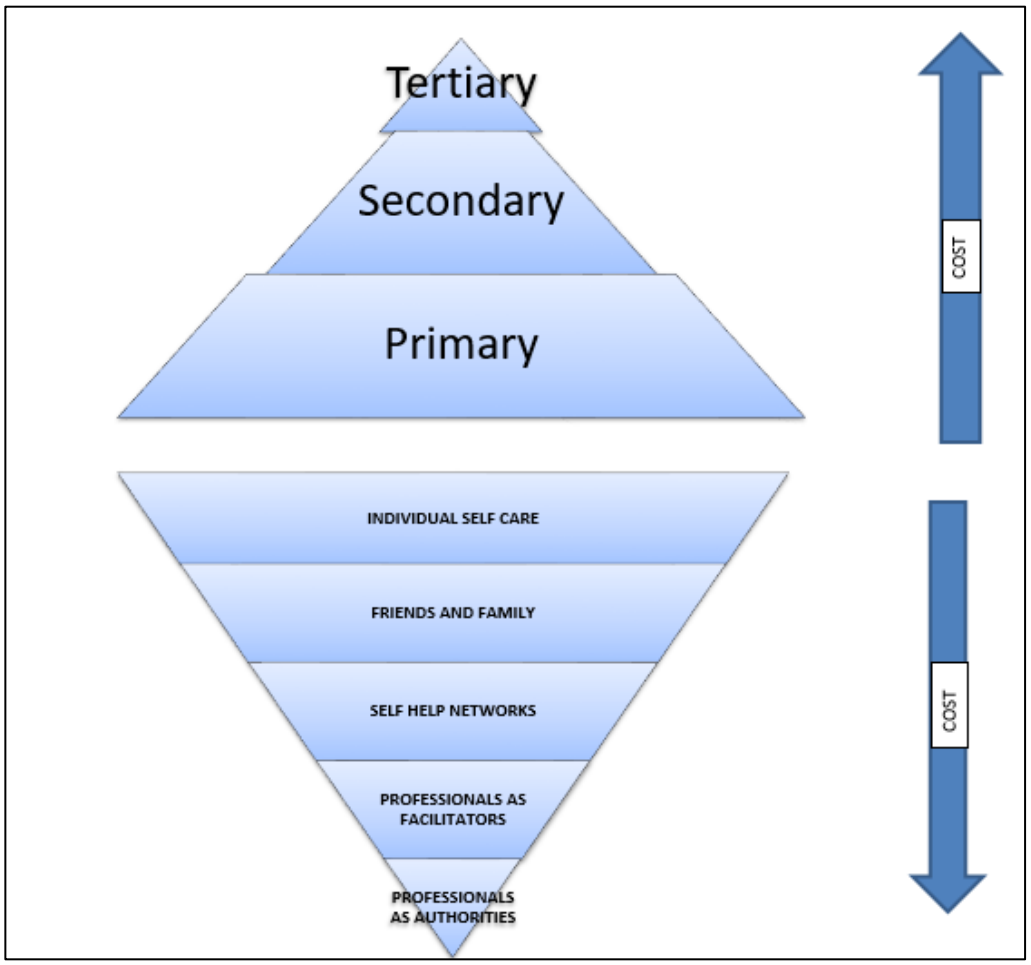

Figure 9.1: Pyramid Showcasing Transformation in Health Care Communication

9.6 Barriers to Telemedicine:

- The technique of telemedicine will fail if the clinicians and personnel involved in operation of the sites both receiving and sending the information do not show inclination in using the technology for the benefit of the patient. Non-supportive staff, who are not interested in learning and improvising new skills and do not have the potential to keep a fully functional telemedicine unit will become a barrier and reason for failure of the Telemedicine unit. Such personnel will prove to be deleterious, intrusive and useless. They may lead to mishaps, multiple technical breakdowns in the unit failing to offer support to the patients as well as spreading this tendency of disinterest, and non-enthusiasm amongst fellow clinicians. It would always be advisable to identify the interest of clinicians and turn them into telemedicine champions in that area of their interest.
- Like mentioned in the above point it is always useful and essential to identify the telemedicine champions, once identified the next step would be to provide vital significant information of key aspects on those particular topics to these telemedicine

champions and provide them support. By providing such necessary and required support to these personnel other personnel can also be influenced with their enthusiasm knowledge and excitement.

- The field of telemedicine being new and technically and clinically demanding the technology could prove to be frightening and apprehensive for new clinicians. Most of the clinicians working in telemedicine are fresh recruits who lack practical experience and expertise in clinical management. At this stage such naïve clinicians usually have special needs, nonspecific agendas who concentrate more on policy than on practice. Such a team would not have a good understanding towards the clinical world.
- The technology involved for the use of telemedicine is available in special rooms. If such special rooms are not easily accessible, inconvenient, difficult to reach it becomes difficult for these clinicians who are busy and occupied to be helpful in telemedicine as utilizing such inaccessible facilities is difficult and cumbersome.
- Training is a vital part of Telemedicine. Either separate sessions or meetings can be conducted for making the clinicians familiar to Telemedicine or the technicians and personnel involved in telemedicine should get trained in operating video conferencing and telemedicine machinery by constantly and continuously using these equipment study how they are operated, ensure they are non-threatening and do away with all the apprehensions and anxieties that could arise while operating this machinery. It is important that the clinicians accept telemedicine to be a part of their normal daily routine.
- It is very imperative that the concept of Telemedicine and their effectiveness with regard to making it a successful initiative be evaluated before it is implemented. It is important that before the concept of Telemedicine is applied, we assess that it will be able to achieve the required outcomes, in the pre-decided time period and that the program is sustainable, all the protocol during implementation is followed and that the program imparts or gives financial stability and takes care of the cost of the staff, equipment and technical support.
- It is advised that we learn from the existing several telemedicine units as it is a herculean task to establish such a service. Crossing several legal, cultural, ethical barriers, understanding in detail the sector of health-care telemedicine planning it establishment properly can help in reaping maximum benefits from this sector.

9.7 Legal and Ethical Aspects of Telemedicine:

The issues of concern regarding the legal and ethical aspects of telemedicine are confidentiality, privacy of patient records and jurisdictional issues especially when teleconsultation is happening in cross border centers. Another issue of concern with regards to telemedicine is reimbursement for care provided using a telemedicine service. When the centers involved in Telemedicine are in different states or nations medicolegal aspects of both the sides should be taken into consideration when framing policies and making rules and regulations. If all these factors are taken into consideration in a judicious manner the medico legal aspects can be kept to minimal making practicing hassle free for the practicing personnel. It goes without saying that the face-to-face consultation is the best way to provide genuine clinical care however we must not forget that telemedicine has made boundaries across state to disappear and facilitated the access to get the best consultation clinical care surpassing and overcoming all boundaries and geographical hindrances for making the best

medical facilities accessible and available to areas where it is difficult to reach, for patients who are fragile, have mobility issues providing best medical care at decreased cost. Recent pandemic like situation has proven to us that Telemedicine is now an indispensable part of heath care facility. The recent COVID-19 pandemic in fact has proven to us that telemedicine is a boon in disguise saving many lives during the pandemic, giving medical care while being successful in avoiding any physical contact and diminishing the chances of spread of virus any further. Also informed consent, patient privacy, protection of physicians laws and regulations all need to considered. The issue of informed consent requires to be abided by and taken into consideration. It is imperative that the patient be made aware of the facts, rules and regulations about what he/she is getting into, its advantages, disadvantages 'and consequences.

The patient should be made aware that through the use of Telemedicine efforts are being made to correspond with and provide health and social services to them. Patients who have no access to health care, patient with deformities and patients in remote areas should be made aware of the various advantages of implementing Telemedicine for the purpose of health consultation. However, one should always remember that the use of telemedicine procedure for consultation and evaluation purpose also involves the process and procedures of authorization, accreditation of information along with protecting legally the patient's personal data and critical aspects related to regulatory processes. With all this as a good practice and keeping in view that the procedure should happen hassle free with no qualms it is stressed that video consultation be preferred and such a video consultation be recorded and the patient be informed in prior about such procedure. Although the effectiveness of such video consultations may not be very promising and is in fact debatable he procedure however assures patient safety, satisfaction to both patient and healthcare providers along with quality service thus making the final adoption and implementation of the service in full capacity a little easier. In spite of all these facts however still telehealth stands out to be a supplementary method and a substitute for face-to-face methods of health care delivery. Several countries across globe practice the concept of Tele pharmacy wherein the pharmacist and the patient seeking advice or treatment are no in the same geographical place and through innovative technology services are provided. To govern and look into such facilities providing telemedicine or tele pharmacy these countries have a Code of Medical Ethics in Telemedicine Practice in place.

Although the service of telemedicine is being considered as indispensable it is intertwined in ethical and legal issues and also standard specific rules should and must be applied in order to ensure equitable access, quality of care, sustainable costs, professional liability, respect of patient privacy, data protection and confidentiality. Thus, ensuring that though telemedicine services have wide applications they should act as complementary or supplementary services to the traditional healthcare services and not as a complete substitute to health professionals. In fact, we cannot out do or deny the fundamental role of these health professionals in providing therapeutic opinion and care.

9.8 Applications:

The most important application of telemedicine is to help or facilitate monitoring of patients suffering from chronic illnesses conveniently and effectively in reasonable expenditure. This facility can help in recording and storing this data of patients who require monitoring

for their vitals like blood pressure, glucose levels, and heart rate. This kind of access will be immensely helpful for doctors to manage their patient's health and take immediate action in case of any health emergency.

The use of technology and telemedicine helps and aids to do follow-up with patients especially residing in remote areas, for aged bed ridden patients whose mobility is a matter of concern telemedicine aids in providing telecare. The use of telemedicine decreases the chances of last- minute cancellations and no shows thus avoiding the chances of missing follow ups at the same time increasing profitability in practice. With the aid of telemedicine, the concerned physician or his staff is able to check on with the patient, enquire on the patients' health, follow up if drug regimen is being perfectly followed, prescriptions renewal can happen on time and this overall avoids the chances of skipping medication and putting health at risk. With the facility of telemedicine, the clinician or physician gets the flexibility of working hours travel expenses for both patient and physician are decreased. Thus, Telemedicine not only bring doctors closer to their patients but also increase the possibilities of improving patient care vastly.

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ISBN: 978-81-19149-00-1

8. Role of Pharmacist in Reducing the Health Care Cost

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Abstract:

The health care cost is escalating at an incredible rate worldwide. The amount of money spent on medications and resolving the medication related issues keep increasing. A big concern in healthcare systems is the high occurrence of pharmaceutical errors and incorrect prescribing, which sometimes lead to adverse medical complications, many of which are avoidable. As a result, pharmacists have huge opportunity to reduce health care costs dramatically due to their expertise in identifying, resolving and preventing drug inaccuracies and other difficulties.

Now days there are more pharmacists working in clinically advanced jobs than ever before hence there is a lot clinical pharmacy practice growth in recent decades. The majority of published research demonstrates that pharmacist provided services and clinical interventions to improve patient outcomes, lower the risk of potential adverse medication events, and are cost-effective or have favorable cost benefit ratio.

In a variety of contexts, pharmacists can help to save a lot of money on healthcare. There is, however, a dearth of evidence in the literature showing the precise elements of a pharmacist's job that are the most efficient and profitable. Future high-quality economic evaluations that employ sound techniques and study designs will be necessary to determine which pharmacy services offer patients the greatest therapeutic benefits and the biggest financial savings for healthcare budgets.

Keywords:

Pharmacoeconomics, Pharmaceutical care, Clinical Pharmacy, Cost effectiveness, Economic evaluation.

8.1 Escalating Price of Healthcare: [1-10]

The age of the global population, technological advancements, the prevalence of pharmaceutical errors and rising annual spending on medications have all contributed to rising healthcare expenses. Health care organizations are confronted by the rising prevalence of chronic diseases and poly pharmacy among older persons as the world's population ages. The pressure on healthcare institutions to find and execute cost-control strategies has increased due to the rise in the number of medications that older people are taking and the rising cost of newer pharmacotherapies.

By carefully examining the pharmacotherapy of older patients with many medical conditions, pharmacists play a significant part in reducing expenses. The decrease in incorrect prescriptions for drugs results in cost savings for each individual drug as well as a decreased risk of adverse drug events (ADEs), which frequently lengthen and cost-prohibitive hospital stays. Despite the capital invested in their provision, health care services must prove that they continue to be cost effective in tight financial situations.

8.3 Cost Avoidance, Cost Reduction and Pharmacoeconomics: [3,11-12]

The continued high cost of medications highlights the pharmacoeconomic evaluation studies' growing significance. These studies give us the ability to pin point, quality and contrast the price of various pharmacotherapies or services and the impact they will have on patient health and health care spending.

Pharmacist can have a significant impact on health care decision makers in this area by helping to better allocate resources and funds in order to maximise population health through the use of medications. Pharmacists are the key players in reducing healthcare spending through cost avoidance and medication cost savings due to them in depth knowledge of medications.

Cost savings refer to decreases in current spending brought on by adjustments to the cost of patient's care, such as when it is appropriate transitioning from intravenous to oral therapy. Cost avoidance, on the other hand, refers to an intervention that lowers prospective future spending that may have happened in the absence of the intervention.

8.4 Medication Errors, Inappropriate Prescribing and Ades: []13-15]

It is noted that the medication errors and inappropriate prescribing are significant issues for the healthcare systems, both financially and clinically. They can significantly affect patient morbidity and mortality and can contribute to adverse drug reactions and events, particularly in elderly patients. ADEs may lead to higher health care expenses by lengthening hospital stays and increasing health care consumption. By minimizing hospital admission or shortening hospital stays, pharmacists have shown to have a positive impact on preventing drug mistakes and restricting improper prescribing.

8.5 Role of Pharmacist in Reducing Cost in Following Health Care Systems:

A. Community Pharmacists: [10,16]

One of the most accessible healthcare practitioners, community pharmacists are in a unique position to offer their community a primary health care service that is patient focused. The majority of primary care physicians lack the time necessary to deliver all of the preventive and chronic disease services that patients need; in these cases, other members of the multidisciplinary team can fill in the gaps. Many of these gaps can be filled by the pharmacists, who have greater time and the necessary skills to deliver high quality patient centered health care.

B. Chronic Disease Management: [17-21]

Chronic diseases are the leading cause of death and disability worldwide, and their management accounts for more than two thirds of global healthcare expenditure. Pharmacist has the potential to manage chronic illness more effectively while reducing healthcare expenditures significantly. Community pharmacists serve as the primary healthcare providers for this patient population. They are specially trained to lessen the severity of disease, to monitor medication therapy to achieve desired clinical effects, to decrease adverse health events, and, when necessary, to recommend pharmacotherapy to patients or prescribers. The growing involvement of pharmacists in chronic disease management is in line with the high level of education and training required for the job. Community pharmacists are in a perfect position to conduct health exams for illness prevention and progression as well as to help with new disease diagnosis. Participation of community pharmacists in the management of chronic diseases has been shown to have both clinical and financial advantages. Community pharmacists are expected to play bigger roles in managing chronic diseases and contribute to significant healthcare cost savings.

C. Adherence: [22-23]

Medication adherence may be defined as "the extent to which patients take medications as prescribed by their healthcare providers. The degree to which people take their prescribed drugs as directed by their medical professionals is referred to as medication adherence. Potential disease progression, pharmacotherapeutic failure, and hospitalization are all linked to nonadherence. Community pharmacists are uniquely positioned to identify patients who may not be taking their medications as prescribed, the causes of this, and can intervene at the point of medication supply by offering education and counselling where necessary. As a result, community pharmacists can significantly affect patient adherence.

D. Medicines Use Review: [24]

The use of medications by patients should be examined whether it is acceptable before adherence is promoted, it is crucial to emphasize. Adherence may have negative effects, especially in the case of older individuals who may be taking many medications. The purpose of medicine use review (MUR), which takes place in private between a patient and a pharmacist, is to increase the patients understanding, adherence and use of medications. A pharmacist has the chance to access a patient's pharmacotherapy during MUR's including both prescribed and over the counter medications. Pharmacists are able to spot potentially improper medications that a patient may not be taking, reducing waste and improving treatment.

E. Selection of OTC Items: [25-26]

The number of medicines available without a prescription is growing rapidly. Pharmacists play an important role in safeguarding their patients, especially the elderly, from potentially inappropriate use of OTC medicines. Pharmacists frequently offer guidance or non-pharmacological methods as first line treatments, preventing needless purchase of an OTC product. If an OTC product is necessary, pharmacists assist their patients in selecting a

suitable and safe solution based on their unique needs. In order to save money for the patient and the healthcare system, pharmacists advise choosing generic medications rather than expensive branded ones. ADRs and hospital admissions have been linked to self-medication using OTC medications. Patients can reduce their continued use of healthcare by avoiding unnecessary or potentially harmful over-the counter medications with the help of a community pharmacist's recommendations and advice.

F. Management of Minor Ailments: [27-28]

Community pharmacist can have a significant impact on the clinical and financial burden of minor illness visits on other, more expensive parts of the health care system. Pharmacists, who regularly treat ailments including the common cold, the flu, hay fever, a nd different aches and pains, have received specialised training in handling these self-limiting diseases. The financial advantages of minor illness programs are evident. It is a waste of time and resources for patients to visit more expensive healthcare facilities for minor ailments that may be treated in a neighborhood pharmacy.

G. Other Services Available in Community Pharmacies: [29-30]

Both the public and government funded healthcare systems will experience significant cost savings as a result of the delivery of new services through neighborhood pharmacies. The need for patients to seek out more expensive sectors of the healthcare system can be decreased by increasing the amount of medications and services that community pharmacists are able to offer. When compared to physician administered vaccination services, pharmacy provided vaccination services have broadened the range of practice of pharmacist and appear to be a less expensive alternative.

H. Hospital Pharmacists: [31-34]

One of the most important members of the multidisciplinary team actively involved in patient centered care is hospital pharmacist. Pharmacist managed pharmaceutical therapy has been linked to decreased medication mistakes, adverse drug reactions and mortality when provided as a core clinical service. Hospital pharmacist is performing sophisticated clinical work in a variety of specialized roles in many developed nations and there is a rise in the number of independent and supplemental pharmacist prescribers. Specializing enables the pharmacist to provide patients with improved care or care for a chosen set of patients, which may prove advantageous in lowering costs for health care providers.

Pharmacist interventions, which have been defined as “any activity by a clinical pharmacist that directly results in a change in patient management or therapy”, are a circular part of a hospital pharmacist’s responsibility in reducing medication related problems. Regarding the cost- effectiveness of pharmacist treatments and related indicators, such as health outcomes and quality of life, the evidence from the literature is extremely conflicting. It is challenging to determine which pharmacist treatments were the most cost effective, despite the fact that numerous studies have demonstrated that pharmacist interventions had a favorable influence on hospital budgets. Cost saving measures may involve stopping unneeded medications, switching to less expensive medications or changing the delivery route.

I. Medicines Reconciliation and Transitions of Care: [35-38]

Pharmacy professionals are able to get the most accurate and detailed drug histories compared to other healthcare professionals. In comparison to alternative reconciliation process, pharmacist led reconciliation has been found to have the largest predicted cost advantages. As a patient's care transitions, where there is a higher risk of medication error are managed, hospital pharmacists are given the chance to play more protective roles. According to a cost-effectiveness analysis, pharmacists discharge counselling resulted in cost savings. Pharmacy discharge counselling was cost effective in some scenarios, according to a cost effectiveness review, although all scenarios had low willingness to pay values. Those who were aged and are at high risk seemed to gain the most from this programme.

J. Inpatient Medication Review: [39]

Hospital admission seems to be a good time for a pharmacist to thoroughly review a patient's pharmacotherapy; this is especially important for patients who may have had a drug related hospitalization or who have complicated medication regimens, like elderly patients with multiple medical conditions receiving poly pharmacy. Hospital pharmacists can identify any MRPs through medication reviews and create recommendations for how to address these issues with other healthcare specialists. MRPs can result in hospitalization as well as an increase in length of stay and cost of stay which can be quite expensive for healthcare providers. In contrast to the primary care setting, a hospital pharmacist has access to all patient data, may do a more extensive medication review and can evaluate the pharmacotherapy in light of the patient's presenting symptoms and conditions.

These frequently take place in conjunction with the admission medicine reconciliation. In addition, the pharmacist can speak with the patient in person and have a face to face conversation with the prescriber about any outstanding MRPs. A study of the literature revealed no trials in which the intervention cost surpassed the benefit, despite the fact that there are very few reliable health economic assessments focusing on prescription reviews by hospital pharmacists. Notwithstanding the lack of conclusive studies on the subject of clinical and financial effectiveness, hospital pharmacist medication evaluations are now widely acknowledged to be valuable in compared to conventional care. Yet, t would be helpful to conduct more research to support this assertion.

K. Ward Rounds: [40-43]

During daily ward visits, hospital pharmacists have offered their clinical services to the wards, addressing any MRPs found with the proper interventions. The role of the pharmacist in prescribing is often retroactive, therefore there may be significant gaps in time between the time of the prescription and the pharmacist's intervention, raising the possibility of expensive adverse drug events. A pharmacist may therefore benefit more from being there when writing a prescription since they can offer their specific knowledge at a time when it may be most needed. It has been demonstrated that when a pharmacist participates in consultant led ward rounds in addition to the ward pharmacist visit, a patient receives a lot more interventions than with only the ward pharmacist visit.

Although participating in daily ward rounds could take up some of a pharmacist's time, it is a great chance to stop ADEs and drastically lower healthcare expenses. Similar to preadmission rounds, having a pharmacist present enables early correction of inconsistencies in the drug history, which can lessen patient risk and prescribing costs.

L. Specialized Roles: [44-48]

In an ICU context, pharmacists are highly regarded professionals because they can advise doctors on intricate pharmacological regimens for critically ill patients, which sometimes involve expensive drugs. In this high risk setting, pharmacists contribute to beneficial outcomes by preventing ADEs, lowering morbidity and mortality and containing overall healthcare expenses. Pharmacists play a significant role in promoting antimicrobial stewardship globally in the face of rising antimicrobial resistance. Today, there are many hospitals with pharmacists who focus on this aspect of stewardship, ensuring the prudent use of antibiotics with better patient outcomes. These pharmacists are frequently involved in the creation of the hospitals antimicrobial guidelines. One of the main duties of this specialist position is to streamline antimicrobial therapy, which results in cost savings by ending the improper use of specific medications and encouraging the switch from parenteral to oral administration without impairing patient care. These reductions are mostly achieved through decreased length of stay and antibiotic costs.

M. Chemotherapy Services: [49-51]

Antineoplastic agent prescriptions have increased as a result of the global increase in cancer incidence. Chemotherapy regimens can be quite complicated and are more prone to error since frequent dosage modifications are required. Because the medicines limited therapeutic indices make medication errors involving these regimens potentially fatal, pharmacist involvement is essential.

N. Long-Term Care: [52-54]

Elderly patient receiving long term care are frequently co morbidly ill, making them more vulnerable to improper prescriptions. Despite the fact, that these patients frequently need complex pharmaceutical regimens. Pharmacists can significantly enhance the standard of drug administration. Doctors benefit from the pharmacist's prescription review since it saves them time, especially when it comes to patients who are not examined frequently. Overall, there is a lot of conflicting information regarding the value of pharmacists in long term care settings. By minimizing potentially inappropriate prescriptions and MRPs, pharmacists can enhance clinical outcomes; nevertheless, the majority of effective treatments reported in the literature were interdisciplinary in nature.

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ISBN: 978-81-19149-00-1

7. Clinical Services, Reviewing Medication for Safety and Efficacy, and Providing Drug Information

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Abstract:

The traditional responsibilities of pharmacists are to prepare and distribute medications, but this has restricted their ability to collaborate more closely with other healthcare professionals to increase the efficacy and safety of medications. But now in this era the pharmacist's duties are changed to improve the health allied lines for the better action. Throughout healthcare institutions, pharmacists play a critical system-level role in organizing and directing initiatives to improve medication safety and efficacy programs. These strategies could involve creating high-alert drug guidelines that are risk-specific. Pharmacists should focus on development of soft skills for the employees who work one-on-one with patient and Physicians to improve the services with more efficacy and safety.

Keywords:

Clinical services, Review, DI, Medication.

7.1 Clinical Services:

Clinical service is the ability of a drug to show or produce desired result and beneficial effect. The pharmacist act as a bridge between the physicians and the patient for the more beneficial services. To encourage the best possible patient results, the pharmacists collaborate with other members of the healthcare allied team for the services.[1]

7.1.1 Pharmacy Services for Hospitalized Patients:

The use of medications for patients who need to be hospitalized is the area of expertise of acute care (inpatient) pharmacists. Every patient who receives treatment through hospital services will get specialised attention from a clinical pharmacist with knowledge in the area of concern.[2]

Pharmacists work with patients in the following ways:

- Ask you questions about the medications you are taking at home
- Attend daily rounds with the health care team
- Make sure you are getting the right medication therapy during your stay
- Monitor how your medications are working
- Monitor for possible side effects from medications
- Teach you about your medications
- Help you receive the same or similar medications when you leave the hospital
- Address your questions and concerns about medications.[3]

A. Anticoagulation Case Management Service: The Anticoagulation Case Management Service (ACMS) offers anticoagulant treatment to patients who have established primary care relationships with a doctor, a pharmacist, as well as with other healthcare professionals.

B. The Pain Management Clinic: It offers patients the advantage of collaborating with medical professionals in a team-based environment. Under the terms of a joint practice agreement, our clinical specialists in pain management collaborate with doctors to offer patients with multidisciplinary care while it also improves the pharmacy and medical research and innovative practical teaching for the students as well.

7.2 Pharmacotherapy Clinic:

The care and management of diabetes, high blood pressure, and excessive cholesterol are areas of expertise for the Pharmacotherapy Clinic. In this clinic, pharmacists not only educate patients but also work more closely with patients between doctor visits to more carefully manage chronic disorders.

The services which are approved by the organization for the pharmacist are:

- **Point-of Care (POC) Testing for Flu and Strep:** According to Clinical Laboratory Improvement Amendments (CLIA), In the pharmacy premises the pharmacists are provided with kits to test for the Flu and strep to attract the patients with collaborative practice with physicians. Patients can have these drugs dispensed immediately after positive POC testing.
- **Smoking Cessation Counselling:** The counselling has to be taken compulsory for the patient to withdraw the bad habits for the survive of life. The pharmacist should give the awareness about the disease caused by the smoking, alcohol and the pharmacists tell the condition of his status due to smoking and alcohol.
- **Contraceptive Prescribing:** In an effort to improve access to contraceptives and reduce unintended pregnancy rates, there is a nationwide push to allow pharmacists to prescribe hormonal contraceptives.
- **Pharmacokinetic Testing:** Pharmacist's knowledge of pharmacokinetics, drug transport, and drug metabolism make them ideally suited to become involved in the expanding field of pharmacokinetic testing.
- **Expanded Immunization Programs:** "Immunizations have become a mainstay for community pharmacy and the pharmacists are not just to give a flu shot, but to perform

an entire immunization needs assessment on patients." The service must also be started in India for betterment of safety and efficacy. So that pharmacist plays an important role in clinical services.[4,5]

- **Implementing New Services:** The pharmacists must be involved in advocating for more clinical services in the pharmacy to understand and to know the local pharmacy problems and regulations and that is the key way to success in clinical services. Pharmacovigilance is a software's, where the pharmacists can study detail about the drugs with their side effect. Pharmacovigilance mainly tells on adverse and side effect. Using innovative methods like Bio-informatics, molecular docking and quality by design helps in future generation development of clinical services.[6]

7.3 Pharmacists at the FDA: Drug Information Specialists:

Proper scheduling of new services is essential. Training requirements for different clinical services vary from state to state. New graduates are quite familiar with many of these services. There are many organizations which help to spread a wide awareness regarding latest developments and changes in health sector. There is a need for proper management team in every health institution to follow updated guidelines to

Gain better understanding of services in improving health literacy and its environment.

Teach health care leaders to work collectively across organizational boundaries to prioritize overall patient care.[7]

Technology advancements in recent years have made easier and less time-consuming works so that the pharmacists can take care the patient. Examples include electronic health records, clinical decision support systems, robotics that automate the production and distribution of medications, and machine-readable coding on pharmaceutical packaging. Due to the usage of these technologies, hospital pharmacists are working outside the hospital pharmacy and devoting more of their time to pharmaceutical therapy management tasks than they did in the past.

Health care system is vast and diversified. The health care services are not only about-well-being of the patient but also caters to very sensitive matter concerned to patient rights, autonomy, decision-making and overall satisfaction.

Zermansky et al., was the first to use the term clinical reviews and defined as "the process where a health professional analyses the patient, the ailment, and the pharmacological treatment during a consultation". It requires evaluating each therapy's efficacy in treating patients as well as how the illnesses being treated are developing. The patient's condition and understanding of its treatment, compliance, current and potential adverse effects, interactions, and other considerations are all taken into consideration. The outcome of the review will be a choice regarding the course of the therapy whether to continue or stop.[8]

Medication review is primarily a diagnostic intervention that seeks to pinpoint issues for the patient, prescriber, or both to address, but it can also be seen as an educational intervention to enhance patient understanding and adherence.

The main goal of medication reviews is to increase the effectiveness, safety, and proper usage of medications. Several interventions that may be carried out by prescribers themselves or by other practitioners who provide advice to prescribers are collectively referred to as "medication reviews".[9]

Review of prescriptions, compliance and concordance, and clinical medications are the three distinct review types. Medication review is widely advised, and regularly covered by health care insurance in various nations in order to decrease the incidence of avoidable adverse drug events and hospital admissions. This involves identifying drug-related issues and advising interventions.

7.4 Principles of Medication Review:

- All patients should have a chance to raise questions and highlight problems about their medicines.
- Medication review seeks to improve or optimise impact of treatment for an individual patient The review is undertaken in a systematic way by a competent person.
- Any changes resulting from the review are agreed with the patient.
- The review is documented in the patient notes.
- The impact of any change is monitored.
- The following documentation on health conditions can be kept up to date by doing medication reviews.[10]

A. Health Status, Physical and Cognitive Outcome Measures: Medication review aids in seeing improvements in clinical status, health status, and patient's perceptions of the severity of their illnesses; nevertheless, it also results in a slight decline in self-rated health.

B. Quality of life: The medication review report, outlines how drug reviews affects the quality of life which includes low risk and high risk.

C. Drug-related outcome measures: An effect of medication review was found on most drug-related outcome measures (the number of drugs, the number of drug changes, the number of drug-related problems and the number of drugs with a dosage decrease), but not on the number of drugs with dosage increase.

D. Drug-related problems: This review decreases the number of drug-related problems. The trials assessing the effect of medication review on the number of patients with drug-related problem were conflicting with their treatment.

E. Number of Drug Changes and Number of Drugs with A Dosage Decrease or Increase:

Two other trials with overall high risk of bias, including intervention patients, found an increase of the number of drugs with a dosage decrease, whereas no difference was found with regard to the number of drugs with dosage increase. Furthermore, no effect of medication review was found on the number of individual doses per day and the dosing frequency per day.

F. Economical outcomes: Trials using various other outcome measures for drug and supply costs did generally not observe effect of medication review on costs Besides this, Burns et al found no decrease or increase of costs related to in-patient and outpatient visits.

G. Sensitivity analyses: Sensitivity analysis often involves re-analysing the same outcome using multiple methods or different definitions of the outcome with the main objective of determining how these changes affect the conclusions.[11]

7.5 Drug Information (DI):

Medication information is given in response to inquiries from other healthcare-providing organizations, committees, patients, and the general population. It can be done verbally or in writing form. Another definition of DI is the understanding of information on any chemical intended for use in illness diagnosis, prevention, or therapy that is learned by research, investigation, or practical experience.

It includes all forms of information delivery, including information that is both subjective and objective, as well as knowledge gathered from academic research or real-world experience. Independent drug information centers are recognized by the WHO as a crucial element of national initiatives to support the responsible use of medications.[12]

To improve drug knowledge, enable rational prescribing, and decrease medication errors, pharmacists offer a specialized service known as drug information service. This service is offered in response to allied health professional's requests for information regarding medication-related difficulties involving patient pharmacotherapy and medication management.

According to Review of the literature indicates that the survey was carried out among hospital pharmacy managers by leaving the questionnaire and picking it up at a later time. Before completing the questionnaire, participants were given a briefing on the study's goals and non-invasiveness. Despite being exempt from review; the study was produced upon request along with a letter addressed to the relevant hospital. [13]

Drug information sources have been traditionally classified in three different categories: primary, secondary, and tertiary.

- **Primary resources:** This literature consists of clinical research studies and reports, both published and unpublished. Not all literature published in a journal is classified as primary literature.
- **Secondary resources:** Secondary literature refers to references that either index or abstract the primary literature, with the goal of directing the user to relevant primary literature.
- **Tertiary resources:** These sources provide information that has been summarized and distilled by the author or editor to provide a quick easy summary of a topic. Some examples of tertiary resources include textbooks, compendia, review articles in journals, and other general information, such as may be found on the Internet. [14]

These are some of the hand books and the online resources which gives the more knowledge about the drug interactions and adverse effect during the treatment. The software's are Micromedex, Iowa Drug Information Service, Meyler's Side Effects on Drugs, Marindale's Extra Pharmacopoeia, American Hospital Formulary Services Drug Information and hand books like - Pharmacotherapy: A Pathophysiological effect, Applied Therapeutics: The clinical use of Drugs, Paediatric Dosage Handbook, Drugs in Pregnancy and lactation, British National formulary, Australian Medicine Handbook.

The different queries sought from drug information services are: These queries are received from Government as well as private hospital sectors. For every month the queries or the effect are documented and produced to the respective department for the further action if needed.

Due to a lack of current literature, poor documentation, and insufficient information transmission, the majority of developing nations experience a lack of drug information. Clinical pharmacists are well-trained for this function because they are known as "Medicines Specialists."

One of the core duties of clinical pharmacists is to provide drugs and therapeutic information (DTI) to clinicians. But so far, due to an increasing patient load with co-morbid illnesses, the availability of more pharmacological molecules on the market, and polypharmacy, DTI services appear to be important in the present healthcare system. So, offering DTI aids practitioners in rationalizing the course of treatment for their patients.[15]

7.5.1 Clinical Pharmacists' Responsibilities Within Drug Information Services Are:

- Information regarding the services offered is communicated.
- Responds to inquiries in accordance with the urgency.
- Maintains a written system in place to record the inquiry's and the inquirer's specifics.
- Records the queries & their response references.
- Stores drug information service documents.
- Assures that the service is regularly assessed.
- Ensures that the drug information service has been delivered promptly and satisfactorily by regularly seeking user input.

Passive intervention is defined as the involvement of a clinical pharmacist in the establishment of Drug Information Services that are most beneficial to prescribers or other healthcare providers and to see the enhanced service's quality for the health science.

Doctors, pharmacists, and staff nurses frequently used an innovative method named the "drug information query box" and thought it was a simple way to make requests. The clinical pharmacist conducted a quality assurance for the responses to drug information requests, and the outcomes were "well accepted."

This presents a significant possibility for further improvement with the engagement of more healthcare experts.[16]

7.5.2 Drug Information Resources Available:

Table 7.1: Drug Information Resources Available

Resources by Question Type		
Question Type	**First Choices**	**Next Choices**
Adverse effects	AHFS Drug Information, Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX, UpToDate	DailyMed , Manufacturers' web sites, PubMed
Bioequivalency	FDA Electronic Orange Book	AHFS Drug Information
Chemical Data	AHFS Drug Information, NLM Drug Information Portal	MICROMEDEX
Clinical Trials	ClinicalTrials.gov	
Comparative Information	AHFS Drug Information, Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX	EMBASE , PubMed
Contraindications	AHFS Drug Information, Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX, Gold Standard (Clincal Key)	Manufacturers' websites, NLM Drug Information Portal, PubMed
Cost	UpToDate	Commercial websites such as GoodRX.com †
Disease state information	Pharmacotherapy: A Pathophysiologic Approach, 11th ed , Dynamed , MEDLINEPlus, Stat!Ref, UpToDate	MICROMEDEX , Natural Medicines , Clinical Key
Dosage Recommendations	AHFS Drug Information, Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX, Gold Standard (Clincal Key)	Daily Med, Manufacturers' websites
Drug administration	AHFS Drug Information, Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX, Gold Standard (Clincal Key)	Manufacturers' websites, NLM Drug Information Portal
Drug interactions (drug-drug, drug-food, drug-lab tests, drug-disease, etc.)	Facts & Comparisons (*Licensed for academic use only*), MICROMEDEX, Natural Medicines, UpToDate (Lexi-Interact) Drug Interactions Program	Gold Standard (Clinical Key) , PubMed

Resources by Question Type		
Question Type	**First Choices**	**Next Choices**
Drugs in pregnancy and lactation	Facts & Comparisons (*Licensed for academic use only*) , MICROMEDEX (ReproRisk), Drugs in Pregnancy and Lactation (Briggs), LactMed, TERIS	AHFS Drug Information , Gold Standard (Clincal Key) , Natural Medicines
Herbal, natural & homepathic products, dietary supplements	Natural Medicines	CINAHL Plus , EMBASE , MICROMEDEX , product websites
Identification (foreign)	Facts & Comparisons (*Licensed for academic use only*) , MICROMEDEX (Martindale's), European Medicines Agency (EMEA)	EMBASE , Web
Identification (domestic)	Facts & Comparisons (*Licensed for academic use only*) , MICROMEDEX	product websites (see How Supplied section of package insert)

7.6 Conclusions:

Pharmacists also have a crucial system-level role in planning and leading medication safety programs and improvement initiatives within health care organizations. These initiatives may include developing risk-specific protocols for high-alert medications; identifying and evaluating high-risk processes.

Since the common resources employed did not contain information about the local availability, the adoption of the National Formulary (NF) may be a better solution to this issue as it can serve as a better alternative to other resources in such circumstances and alternatives accessible. This gives more and better information.

The drug information service is thought to be enhanced overall by upgrading the staff, i.e., hiring pharmacists with higher qualifications, training in drug information service, and relevant experience in the field. So that clinical efficacy and safety can be enhanced. In order to respond to a range of DI demands, it is crucial for pharmacists to choose the right resources and stay up to date on new literature and techniques.

When the "five rights" are followed, meaning the right dose of the right medication is administered to the right patient, at the right time, and by the right route. The five rights must be customized to each patient because they depend on their age, health, physiologic status, and other considerations including allergies. In the past, dispensing has been the primary way that pharmacists have contributed to pharmaceutical safety, but in present the Pharmacists play an important role in clinical services as well writing the medication reviews with drug information also maintains the efficacy of the drug and safety of a patient.

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ISBN: 978-81-19149-00-1

5. Rural Pharmacy and Prescription Drugs Overview

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Abstract:

What particular education and training are colleges and schools of pharmacy offering graduates who want to practise pharmacy in rural health? is the topic of this review. Rural areas are experiencing an increasing number of pharmacy closures. Closures reduce adherence to prescribed drugs and interfere with access to medications. A potential answer to this issue is telepharmacy, however there is no data on how well it affects the quality of medicine use. By contrasting the standard of telepharmacies serving rural areas and the traditional pharmacies that support them, our study aimed to close this gap. An online evaluation of websites includes all colleges and universities that were recognised by the Accreditation Council for Pharmaceutical Education as of December 2011 or those who have precandidate status. We discovered a diverse range of course options, from formally established programmes in rural pharmacy to no descriptions of courses or experiences in a rural setting. Although it is good that more pharmacy colleges and schools are offering either obligatory or elective courses in rural health, more education and training with this focus is essential to assist address the unmet need for high-quality pharmacy services for rural areas.

Keywords:

Druga, Overview, Pharmacy, Rural.

5.1 Introduction:

In remote locations without access to physicians or where accessing their services would be prohibitively expensive, pharmacists play a significant role in delivering healthcare services through community pharmacy services. A pharmacist who dispenses medications also offers consulting, counselling, and pharmacological information to patients and other medical professionals in order to satisfy their requirements and ensure compliance. ensuring better healthcare for everyone. Pharmacists can reduce a variety of medical errors by raising patients' health literacy and maintaining a careful check and balance.

Pharmacies and pharmacists are essential for the safe dispensing of pharmaceuticals, patient education, and patient safety. Rural community pharmacies must overcome a number of obstacles in order to remain operational, including low purchasing volumes, tight profit margins, unfavorable insurance policies, and small pharmacy personnel. Due to lack of

transportation choices, severe weather, or the patient being too ill to make the long trip to the closest pharmacy, timely access to pharmaceutical services can be impeded when there isn't a pharmacy close by.

While the growth of tele pharmacy and online mail order pharmacies could imply that access is no longer restricted by geography, many rural individuals lack the necessary tools, technological know-how, and/or access to reasonably priced broadband internet for these services. In several states, tele pharmacy is now prohibited by law or regulation. The health of rural residents will continue to benefit greatly from the services provided by rural pharmacies and pharmacists.

Pharmacy services go beyond simply dispensing prescription medications, a function that online mail order pharmacies are increasingly filling. Moreover, pharmacists serve other healthcare facilities and providers like hospitals, skilled nursing facilities, and hospice care by giving advice on over-the-counter medications, administering vaccinations, and providing support. Access to pharmacy services is crucial for the health of rural inhabitants because they are more likely to be older and suffer from chronic illnesses than urban residents. A relationship with a pharmacist who, in conjunction with their doctor, can assist them manage their medications can be especially helpful for older persons who live in remote areas and may have many prescriptions. Pharmacy services are crucial to meeting the healthcare needs of all rural inhabitants, regardless of the patient's age. In rural, pharmacists Prescription Store offered care coordination services, set up follow-up appointments, and decreased the number of trips needed to pick up drugs by offering synchronization services.

The range of healthcare services includes pharmaceutical care, which is essential. As a member of the healthcare team, pharmacists counsel patients and offer guidance to doctors, nurses, and case managers. They have crucial roles in discovering drug interactions, preventing prescription errors, and encouraging medication adherence. Due to dwindling rural populations, growing competition from chain and online pharmacies, greater prescription drug costs for low-volume pharmacies, and the challenge of replacing retiring pharmacists, many independent, rural pharmacies are fighting to operate.

In rural hospitals and Critical Access Hospitals, the job of the rural pharmacist varies. A hospital pharmacist may perform the following roles:

A. Administering and controlling the distribution of pharmaceuticals across the hospital, remote locations, and emergency medical service providers.
B. Creating custom pharmaceuticals.
C. Drug inventory control.
D. Evaluation and reconciliation of the medication regimen upon admission and discharge.
E. Coordinating, modifying, and tracking drug therapy.
F. Budget and personnel management for the department.
G. Adherence to all pharmacy laws and regulations, both state and federal.
H. All pharmacy policies, processes, and services are created and maintained.
I. Customer, employees, and health professions pupil education.
J. Teaching pharmacy students.

K. Directing or taking part in measures to improve quality, such as reducing adverse drug events and antibiotic stewardship.
L. Giving immunizations to hospital employees and/or the neighborhood.

A hospital pharmacist in a rural location may have different responsibilities from those of a hospital pharmacist in an urban setting due to budgetary and staffing constraints. Some difficulties include:

A. The obligation and challenge of staffing the pharmacy, which includes selecting full-time, part-time, temporary, or as-needed employees as well as pharmacy technicians.
B. Involvement in a variety of hospital task teams and committees that deal with drugs.
C. Insufficient time to staff the pharmacy on location; after hours, remote order processing services are needed.
D. A formulary that isn't very robust because of financial restrictions or a lack of staff availability.
E. The requirement to be able to give pharmaceutical services over the phone and/or through remote computer access in order to maintain continuity of care while not present.

As a member of the healthcare team, pharmacists counsel patients and offer guidance to doctors, nurses, and case managers. They have crucial roles in discovering drug interactions, preventing prescription errors, and encouraging medication adherence. Your neighborhood pharmacy's care staffs are familiar with your health insurance position and can frequently work with you to identify the best cost-effective answer to your needs. No matter what condition you're trying to address, this results in lower total expenditures for both over-the-counter and prescription treatments.

In contrast, your neighborhood pharmacist can evaluate your prescription, look over your insurance and what it covers, and then immediately substitute something that is more practical for you, cheaper, or easier to take. Even better, they can frequently make these changes right away in a matter of minutes. It is quick, effective, and less expensive.

Contrary to popular belief, pharmacists don't just deal with problems involving medications. Above all, you should think of your pharmacy care team as a patient and readily available source of guidance when it's most needed. Your neighborhood pharmacy can assist you in achieving your most critical healthcare objectives no matter what your healthcare issue is.

It is commonly known that rural pharmacies face difficulties. Finding qualified healthcare workers to work at the facilities is frequently difficult, which can greatly lower the standard of care provided. Covid-19 has presented fresh difficulties for the world's health care systems, and particularly for neighborhood pharmacies.

Rural pharmacies must adjust to the pandemic's ever-changing realities in order to stay operating. Conventional safety measures including avoiding social contact, limiting the number of patients, and using delivery services have all been strongly advised and widely used. Perhaps more importantly, neighborhood pharmacies have modernized their working

procedures to keep up with the trends. Some of measures include creating protocols to accept prescriptions from the interim Telehealth extensions and working in teams and shifts to reduce the dangers of cross-infections.

However, these issues pale in comparison to the difficulties faced by rural pharmacies in providing access to prescription medications. Those who require ongoing care are more at risk. Those who depend on pharmaceutical supply, for instance, can experience pain due to a reduction in resource availability. They might also pass up the chance to talk about any issues they are having with their medicine. Also, pharmacies must weigh the hazards of frequent hospital trips against boosting medicine supplies to monthly dosages.

Rural pharmacies must also prepare for the arrival of the COVID-19 vaccination in addition to all of the aforementioned factors. They are ideally situated to carry out vaccination administration and guarantee that everyone receives a dosage.

The third-largest group of healthcare professionals in the world are pharmacists, and in India, the field of pharmacy has been developing substantially over the past ten years. By maximizing the health benefits and safety of pharmaceuticals, pharmacists today have expanded their function beyond drug distribution to include pharmaceutical care. The quantity of work-related activities has grown, which has either a direct or indirect impact on pharmacists' job satisfaction and the caliber of work performed. Work satisfaction is characterized as an employee's response to their responsibilities inside the company where they work.

5.2 Conclusion:

The purpose of the study was to evaluate the self-reported level of vital services and public health service delivery in rural areas. The degree of alignment between the practice of pharmacy and providing vital public health services has not yet been evaluated; instead, it has only been examined in the literature. Due to this misalignment, the important contributions provided by pharmacists are not recognized by the larger healthcare community. Additionally, it jeopardises pharmacists' ability to study and emulate the positive public health contributions made by pharmacists in other contexts.

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Edited Book

Recent Advances In Pharmaceutical Sciences

(Volume 14)

Dr. Vivekanand Kisan Chatap

Publisher

Innovare Academic Sciences Pvt Ltd
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Email: info@innovareacademics.in | https://innovareacademics.in/

Edited Book: Recent Advances in Pharmaceutical Sciences (Volume 14)

Publication Year: July. 2023

MRP: INR 500

ISBN: 978-81-958789-9-4

Publisher and address:

Innovare Academic Sciences Pvt Ltd

T-8, Mahaveer Apartment, Near SIRT College, Ayodhya Bypass, Bhopal 462041, MP, India. Phone: +91 9425108574

Email: info@innovareacademics.in | https://innovareacademics.in/

Printer: Innovare Academic Sciences Pvt Ltd

About the Book

Pharmaceutical sciences include broad range of multidisciplinary subject seeking to foster the integration of areas of knowledge that focus on all facet of drug and therapies. Pharmaceutical sciences ranges from identification and control of organism causing disease, design of drug, formulation, clinical trial, metabolism, quality control and audit of drugs, manufacturing, plant-based source of medicines, food sciences, public, to environmental health for improving the quality of human life.

The Chapter of the compiled edited book contains advanced knowledge and the updated research outcomes to update the readers. It touched on addressing the recent advancement of pharmaceutical sciences through the different approaches with the aim for the betterment of society and health of well-being. Additionally, its multidisciplinary nature in pharmaceutical sciences contributes valuably to other research areas like medical, biological, and chemical sciences.

The edited book aims to bring authors to one platform with the different subjects of Pharmaceutical sciences and share their knowledge for further research.

We hope that this book may interest a broad readership for upgrading and acquiring the latest information for the extension of the study.

Its continuous volume will come one by one to share more information and knowledge on recent advancements in pharmaceutical science.

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Chapter-01

ASSESSMENT OF CAUSALITY, PREVENTABILITY AND SEVERITY OF CUTANEOUS ADVERSE DRUG REACTIONS

Rajesh Hadia*, Rahul Trivedi, Cyril Sajan, Varunsingh Saggu, Sunil Baile, Sunil Kardani, Hemraj Singh Rajput

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ABSTRACT: Drug regulatory authorities have the responsibility of ensuring the safety, efficacy and quality of all marketed products. However, identifying rare adverse reactions (ADR) and delayed side effects during clinical trials can be challenging due to the lack of follow-up. Therefore, pharmacovigilance plays a significant role in establishing the safety profile of marketed drugs. This study aimed to establish the safety profile of drugs through pharmacovigilance. The study was conducted by the Department of Pharmacy Practice at a drug information centre in collaboration with the Department of Pharmacology at a private multi-specialty hospital. ADR reporting forms of the Central Drug Standard Control Organization were used to collect data on patient demographic details, clinical history, and co-morbid conditions like diabetes mellitus, hypertension, asthma, and history of drug allergies. The chance of preventability was found to be very low, and most ADRs were not preventable. The severity of ADRs was moderate, which was attributed to a history of allergy and multiple drug therapy. The study found that 86% of ADRs were not preventable, while 14% were preventable according to the Schumock and Thornton scale. The preventable cases were due to a history of reactions upon administration of the same drug, suggesting the use of drug alert cards in such cases. The major risk factors for the development of ADRs include self-medication, lack of awareness regarding the dose and frequency of administration, and polypharmacy. These risks can be mitigated by prescribing required drugs only and educating patients on their medications. In conclusion, pharmacovigilance plays a vital role in establishing the safety profile of marketed drugs. The study

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Chapter-05

DESIGN CHARACTERIZATION AND FORMULATION OF *IN SITU* GELLING OPHTHALMIC DRUG DELIVERY SYSTEM CONTAINING PLANT DERIVED PHENOLS

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ABSTRACT: The objective of the present investigation was to formulate and evaluate ion activated *in situ* gel using herbal drug catechin a potential natural antioxidant for the treatment of glaucoma by lowering the oxidative stress. A total of eight formulations were prepared and evaluated for parameters namely physical appearance, gelling capacity, pH measurement, rheological studies, effect of sterilization, drug content, *in vitro* diffusion study, isotonicity evaluation, ocular irritancy studies and stability test. Preformulation studies confirmed that the drug and polymer are compatible with each other. The XSG-2 formulation showed maximum percentage drug release of 95.45% which was considered as optimized formulation and showed 5-6 folds increase in viscosity after gelation which indicated good residence time further formulations was found to be non-irritating with no ocular toxicity and good stability. The results of the current study conclude that the developed catechin loaded ophthalmic *in situ* gel can be considered as a better alternative approach to the conventional eye drop with increase in precorneal residence time, reduced frequency of dosage and patient compliance for the management of glaucoma.

INTRODUCTION

Designing ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical

scientist because of critical and pharmacokinetically specific environment that exists in eye [1]. Conventional pharmaceutical formulations such as solutions, suspensions have many constraints like rapid precorneal elimination, drainage by gravity, normal tear turnover, frequent instillation, enzymatic metabolism, nasolacrimal drainage, conjuctival absorption, absence of controlled release and bio adhesive properties [2] Residence time of most conventional ocular solutions is 5-25 min and only 5% of topically applied drug is absorbed[2] and reaches the deeper tissues so, it is necessary to develop a novel safe and patient complaint formulation and drug delivery devices, which may surpass these barriers and maintain drug level in tissues. Due to the drawbacks with this route, new approaches have been investigated by means of the polymeric drug delivery system based on the concept of *in situ* gel formation which exhibit reversible phase transitions (sol-gel) and pseudo plastic behavior which is aimed at longer precorneal residence time, improved ocular bioavailability and patient acceptability [3]

Eye is a unique organ because of its constant exposure to light, atmospheric oxygen, environmental chemicals, and physical abrasion. Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species (ROS) under optimal conditions the rate and magnitude of oxidant formation is balanced by the rate of oxidant elimination through the action of antioxidants. But under normal conditions excess oxidants may cause macromolecular damage. An imbalance between pro-oxidants and antioxidants, in favor of the former, results in oxidative stress.

Glaucoma is the second leading cause of blindness. It is an ocular disorder with multi-factorial etiology, characterized by a slow and progressive degeneration of retinal ganglion cells and optic nerve axons and intraocular pressure (IOP) elevation, resulting into visual loss and also optic nerve damage. Normal IOP is maintained through a balance between the aqueous humor and the amount drained. In glaucoma, excess fluid typically builds up because of a blockage of the drainage channels or filtering tissue called the trabecular meshwork

In present investigation attempt has been made to formulate and evaluate *in situ* gelling ophthalmic drug delivery system comprising of plant phenol catechin, using natural polymers like xanthan gum, sodium alginate and gellan gum. In this system gelling of polymer is triggered by ionic interaction of the polymer and divalent ions of the tear fluid forming a viscoelasticgel.[1]

Plants are considered to be chemical factories as they contain numerous chemical compounds like alkaloids, glycosides, saponins, resins,

flavonoid and polyphenols which have many therapeutic effects. Due to toxicity, side effects and various interaction of synthetic drugs today there is growing interest in phytoconstituents of plant based medicine.

Some advantages of extracts derived from plants contain more than one active component that act as a synergist between different phytoconstituents which can be important part for their overall therapeutic effect. It is evident that, use of extracts derived from *Punica granatum*[4], *Moringa olifera*[5], *Camellasinensis*, *Coleus forskohli*[6] *Garcinia cola*, *Ocimum santum, Ginko biloba*[7]etc containing natural antioxidants such as polyphenols, punicalagin, elagic acid, gallic acid, catechin, ellagitanins, epigallocatechin[8], quercitin, forskolin, flavonoid, etc. has created much interest which may be helpful in treatment of glaucoma[9]

Oxidative stress can cause chronic changes in aqueous and vitreous humor, which may induce alterations in the trabecular meshwork and optic nerve head which affects the regulation of extracellular matrix structure and alteration of flow of aqueous humor [9] The only form of therapy to counteract reduction of oxidative stress is by use of natural antioxidants such as catechin, hence there is a need to explore full potential of catechin for treatment of glaucoma there by reducing side effects.

CHARACTERISTICS REQUIRED TO OPTIMIZE DRUG DELIVERY SYSTEMS

- Good corneal penetration.
- Prolonged contact time with corneal tissue.
- Simplicity of installation for the patient.
- Non- irritative and comfortable form

REQUIREMENT OF THE IDEAL SYSTEM

- Free flowing low viscous liquid
- Phase transition from sol to gel should be strong enough to withstand the shear forces in cul-de-sac
- Long residence time
- Enhanced bioavailability
- Reduced systemic absorption and frequent administration

IN-SITU GEL

It refers to polymer solution which can be administered as liquid & undergoes a phase transition to semisolid gel upon exposure to physiological environment. The gelation can be triggered by temperature, pH change, ionic change & also UV induced gelation. Gelation occurs via the cross linking of polymer chain that can be achieved covalent bond formation (chemical cross linking) or non-covalent bond formation (physical cross linking). It is a low viscosity

solution that undergoes phase transition in conjuctival cul-de-sac to form visco elastic gel due to conformational changes of polymer in response to physiological environment. The rate of *in-situ* gel formation is important because between instillation in eye and before a strong gel is formed; the solution or weak gel is produced by the fluid mechanism of eye

APPROACH FOR INSITU GELLING SYSTEM

Chemical reaction approach: ION Activated System

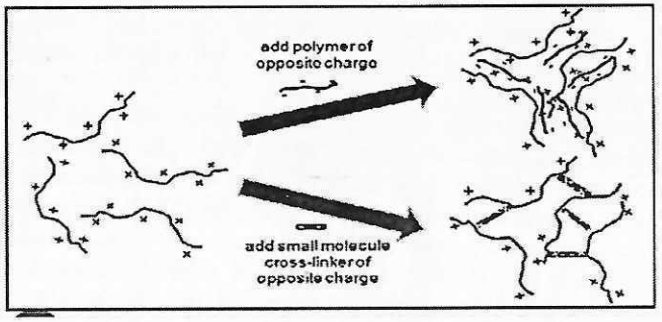

Fig. 1: Mechanism of ions dependent *in-situ* gels

In this approach polymers undergo phase transition in presence of various ions such as K + ,Ca2+,Mg2+,Na+

Mechanism: In this system gelling of the polymer is triggered by ionic interaction of the polymer and divalent ions of the tear fluid. When anionic polymers come in contact with cationic ions of the tear fluid it forms gel. Rate of gelation depend on the osmotic gradient across the surface of the gel. The electrolyte of the tear fluid and especially Na+ , Ca2+ and Mg2+ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which shows osmotically induced gelation is Xanthan gum, Gellan gum, Hyaluronic acid and Alginates

ADVANTAGES OF *IN-SITU* OCULAR DRUG DELIVERY SYSTEMS

- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time.
- Drug effect is prolonged hence frequent instillation of drug is not required.
- For patient compliance and enhance therapeutic performance of drug.

- Generally more comfortable than insoluble or soluble insertion
- System provides ease of administration

MATERIALS AND METHODS

MATERIALS

Catechin and gallic acid procured from Yucca Enterprises Pvt Ltd., Mumbai, Xanthan gum (Lucid Colloids Ltd., Mumbai), Sodium alginate (Micro labs., Bangalore), Gellan gum (Life Expressions., Bangalore)

METHODS

Preparation of standard calibration curve of drug catechin using folin ciocalteu reagent

Principle of Folin Ciocalteu Method

The Folin-Ciocalteu (F–C) reagent is sensitive to reducing compounds polyphenols and produces a blue colour complex. The F-C assay relies on the transfer of reducing equivalents (electrons)in the alkaline medium from phenolic compounds to phosphor molybdic/phosphotungstic acid complexes manifested in the formation of blue color complexes that are determined on a UV-visible spectrophotometer

Procedure: Pure drug catechin was accurately weighed and dissolved in distilled water to obtain stock solution of concentration 100µg/ml further aliquots of different concentration were taken, folin reagent and sodium carbonate solution added for the development of blue color and volume was made up with distilled water to get final concentration in the range of 2-18µg/ml. Samples were measured in the UV Visible range at 760nm against blank solution[10]

Drug-polymer compatibility study

Assessment of the potential compatibility between the active pharmaceutical ingredient and different excipients is an essential part of the preformulation study to predict the shelf life of the dosage form one should know the stability aspects of the active ingredient in presence of other components of the formulation.

Procedure: Physical mixture of catechin with sodium alginate, gellan gum and xanthan gum were characterized by IR spectral studies of samples taken using Fourier Transform Infrared Spectroscopy (FT-IR) Thermo, USA. Model –Nicolet IR 200. Mixture was prepared in the ratio of 1:1 in ambered colored glass bottles. Compatibility testing was carried out as per ICH guidelines at 40°C and 75%RH for a period of 28 d[11] to detect any possible interaction in the mixture.

Preparation of catechin *in situ* gelling system

Table 1: Formulation design of *in situ* gelling system

INGREDIENTS (%w/v)	XSG-1	XSG-2	XSG-3	XSG-4	XSG-5	XSG-6	XSG-7	XSG-8
Catechin	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Xanthan gum	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium Alginate	0.1	0.2	0.4	0.8	0.2	0.2	0.2	0.2
Gellan gum	0.3	0.3	0.3	0.3	0.4	0.6	0.8	1
Potassium Chloride	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19
Benzalkonium chloride	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Distilled water q/s	100	100	100	100	100	100	100	100

XSG-1 TO XSG-8 is formulation code (Xanthan gum sodium alginate gellan gum 1 to 8)

The main prerequisites of an *in situ* gel are gelling capacity and viscosity. The formulation should be free flowing low viscous liquid which undergoes phase transition from sol to gel which should be strong enough to withstand shear forces in *cul de sac* providing longer residence time.

Polymer dispersion is prepared first in distilled water. The gum derivatives were allowed to swell overnight then, aqueous solution of catechin was prepared. Agents for adjustment of tonicity and preservatives were added. The solution was added to the polymeric dispersion and mixed properly. pH was adjusted to 7.4[12] with 0.1N NaOH/Hcl and volume was made up with distilled water which was kept on magnetic stirrer to obtain a homogenized mixture.

Characterization of catechin *in situ* gel

Physical appearance

Formulations were examined for clarity under fluorescent light alternatively against white and black backgrounds for any particulate matter, homogeneity or phase separation

pH

Ophthalmic formulations should have a pH range between 5 and 7.4 to maintain its stability and at the same time, there would be no irritation

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to the patient's eye on administration. The pH of ophthalmic formulation was determined using digital pH meter[13]

***In vitro* gelation study**

Gelling strength of formulations were determined by placing 100 µl of polymeric solution in vials containing 2 ml of freshly prepared simulated tear fluid. phase transition of solution to stiff viscous gel was observed[14] The *in vitro* gelling capacity were graded in three categories on the basis of gelation time and period for which formed gel remains.

(+)- Gels after few minutes and dissolves quickly

(++)- Gels immediately and remains for <4 to 5 h

(+++)- Gels immediately and remains for > 8 h

Sl No	The composition of the simulated tear fluid	
1	Sodium chloride	0.670gm
2	Sodium bicarbonate	0.200gm
3	Calcium chloride	0.08g
4	de ionized water	100ml

Drug content estimation

Accurately 1ml of formulation was taken and diluted with 0.5ml folin reagent, 1.5ml of 10% sodium carbonate solution and volume was made up to 10ml with distilled water to make a final concentration of 10µg/ml. The sample was analyzed by UV/Visible spectrophotometer. The drug content was measured at 760nm[15] against the blank solution which contained sodium carbonate solution and folin reagent.

Rheology analysis

Flow behaviour is an indirect measure of product consistency and quality. it is a measurement of viscous behaviour of non newtonian fluids. It plays role in optimization of the polymer concentration in the formulation of insitu gelling system Viscosity of instilled formulation is an important factor in determining residence time of drug in the eye.

Procedure: It was determined using Anton paar DV-2P Brookfield viscometer. Formulations were mixed with the tear fluid having pH 7.4 in the ratio of 1:3 and placed in the small volume adapter and analyzed using different spindles. The angular velocity of the spindle was increased from 0.3 till 200rpm and the viscosities of the gel were measured with the time gap of 3 mins and the viscosities were recorded[16].

Effect of sterilization on viscosity of *in situ* gelling system

To check the rigours of sterilization effects on formulations, they were subjected to sterilization by autoclaving process at 121 ^{0}C for a period

of 15-20 mins[13] and determination of viscosity was carried out using Brookfield viscometer.

In vitro drug release study of _in situ_ gelling system

The release studies of prepared formulations were carried out by using Franz Diffusion Cell across dialysis membrane. The formulations were placed in donor compartment with simulated tear fluid in the receptor compartment. Between donor and receptor dialysis membrane is placed then whole assembly is placed in thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C±0.5°C[14] 3ml of sample was withdrawn at predetermined time interval of 1 hr to 6 hr and same volume of fresh was replaced. To the samples 0.5ml of folin reagent, 1.5ml 10%w/v of sodium carbonate solution was added and volume was made up to 10ml with distilled water. The samples were analyzed by UV/Visible spectrophotometer at 760nm using blank reagent.

Isotonicity evaluation

Isotonicity is important characteristic of the ophthalmic preparations. Isotonicity has to be maintained to prevent tissue damage or irritation of eye. Formulations were subjected to isotonicity testing to evaluate their isotonic, hypotonic and hypertonic nature. The formulations were mixed with one drop of blood and observed under microscope at 45x magnification[17] and compared with 0.9 % sodium chloride and also standard marketed ciprofloxacin eye drop.

Ocular irritancy studies

The ocular irritancy study was carried out according to Draize test protocol on New Zealand white albino rabbits each weighing 2-3kg. Animals were housed individually in restraining box equipped with water and food in an environment maintained at temperature of 23±1°C and 45-65% RH. Cross over study design was carried out and scoring was done according with Draize test protocol and OECD guidelines.

100µl of optimized formulation was instilled into the lower *cul-de-sac* to the right eye of the rabbit and left eye was considered as control. In order to prevent loss of drug the lower eye lid was gently held together for 5-10 sec. The sterile formulation was instilled twice a day with 3d washing period and the rabbits were observed periodically for redness, excessive tearing and inflammation of the eye after 1h, 24h, 48h and 1 week[17]

Stability studies

Stability may be defined as the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological therapeutic and toxicological specification. Stability of pharmaceutical product is a critical parameter which may affect the purity, potency and safety. Changes in the drug stability can

risk potential patient safety by forming a toxic degradation product or deliver a lower dose than expected so it is essential to know the purity and behavior of the drug substances under various environmental conditions.

Procedure: The stability studies were carried out on the developed formulations as per the ICH guidelines. Formulations were stored in tightly closed amber colored glass vials sealed with aluminum foil at room temperature 25°C±2°C and 40°C±2°C, 75% RH Samples were evaluated on 1st, 3rd, 7th, 14th, 21st and 28th day for clarity, pH, drug content, gelling capacity and viscosity[18].

Antioxidant activity studies

Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species. It is a reaction of ferrous ion (Fe^{+2}) with 1, 10-phenanthroline. Ferrous ion specifically forms red-orange tri-phenanthroline complex which absorbs at 510nm. To the series of volumetric flask 0.25 ml of 1Mm ferrous ammonium sulphate was added, 1.5 ml of different concentrations of drug solution ranging from 2-20µg/ml drug solutions was added then 62.5µl of 5Mm hydrogen peroxide solution was added and incubated in dark for 5 min in the incubator, next to the above dilution 1.5 ml of 1mm 1,10 phenanthroline solution was added which resulted in the formation of red-orange complex color and was again incubated for 10 min. Absorbance's was taken at 510nm against blank distilled water using UV/Visible spectroscopy[19,20] and the percentage inhibitory effect was calculated and compared with standard Gallic acid.

RESULTS

The linear regression analysis was done on absorbance data. Linear regression equation Absorbance= 0.051x+0.029 (y=mx+c) was generated. Compatibility study between drug and excipients was done by characterizing the physical mixture of drug and polymer by FTIR spectral analysis to access any chemical alteration of the drug characteristics through its functional groups

In situ gels were formulated by ion activated method using different concentration of polymers. The formulations were subjected to different evaluation parameters like pH, visual appearance, gel formation time, gel erosion time, drug content, rheology study, *in vitro* drug release, isotonicity and stability study. Antioxidant study for a pure drug catechin was carried out and found that IC_{50} values of catechin was found to comparable with that of standard gallic acid indicating potent antioxidant activity and good choice of herbal drug for treatment of ocular diseases.

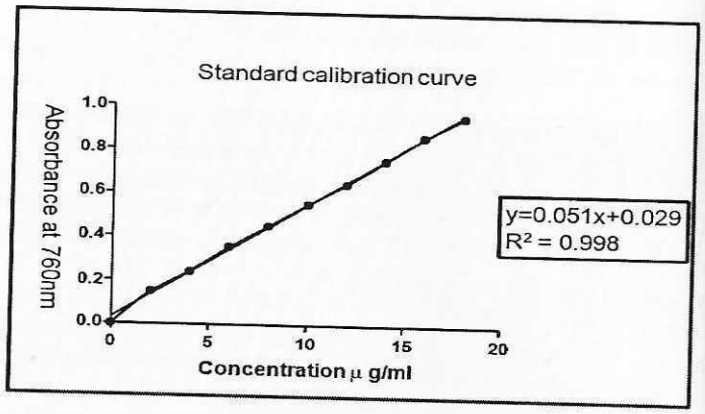

Fig. 2: Standard Calibration Curve

Compatibility study using FTIR spectroscopy

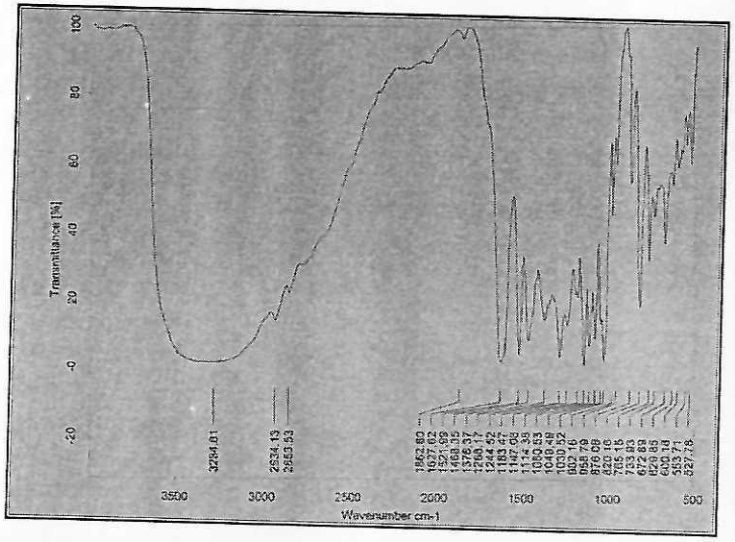

Fig. 3: FTIR spectrum of Catechin

IR Spectral peaks(wavelength cm^{-1}) of catechin exposed to 40 °C/ 75 %RH for 28d				
-OH group	>C=C<	Benzopyrone	C-O-C bending	C-C bending
3284.61	2934.13	1627.62	1244.52	1114.38

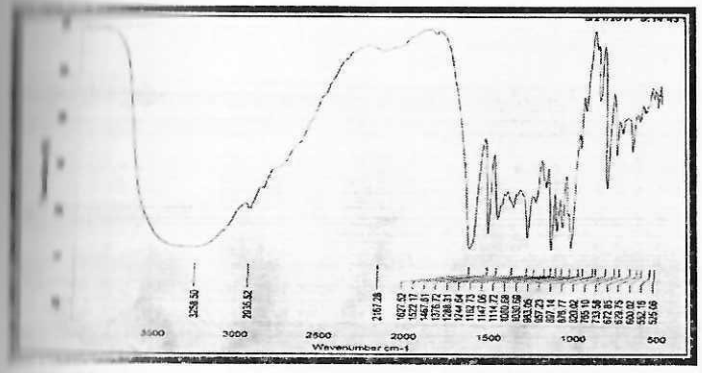

Fig. 4: FTIR spectrum of catechin, gellan gum, xanthan gum and sodium alginate

IR Spectral peaks(wavelength cm^{-1}) of physical mixture of catechin, xanthan gum,sodium alginate and gellan gum exposed to 40 °C/ 75 %RH for 28d				
-OH group	>C=C<	Benzopyrone	C-O-C bending	C-C bending
3258.50	2935.52	1627.52	1244.64	1114.72

Table: 2 Evaluation of various physicochemical parameters of *in situ* gel

Formulation code	Visual appearance	pH (at 25°C)	Gel formation time	Gel erosion time	Drug content (%)
XSG-1	Reddish brown	7.27±0.02	+	++	99.41±0.0007
XSG-2	Reddish brown	7.25±0.03	+++	+++	99.80±0.0030
XSG-3	Reddish brown	7.22±0.03	+++	+++	92.74±0.0040
XSG-4	Reddish brown	7.24±0.05	+++	+++	99.21±0.0047
XSG-5	Reddish brown	6.88±0.06	+++	+++	97.64±0.0070
XSG-6	Reddish brown	7.40±0.007	++	+++	96.73±0.0030
XSG-7	Reddish brown	7.30±0.01	+++	+++	95.62±0.0020
XSG-8	Reddish brown	7.36±0.04	+++	+++	91.89±0.0080

Table 3: Viscosity values for *in situ* formed gels before and after sterilization and % viscosity variation

Formulation code	Viscosity value for in situ formed gels (cps) Before sterilization[a] After sterilization[b]		% viscosity variation	
	Before gelation	After gelation	Before gelation	After gelation
XSG-1	332.2[a] 347.8[b]	1475.2[a] 1512.8[b]	4.69%	2.54%
XSG-2	415.3[a] 410.8[b]	2163.1[a] 2148.6[b]	-1.08%	-0.67%
XSG-3	1641.2[a] 1630.6[b]	4036.2[a] 4022.8[b]	-0.64%	-0.33%
XSG-4	515.8[a] 523.1[b]	2803.2[a] 2761.3[b]	1.41%	-1.49%
XSG-5	2912.6[a] 2336.1[b]	6456.1[a] 6512.1[b]	0.80%	2.41%
XSG-6	4170.3[a] 4023.6[b]	14350[a] 14276[b]	-3.5%	-0.5%
XSG-7	8252.5[a] 9636.6[b]	18472[a] 18838[b]	16.77%	1.98%
XSG-8	6521.6[a] 7245.9[b]	10626[a] 11581[b]	11.10%	8.98%

Table 4: stability studies

Parameters	0 d	3 d	7 d	14 d	21 d	28 d
pH	7.25±0.002	7.24±0.001	7.25±0.003	7.20±0.001	7.30±0.005	7.32±0.004
Physical appearance	Reddish brown solution	Reddish brown solution	Reddish brown solution	Reddish brown solution	Reddish brown solution	Reddish brown solution
(%) Drug content	99.80±0.003	99.41±0.007	98.03±0.004	96.47±0.002	96.86±0.003	96.72±0.003
Gel formation time	Instantly	Instantly	Instantly	Instantly	Instantly	Instantly
Gel erosion time	More than 8 h	More than 8 h	More than 8 h	More than 8 h	More than 8 h	More than 8 h

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Viscosity (sol) At 12rpm	415.3	433.6	489.5	528.6	610.9	633.1
Viscosity (gel) At 12rpm	2136.1	2189.2	2304.6	2436.9	2523.7	2613.8
%viscosity variation	0.00%(sol) 0.00%(gel)	4.40% (sol) 1.21%(gel)	7.89%(sol) 5.27%(gel)	9.98%(sol) 5.74%(gel)	8.56%(sol) 3.60%(gel)	3.36%(sol) 3.57%(gel)

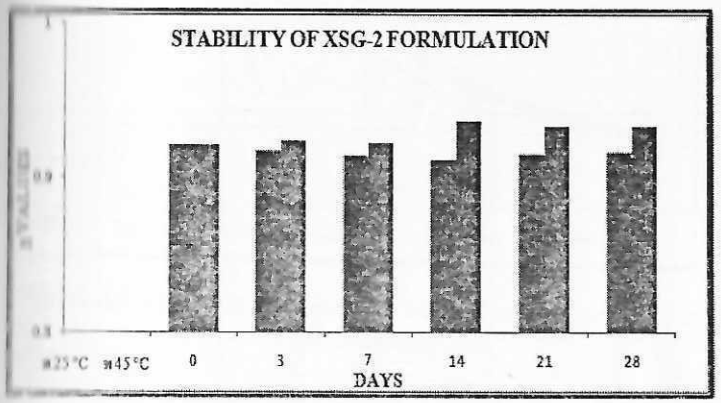
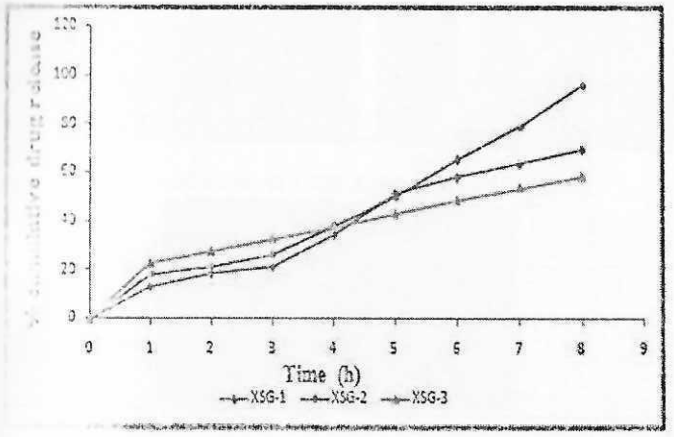


Fig. 5: Comparison of flow behavior index (n) of the optimized formulation based on accelerated stability studies(25°C & 40°C) for 28 d



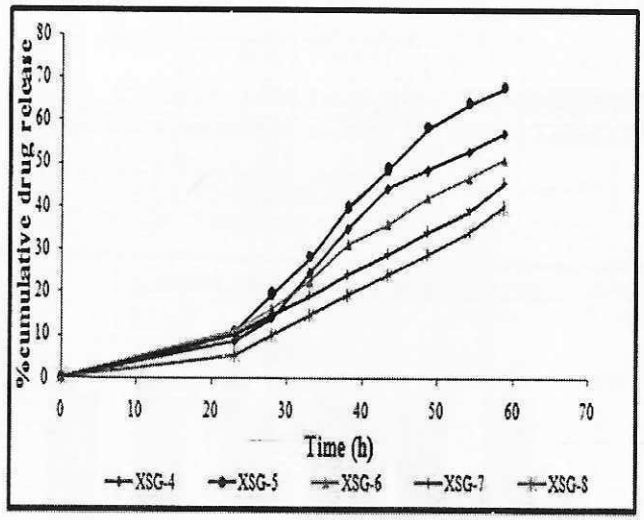


Fig. 6: Comparative *In vitro* diffusion profile of the following formulation

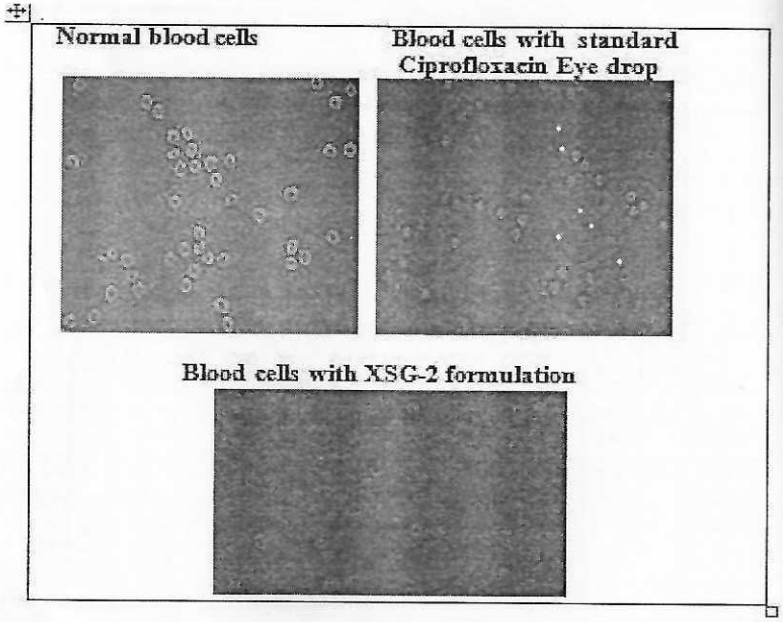


Fig. 7: Isotonicity Study

Eye irritation testing for optimized formulation

Table 5: Opacity Testing

Opacity	Normal rating for opacity	Rating for XSG2 formulation	Area of cornea involved	Normal rating for corneal area involved	Rating for XSG-2 formulation
No opacity	0 none	0	25 % or	1	0
Diffuse area, details of iris clearly visible	1 slight	0	25% to 50%	2	0
Easily discernible translucent areas, details of iris slightly obscured	2 mild	0	50% to 75%	3	0
Opalescent areas, no	3 moderate	0	Greater than 75%	4	0
Opaque, iris invisible	4 severe	0	-	-	0

Table 6: Rabbit Conjunctivaobservations

Redness	Normal rating	Rating
Vessels normal	0 none	0
Vessels Definitely Injected above normal	1 slight	0
More diffuse, Deeper crimson red with individual vesselsnot easily discernible	2 moderate	0
Diffuse beefy red	3 severe	0

Table 7: Rabbit Observation for iris

Values	Normal rating	Rating for XSG-2 formulation
Normal	0 none	0
Folds over normal, congestion, swelling, iris reacts to light	1 slight	0
Action to light, haemorrhage, gross destruction	2 moderate	0

DISCUSSION

The only form of therapy to counteract reduction of oxidative stress is by use of antioxidants there is a need to explore full potential of natural antioxidants like polyphenols. Plants are considered to be chemical factories as they contain numerous chemical compounds. Due to the toxicity, side effects and various interactions of synthetic drug today

is a growing interest in phytoconstituents of plant based medicine. derived from the plants contain more than one active that acts as a synergist between different phytoconstituents can be important part for overall therapeutic effect.

of most ocular disease involves free radical mediated damage. Catechin has an important role as an antioxidant oxidative stress is implicated in number of vision pathologies.

loaded *in situ* gel were formulated by ion gelation method polymers which achieved desired rheological behavior. Based on solubility of the drug, distilled water was selected as a vehicle in the formulation. FTIR studies revealed that there was no signs of peaks indicated compatability between drug and polymers.

All the formulations prepared were clear without any turbidity, particles or impurities. pH of the formulations were between 6.8 to 7.4 which is an acceptable range for ophthalmic preparations. The gelling capability of the formulations was examined by mixing the with simulated tear fluid which gelled instantaneously and more than 8h preserving its integrity which was suitable for study.

Rheological studies play important role in optimization of formulation. Viscosity determines residence time of the drug. Viscosity of the formulations at different angular velocities exhibited pseudo plastic flow pattern which allowed easy instillation as a liquid, which undergoes a rapid sol-gel transition due to the ionic interaction with the tear fluid. Formulation XSG-2 showed 4-6 folds increase in viscosity while others showed 1-2 folds increase in viscosity. All the formulations were subjected to sterilization by means of autoclaving at 121± C for 20 min to check the rigors of sterilization effects on formulation. Formulations XSG-2, XSG-3, XSG-4, XSG-5 and XSG-6 exhibited no significant change in viscosity after sterilization indicating good physical stability. XSG-7 and XSG-8 variation in viscosity this was probably due to the less polymer interaction which showed loss in physical stability upon sterilization.

In vitro drug release showed maximum release up to 8h exhibiting therapeutic efficacy. Significant increases in rate of drug release were observed with decrease in polymer concentration. Among the prepared formulations XSG-4, XSG-3, XSG-1, XSG-5 and XSG-2 showed cumulative drug release of 56.93%, 58.68%, 63.43%, 67.59% and 93.45% at 8 h respectively exhibited sustained release of drug due to the effect of polymers where as it was not seen with XSG-6, XSG-7 and XSG-8 since these exhibited constant drug release.

The formulation XSG-2 containing 0.2% xantham gum and sodium alginate and 0.3% gellan gum showed maximum drug release of 95.45% in 8h which may be due to the formation of hydrogen bonds between drug and polymer which have helped to sustain rate release of drug thus was considered as a optimized formulation

Isotonicity studies revealed that formulations were isotonic with that of blood cells. it was observed that blood cells maintained its integrity and there was no lysis

Ocular toxicity studies were carried out as per draize test protocol which revealed no abnormal clinical signs for cornea, conjunctiva and iris indicating formulation to be nonirritant for ocular administration.

Stability studies for optimized formulation showed that there were no significant changes in viscosity, gelling ability, pH and drug content indicating a stable formulation.

Antioxidant activity of drug catechin found that IC_{50} value of standard gallic acid was found to be 12.10 µg/ml and that of catechin was found to be 15.11µg/ml indicating potent antioxidant activity and a choice of herbal drug for treatment of ocular diseases.

CONCLUSION

Catechin, a polyphenol used in treatment of intraocular pressure related glaucoma were successfully formulated as an ion activated in situ gelling system comprising of natural polymers. XSG-2 was reported as a optimized formulation which showed 95.45% drug release at the end of 8 h. All the formulations showed decrease in viscosity with increase in shear rate thus, exhibited optimum viscosity and pseudo plastic behavior indicating good residence time. It was concluded that there was no significant change in viscosity after sterilization retaining its physical stability. Formulation was nonirritant for ocular administration. Further studies showed that catechin had a potent antioxidant property. The sustained period of drug release may be due to the slow diffusion of drug from combined effect of polymers, which is due to formation of hydrogen bonds between the drug and polymers thus helped in sustain release of a drug and a viable alternative to conventional eye drop.

ACKNOWLEDGEMENT

The authors would like to acknowledge Principal Dr V. G. Jamakandi for providing necessary facilities to carry out the research work.

CONFLICT OF INTEREST

None

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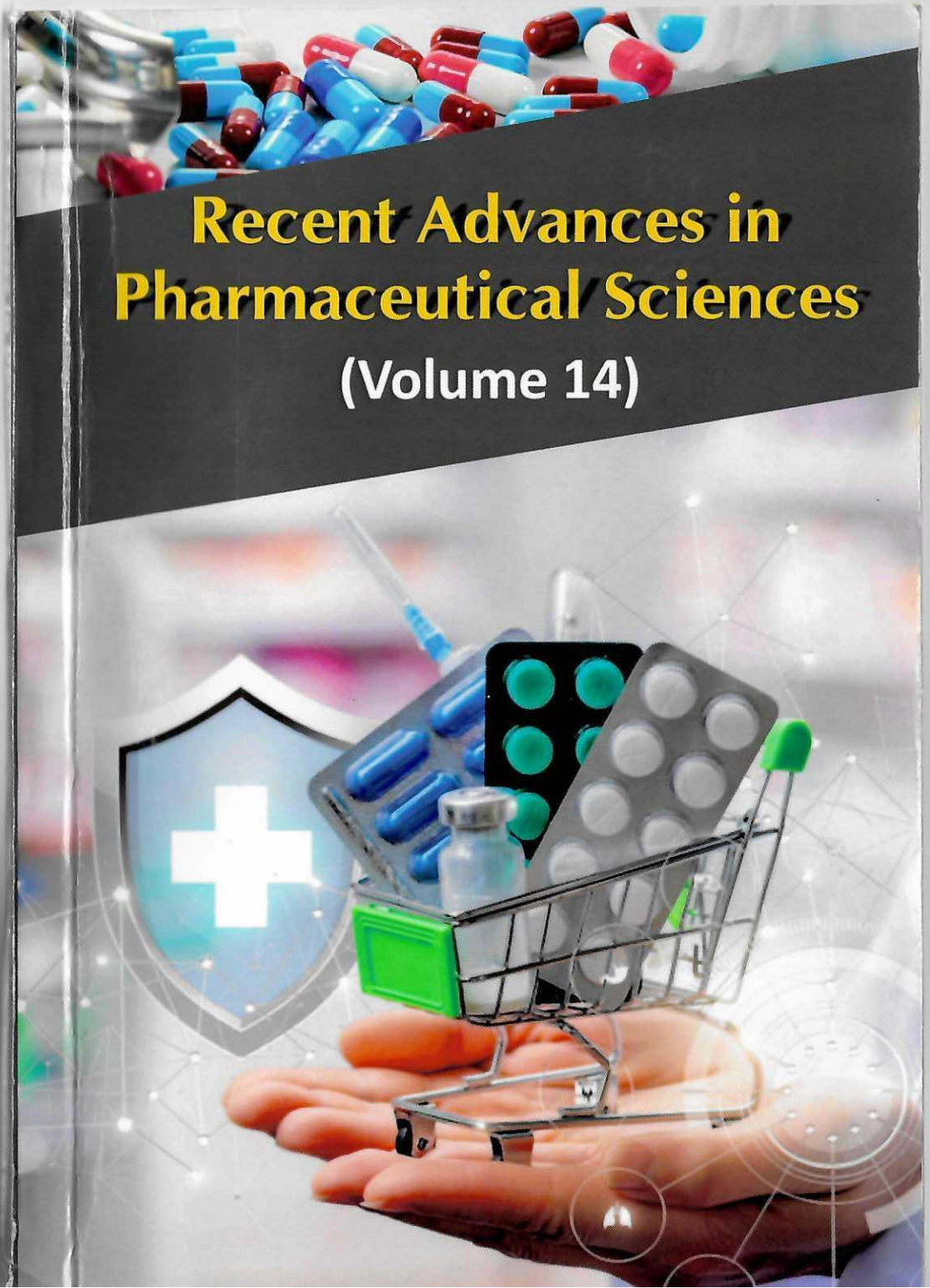

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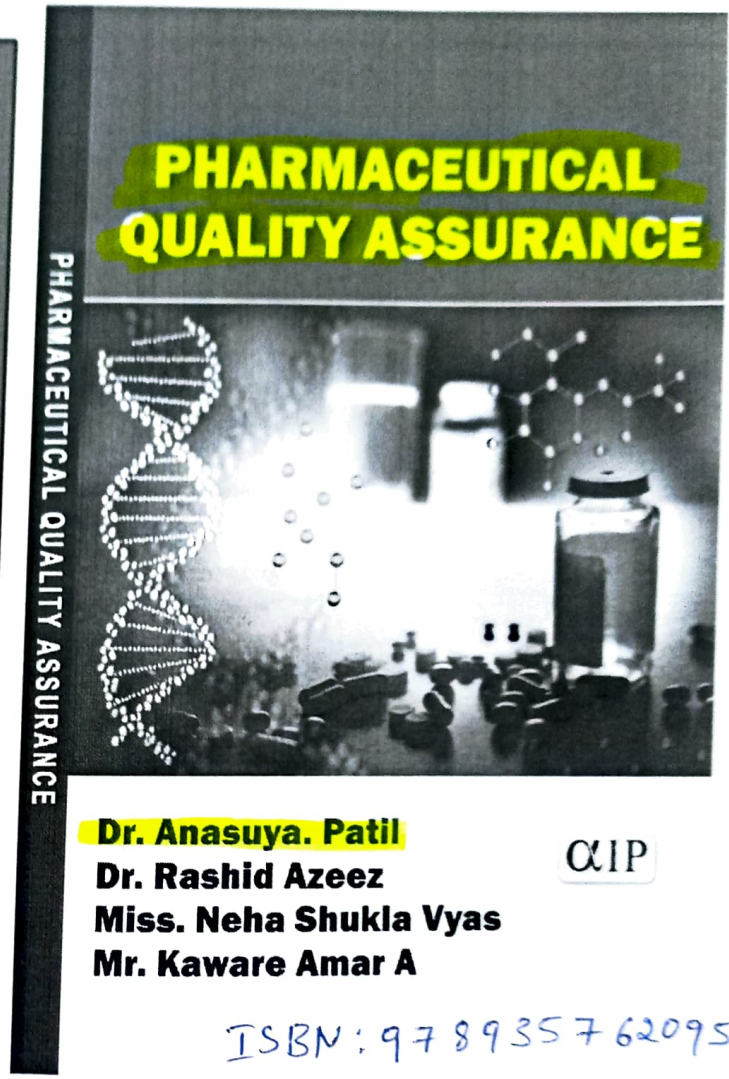

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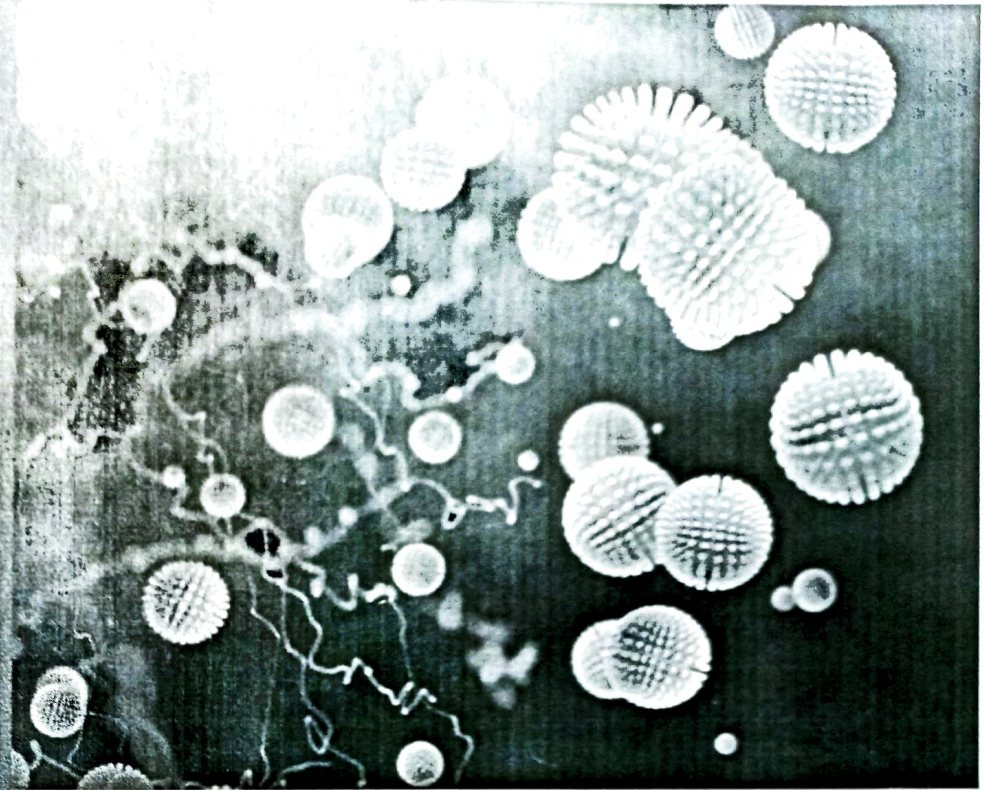

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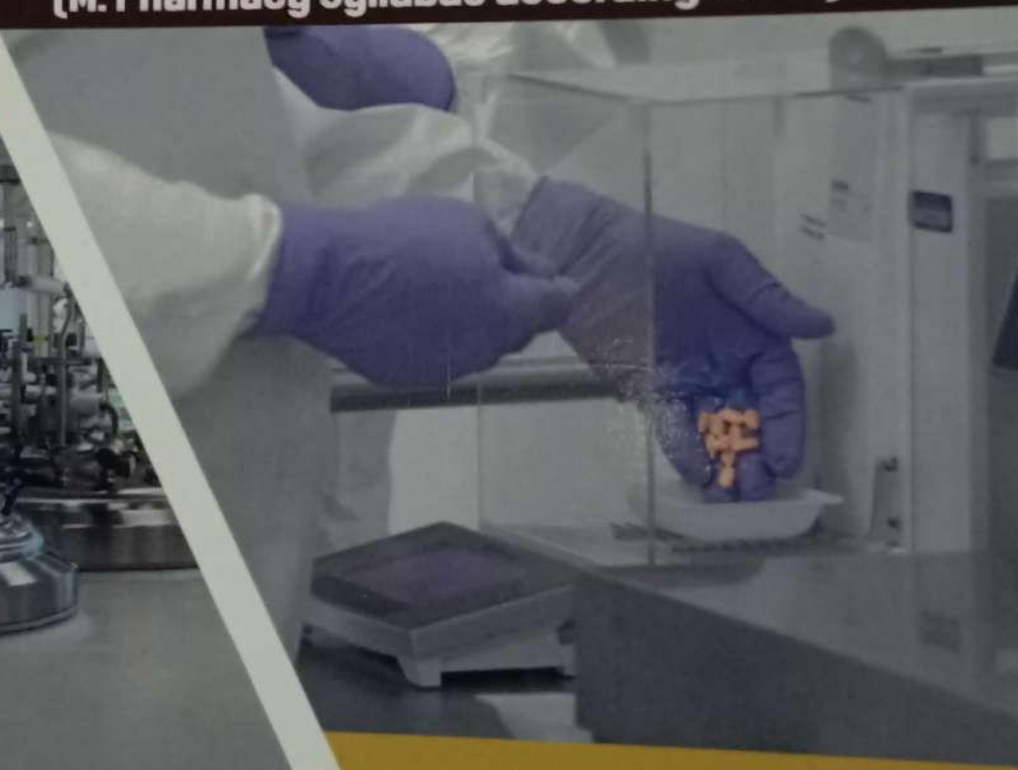

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About the Book :

The laws and regulations governing the pharmaceutical industry were adopted to protect the consuming public by attempting to provide drugs of constituent quality, purity, and efficacy. The Food, Drug and Cosmetic Act (the Act) is a living document in that it is amended frequently and interpreted constantly. The act may be imperfect, but careful attention to its provisions plus an effort of good faith by all persons concerned with drug manufacturing can produce the type of product for which the Act and its regulations strives. Even though the applicable laws and regulations may change with regard to specifics, there are, nonetheless, many constant applicable generally. This book serves an overview of the more significant laws, regulations and Acts. This text book describes the Food, Drug and Cosmetic Act, treats briefly regulations bearing on pharmaceutical manufacturing, looks at the structure, powers, and duties of the Food and Drug administration (FDA), describes state and local laws and regulations, and finally, covers the protection of industrial property and product liability.

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TEXTBOOK ON PHARMACEUTICAL INTELLECTUAL PROPERTY RIGHTS

INTELLECTUAL PROPERTY RIGHTS OF PHARMACEUTICALS

Dr. Anasuya Patil | Dr. Nayyar Parvez
Dr. Sachinkumar Dnyaneshwar Gunjal
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Dr. Rajni Arora | Ms. Nagam Santhi Priya

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About the Book :

The purpose of writing this book is to provide graduate /post graduate level education in the important aspects of legal and regulatory issues that are critical to the pharmaceutical industries. The book focuses on key legal concepts such as intellectual property and the range of regulatory affairs and provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world. These individuals are new or relatively new to the profession with limited or no regulatory affairs knowledge. Many have education and/or experience in science, clinical studies or engineering and understand specific aspects of the healthcare product arena. Throughout the book, these individuals develop basic knowledge and understanding of the regulatory and legal frameworks, regulatory requirements, legislation, processes and procedures.

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TEXTBOOK ON PHARMACEUTICAL REGULATORY AFFAIRS

REGULATORY AFFAIRS OF PHARMACEUTICALS

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GCS PUBLISHERS

MSME REGISTERED COMPANY |UDYAM-AP-04-0018434

ISO 9001-2015 certified|GST NO: 37ISEPK7907Q1ZS

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ISBN 978-81-960493-7-9

Dr. GANESH B. R., Professor

Cardiopulmonary Physiotherapy

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Advance Research Trends in Medical and Clinical Sciences
Volume-2

Editors

Dr. Amit Singh

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MKSES Publisher (India)

MKSES Publisher (India)

Publisher Address: Head Office: 1st Floor, Building No-85A, (Nanak Arcade near Sani Mandir, Parag road, LDA colony, Kanpur Road, Lucknow-226012

Mobile No: +91 9838298016, +91 8299547952 Office Land line No: +91 5223587193

E-mail:mkespublication@gmail.com

Website: www.mksespublications.com

First Published: **February 2023**

ISBN: 978-93-91248-56-7
Page No. 1-118

Preface

Current trends in clinical & medical sciences is a highly interdisciplinary research field is dedicated to disseminating in-depth information and insights into all areas of current medical and clinical sciences. Clinical research is that component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health. The importance of clinical research is that it brings basic biomedical discoveries to the bedside to address patient care from the physical, behavioral, and social perspectives.

The present volume is based on the contributions made by various authors on different important topic of **"Advance Research Trends in Medical and Clinical Sciences Volume-2"** and introduces the subject along the following topics: Role of inflammation and C-reactive protein in schizophrenia; Terrorism: Impact on Mental Health and its combating strategies; Effect of aging on physiological and pathological ocular conditions; Menopause and Quality of Life; Vaccines and Drug development in the treatment of Ebola; Factors associated with incidence of cancer in India; Anopheles: The Deadly Demon and An Introduction to neck pain and posture among Granthies; and The Clinical Effect of Music: Music Therapy.

We must place on record our sincere gratitude to the authors not only for their effort in preparing the papers for the present volume, but also their patience in waiting to see their work in print. Finally, we are also thankful to our publishers **Mrs. Shweta Singh** M/S MKSES Publishers, Lucknow for taking all the efforts in bringing out this volume in short span time.

Editors

Contents

Chapter: 1
Role of inflammation and C-reactive protein in schizophrenia

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Abstract: Schizophrenia is a psychiatric disorder that affects 1% of global population. The etiology of schizophrenia is largely unknown. However, with the augmentation in an understanding of bi-directional communication between the neuronal and immune system, there is a renewed interest in the immune-inflammatory hypothesis of schizophrenia. It is proposed that peripheral inflammation may cause increased permeability of the blood-brain barrier leading to inflammation in the CNS via the release of cytokines by microglial cells. This in turn may affect the processes such as neurogenesis, neurodevelopment, neurotransmitter function, etc. leading to pathophysiology of schizophrenia. There is evidence that an increase in stress hormones may activate the immune system's inflammatory component and trigger the activation of genes that lead to persistent, low-grade inflammation. Thus, the inflammation associated with schizophrenia has been given the name 'chronic systemic encephalitis'. Thus, many of the studies have observed an increased inflammatory response in schizophrenia, characterized by an increase in C-reactive protein, a common inflammatory marker. Even though studies have provided the evidence for the role of inflammation in pathophysiology of schizophrenia, it is too early to consider schizophrenia as an inflammatory disorder. Future, investigations with well-designed studies will usher in our understanding of the role of inflammation in schizophrenia.

Keywords: C-reactive protein, inflammation, IL-6, schizophrenia

Introduction

Schizophrenia is a chronic and severe mental disorder often characterized by abnormal social behavior and failure to understand reality, leading to faulty perception, inappropriate actions and feelings. The word "schizophrenia" comes from the Greek root "schizen" meaning "to split" and "phren" meaning "mind", which translates roughly as "the split of mind". Eugen

Bleuler (1911) originally used the term "schizophrenia" to describe the separation of function between personality, thinking, memory, and perception in the patients. Schizophrenia paralyses the normal life of the patient and hinders general activities such as attending school, working, having children etc. Thus, it is called as the king of all mental illness. Schizophrenia affects approximately 1% of world's population. However, studies suggest that prevalence of schizophrenia can vary across cultures. The symptoms of schizophrenia can be broadly categorized into positive and negative symptoms. The positive symptoms are characterized by hallucination, delusions, disorganized speech and behavior, and the negative symptoms includes removal of normal processes, decrease of emotion, loss of interest, etc. Schizophrenia is lifelong disorders which occur quite early in males (late teenage to early 20s) than the females (late 20s to 30s). However, it affects both the gender equally. Schizophrenia patients have high rate of completed suicide (9-13%), and the attempted suicide rate is as high as 50% during lifetime.[1]

Despite decades of extensive research, the actual causes of schizophrenia are largely unknown. Multiple interacting genes and environmental factors are proposed to cause schizophrenia. However, studies are unable to find the specific gene(s) or environmental factor(s) that may be associated with the disorder. Nevertheless, various other risk factors viz. neurodevelopmental abnormalities, season of birth, neurotransmitter abnormalities, viral infection, inflammation, and immunological abnormalities have been linked with schizophrenia.

Microbial infections and schizophrenia

In recent years, there has been an increase in understanding about the bi-directional communication between the central nervous system and immune system in chronic disorders such as schizophrenia, which has renewed our interest in the immune-inflammatory mechanism of schizophrenia. The concept that the immune-inflammatory mechanisms might play an important role in the pathophysiology of schizophrenia was put forward when the studies observed that schizophrenia occurs more frequently among individuals who are born in the winter and early spring.[2] Further, seasonality in schizophrenia has been correlated with certain infective microbial agents which are more common in a specific season. Thus, infection with these microbial agents is speculated cause inflammation. More specifically the inflammation is thought to be brought about by viral agents during the embryonic stage or childhood days that may cause inflammation in the central nervous system (CNS) and impede

the normal brain and neuro-developmental processes, which may manifest in the form of schizophrenia in adulthood.[3] This hypothesis got support when certain abnormalities were found to be associated with the schizophrenia brain.[4] Studies on influenza, rubella, measles, and herpes simplex viruses have revealed that viral infections during childhood and even preceding the onset of the illness may be an etiological factor for schizophrenia.[5] In a study performed in Northern Finland, it was observed that infection of the central nervous system (CNS) in childhood increases fivefold risk of having a psychiatric disorder in the later stage of life.[6] Even though the previous studies did add to the inflammatory hypothesis of schizophrenia but it has failed to consistently mark a particular infectious agent responsible for schizophrenia. The poor success rate of previous studies may be due to the fact that an infectious agent may remain hidden in the cells or body for long period, or else intracellular infectious agents may silently be hidden in cells of the lymphoid or the nervous system and exacerbate only under certain conditions, such as stress.[7] To address this issue antibody titers against the pathogens were examined in the sera of schizophrenia patients. The results indicated increased antibody-titers against Cytomegalovirus (CMV) and *Toxoplasma gondii* in non-medicated individuals with recent onset of schizophrenia, while no association was found in medicated patients.[8] One of the strengths of the microbial infection hypothesis for schizophrenia is the fact that some microbes specifically viruses have been shown to possess the ability to target specific types of neurons in the CNS. There is now considerable experimental and clinical evidence to show the significant risks of prenatal infection/inflammation as triggers for the development of schizophrenia. Future studies to determine the prophylactic measures to prevent and/or mitigate microbial insults are necessary to reduce the risks for schizophrenia.

Inflammation, immune system abnormality and schizophrenia

Studies have observed an abnormality in markers of inflammation in the blood, cerebrospinal fluid, and central nervous system (CNS) of schizophrenia patient.[9] Further, increased prevalence of certain comorbid infections and associated inflammation are observed in patients with schizophrenia.[10] Additionally, in some subgroups of schizophrenia patient studies have observed an improvement in the condition after the treatment with anti-inflammatory drugs.[11] These findings provide evidence that in some sub-groups of patients with schizophrenia, inflammation may play a key role. Thus, to describe the inflammatory process in schizophrenia the term 'mild localized chronic encephalitis' has been proposed.[12] However, investigations conducted to date to understand the inflammatory process in

schizophrenia have been circumambient with the heterogenous results with some reporting negative results. The non-agreement of the results may be due to small sample size, differential course of disease condition, confounding factors viz. smoking, obesity, medication, comorbidities, and the presence of inflammation only in some subgroups of patients.[13]

Maternal immune response and schizophrenia

Studies based on animal models and in pregnant women pointed out that not only the infectious agents but also the maternal immune response increases the risk of schizophrenia in the offspring.[14] It has been observed that those women who have elevated levels of IL-8 during the second trimester of pregnancy, their offspring have an increased risk for schizophrenia.[15] In addition, it was also observed that fetal exposure to elevated maternal IL-8 leads to structural neuroanatomic alterations of the brain, a condition commonly observed in schizophrenia.[14] The role of maternal immune response in schizophrenia was further evidenced by the studies where it was observed that the induction of maternal immune response with LPS increased IL-1, IL-6, and tumor-necrosis-factor-α (TNF-α) in pregnant mothers, which in turn led to an increase of IL-1 in the fetal serum.[16] Though the above-mentioned studies provide a clue for the involvement of maternal immune response in schizophrenia, the exact mechanism of early immune stimulation and characteristic deficits in adulthood is still unclear.[17] It has been hypothesized that since brain development continues for the first year of life, an infection during early fetal life may lead to the cytokine imbalance in CNS. This may, in turn, cause the cytokines to invade the brain tissues or disrupt the blood-brain barrier and ultimately hampers the development of the brain which leads to schizophrenia.[18] It is now well evident that HLA-G molecules are the novel immune players which maintain immune homeostasis during early pregnancy and can protect the developing fetus from maternal immune attack. It is hypothesized that maternal infections during pregnancy may lead to the disturbance of HLA-G expression which in turn may fail to maintain its otherwise inhibitory potential to down-regulate the detrimental inflammatory cytokines that may neurodevelopmental impairment.[19]

Inflammatory markers and schizophrenia

Although pro-inflammatory cytokines and other acute-phase proteins have become one of the focal points of research in schizophrenia, recently C-reactive protein (CRP) has gathered increased attention as it plays a vital role in the inflammatory response. CRP is an acute

phase protein and a nonspecific marker for systemic inflammation. Its level increases in response to infectious and non-infectious exposures. CRP is synthesized by the hepatocyte cells of the liver in response to the IL-6, IL-1, and TNF-α. It is a homopentamerous non-glycosylated protein with 224 residues. Each of the units of CRP has a molecular weight of 25,039 Da. Although many of the studies have attempted to understand the role of CRP in schizophrenia the results are not in concordance with each other. In one of the earlier studies among Nigerian patients with acute functional psychoses, CRP levels were found to decrease after the treatment with unmodified Electro Convulsive Therapy.[20] The elevated levels of CRP in schizophrenia patients were observed in many of the studies. In a longitudinal study, increased CRP levels were observed in patients experiencing psychotic symptoms, however when the patients came to the non-psychotic state the CRP level came down to normal level. The findings suggest that the increased CRP in the psychotic state is a state-dependent expression of nonspecific humoral immune alteration in schizophrenia.[21] This finding was further strengthened in the subsequent replicative studies where an increased level of CRP was observed in schizophrenia patients with severe clinical symptoms.[22,23] On the contrary, some other studies could not replicate this finding,[24] nonetheless, an association was observed between levels of CRP and the severity of cognitive impairment.[25] Subsequent investigations by the same research group observed an association between increased levels of CRP and Herpes simples virus exposure with the severity of cognitive impairment in schizophrenia. Thus, the findings indicate that infection and inflammation may play a major role in the cognitive deficits associated with schizophrenia.[26] Further investigations are required to understand the relationship between inflammation with cognitive impairment. In our investigation among the India-born Bengali patients, we observed an increased level of CRP among the antipsychotic medicating patients than the psychotropic medication-free patients. The results suggest that antipsychotic medications may have an immunomodulatory effect on CRP levels.[27] The results corroborated with the studies in Arab and Taiwanese schizophrenia patients.[28,29] Contrastingly, a meta-analysis study did not observe the modulatory effect of antipsychotics on CRP levels in schizophrenia.[30] The nonagreement of the results may be due to the genetic heterogeneity of the populations included in the meta-analysis. It is observed that basal CRP levels are modulated by CRP gene polymorphism.[31] On the other hand, studies have observed a correlation between CRP levels in schizophrenia and the development of metabolic syndrome leading to the conclusion that schizophrenia patients are at a greater risk of developing metabolic syndrome.[32] It is now well known that metabolic syndrome is the most important predictor for the development of cardiovascular disease and

type II diabetes and is found to be more prevalent in psychiatric patients than in the general population.[32] A recent meta-analysis of fifty studies also observed a higher CRP level in schizophrenia, which suggests that CRP could be considered a state marker and a trait marker for schizophrenia.[33] In contrast, few of the studies did not find any significant association between CRP and schizophrenia.[34,35] The inconsistencies in the findings may be due to possible confounding factors viz. BMI, substance abuse, effect of specific antipsychotic medication, etc. which were not taken into consideration in most of the previous studies. Table 1 represents studies of CRP in schizophrenia.

Table 1: Studies of C-reactive protein in schizophrenia

Study conducted by	CRP tested in	Level of CRP	Associated CRP observed with
Mazzarello et al., 2004	Serum	↑	Schizophrenia
Okasha et al., 2006	Serum	↔	Nil
Fan et al. 2007	Serum	↑	PANSS
Dickerson et al., 2007	Serum	↑	Lower RBANS cognitive scores
Akanjiet al., 2009	Serum	↑	No association with PANSS & SANS
Vuksan-cusa et al., 2010	Serum	↑	Metabolic syndrome
Solanki et al., 2010	Plasma	↑	No association with PANSS
Fawzi et al. 2011	Serum	↑	PANSS and waist circumference
Meyer et al. 2009	Serum	↑	Antipsychotics
Baptista et	Serum	↑	Olanzapine

al. 2007			treatment
Hope et al., 2009	Plasma	↔	Nil
Carrizo et al., 2008	Serum	↑	Atypical antipsychotic and poor lifestyle habits
Dickerson et al., 2012	Serum	↑	Exposure to HSV & severity of cognitive impairment
Lin et al., 2013	Serum	↑	Chronic schizophrenia under antipsychotic treatment
Wium-Andersen et al., 2013	Plasma	↑	Late and very late onset schizophrenia
Gurung et al., 2018	Serum	↑	Antipsychotic medicating patients

↑= Increase, ↔ = Normal

Mechanism of the association of CRP in schizophrenia

Historically, the brain has largely been considered an immune-privileged organ. Recent studies have shown the presence of lymphatic vasculature in the meninges which suggests a connection between the peripheral immune system and the CNS.[36] Immunological communication via cytokines to the brain is virtually impossible due to the large size of the pro-inflammatory cytokines. As such they have difficulty crossing the blood-brain barrier.[37] However, the peripheral and central communication is brought about by two pathways viz. humoral and neural. The humoral pathway involves the passage of cytokines through leaky regions of the blood-brain barrier (such as the circumventricular organs) or cytokine binding to transport molecules on the blood-brain barrier. The transport of cytokines involving the blood-brain barrier pathway is of special interest in schizophrenia as many of the studies have shown disruption of blood-brain barrier integrity and function in schizophrenia patients.[38] The neural pathway of CNS communication involves the binding of inflammatory cytokines to

peripheral afferent nerve fibers, which in turn translates signals into central inflammatory signals. Recently, the third pathway of CNS communication is discovered which is brought about by the monocytes under the influence of chemokines called chemoattractant protein 1 produced by microglial cells of the brain.[39]

Hitherto the role of inflammation in the pathophysiology of schizophrenia is not clearly understood. It is suggested that vascular-structural brain abnormalities may be one of the etiological factors for schizophrenia.[40] It is hypothesized that chronic inflammation may cause impairment to the microvascular system of the brain and cerebral blood flow.[41] Conversely, inflammation may interfere with neurotransmitter synthesis and neurotransmission.[42] Additionally, research indicates that an increase in norepinephrine after being exposed to stresses may activate the immune system's inflammatory arm and cause the expression of the genes that cause chronic, low-grade inflammation which is characterized by an increase in the levels of CRP.[43] Thus, elevated level of CRP in schizophrenia suggests the involvement of neuroinflammatory mechanisms in the etiopathology of schizophrenia.[44] It is hypothesized that the increase in CRP due to the inflammatory response of the body may increase the permeability of the blood-brain barrier facilitating the access of proinflammatory cytokines to the brain.[45] It is observed that CRP may induce a proinflammatory response in microglia.[46] Therefore, CRP may directly trigger neuroinflammation in the central nervous system.[30]

Conclusion and future prospects

To date, a common agreement has not reached on the inflammatory hypothesis of schizophrenia. At this moment there is a lack of enough evidence to consider schizophrenia as an inflammatory disorder. However, studies have shown that inflammation triggered by some pathogens may play a key role in the etiopathology of schizophrenia, at least in some subset of the patients.[13] It is hypothesized that pathogenic infections during embryonic development may modulate the immune response and neurodevelopment process which may lead to schizophrenia. However, the specific pathogenic organism responsible etiopathology of schizophrenia have not been identified. It is now presumed that multiple etiological factors viz. sociological stressors, infections, genetic, immune, neurodevelopment abnormality etc. may contribute to etiopathology of schizophrenia. Of the all these, some specific factors may play a vital role in different subtypes of schizophrenia.

Studies to date, have provided ample evidence that some neurotransmitter and immunological abnormality are associated with schizophrenia. Therefore, there is a need of contemporaneous studies of neurological and immunological parameters in schizophrenia to throw light in the neuro-inflammatory pathophysiology of schizophrenia. To date much of the studies are focused on the Western populations to understand the role of inflammation in schizophrenia. There are limited studies available from the Asian countries such as India which is having diverse groups of ethnic populations. Therefore, extensive research encompassing a various ethnic population will be necessary to fully comprehend how inflammation contributes to schizophrenia. Future meta-analysis studies of CRP in schizophrenia should also take the population's ethnicity into account as the basal level of CRP in different population is influenced by the CRP gene polymorphism. The role of CRP in the complex disorders is not yet been fully understood. The advent of modern tools and techniques in molecular biology may help to understand the role of CRP in schizophrenia. In conclusion, to date the etiology of schizophrenia remains unclear, future studies focused on neuro-immunological basis of schizophrenia holds a good prospect to understand the etiopathological mechanism of schizophrenia.

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Chapter: 2
Terrorism: Impact on Mental Health and its combating strategies

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Abstract: This chapter explores the ideology of terrorism and various factors which affect its impact on mental health. The integrated approach is a way forward to identify the population at risk and intervene at sociocultural, political, religious, and economic levels, etc. It is important to understand novel strategies for targeted care delivery in a vulnerable population. Therefore, specialized mental healthcare services are required for smaller populations whereas base-level services are for communities.

Keywords: Terrorism, Post-traumatic stress disorder, Social media, Memory modification techniques

Introduction

Terrorism is intentional violence to provoke fear amongst non-combatants.[1] The word terrorism is identified with the French Government's 'Reign of terror' during the revolution (1793-1794) to execute enemies of the State. It can deeply impact the mental health of victims from a biological, psychological, social, religio-political, and economic point of view. Therefore, developing strategies to combat the consequences of terrorism are important for making public health policy.

Terrorism and its Ideology

Terrorism is an aggressive strategy used by an individual or a group to change the perspective of communities, nations, politics, or policies with violent activities. The event of casualties creates terror in the minds of the people. Ideology plays a crucial role in the mind of a terrorist to select a target for his action. People or institutions that have transgressed terrorist ideology are legitimate targets. A four-staged model was proposed in the development of the ideology of an extremist (Figure 1).[2] Deprivation leads to inequality, blaming others for injustice, branding them as evil, and dehumanizing them for direct violent action.

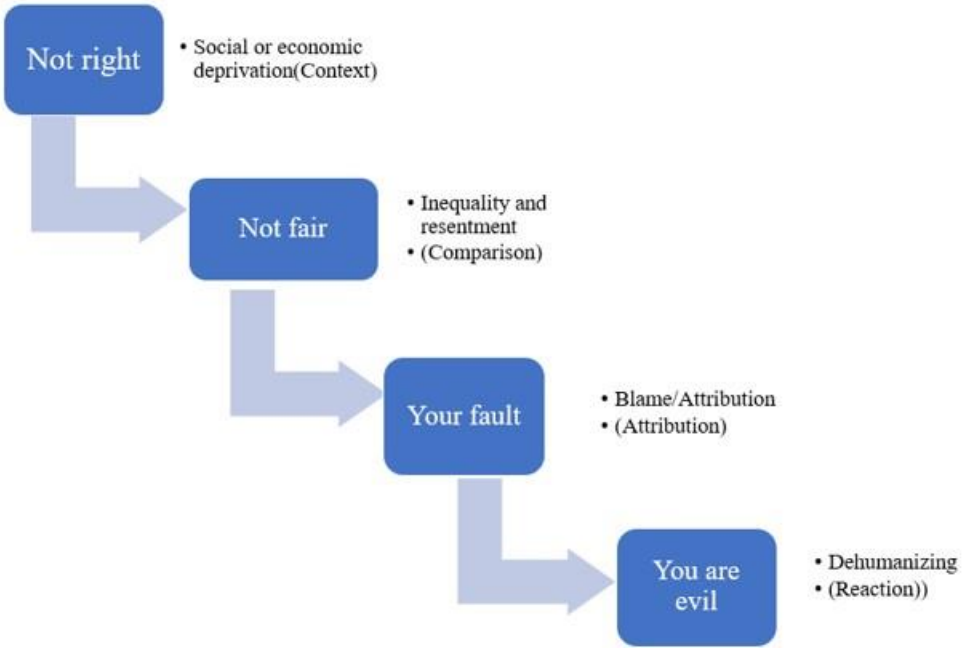

Figure 1: Development of an ideology of extremist

William Perry (1970) had elaborated on the scheme of intellectual and ethical development, from dualism, to multiplicity, to relativism, and finally to commitment.[3] Applying these principles to Radicalization, Lazzari et al suggested that the 'Radicalized' usually and necessarily remains in the 'Dualistic' stage (Table 1).[4]

Table 1: Perry's principles of ethical development in radicalized persons

Perry's stage	Normal development	Radicalized development
Dualism	The knowledge received is not questioned	The person accepts radicalized thoughts, ideas, and norms as 'truth' and rest as 'evil'
Multiplicity	Recognition that there is more than one solution to a problem	Multiplicity frozen. For a problem, there is only one solution, all other solutions are wrong
Relativism	Contextual nature of knowledge	The radicalized person lacks proper ethical/ social

		development. If the family milieu is radicalizing, then the individual is radicalized by the prevailing ideologies.
Commitment with relativism	Integration of one's knowledge with data from external sources	Personal knowledge is not questionable. There is cognitive rigidity to incorporate only ideas and information that does not conflict with the radicalized core values of self and culture.

Global terrorism

Terrorism has become a global phenomenon with the advancement of technology and communication due to which terrorists, weapons, and funds move across national boundaries very easily. Data for such activities are collected and maintained by The National Consortium for the Study of Terrorism and Responses to Terrorism (START) at the University of Maryland in the United States.[5]

A terrorist attack can be classified based on the following three criteria:

1. The attack aimed to attain political, economic, religious, or social goals.
2. These attacks carry some intention to convey an aggressive message to the concerned public through victims of the incident.
3. The action must be outside the context of legitimate warfare activities.[6]

The Global Terrorism Index reported the total number of deaths due to terrorism in 2017 was 18,814 wherein 84% of deaths were from ten countries with the proportion as, Afghanistan (25%); Iraq (23%); Nigeria (8%); Somalia (8%); Syria (6%); Pakistan (5%); Egypt (3%); Democratic Republic of Congo; Central African Republic (2%) and India (2%). A substantial hike was observed in North Africa, the Middle East, South Asia, and Sub-Saharan Africa between 2002 and 2017. [7]

Terrorism in India

In this era of a globalized world, no country is immune to the threat of terrorism. India has borne the brunt of terrorism and has witnessed the extensive loss of lives and property in the past few decades. India faced terrorism and violent extremism during the religion-based partition in 1947, which created: India and Pakistan. Pakistan lays claim to a Muslim-dominated Kashmir. In addition, causes for insurgencies are politico-religious violence, ethnic-subregional nationalism, socio-economic conditions, and politics of identity. Terrorism in India can be broadly categorized into three parts [Figure 2].

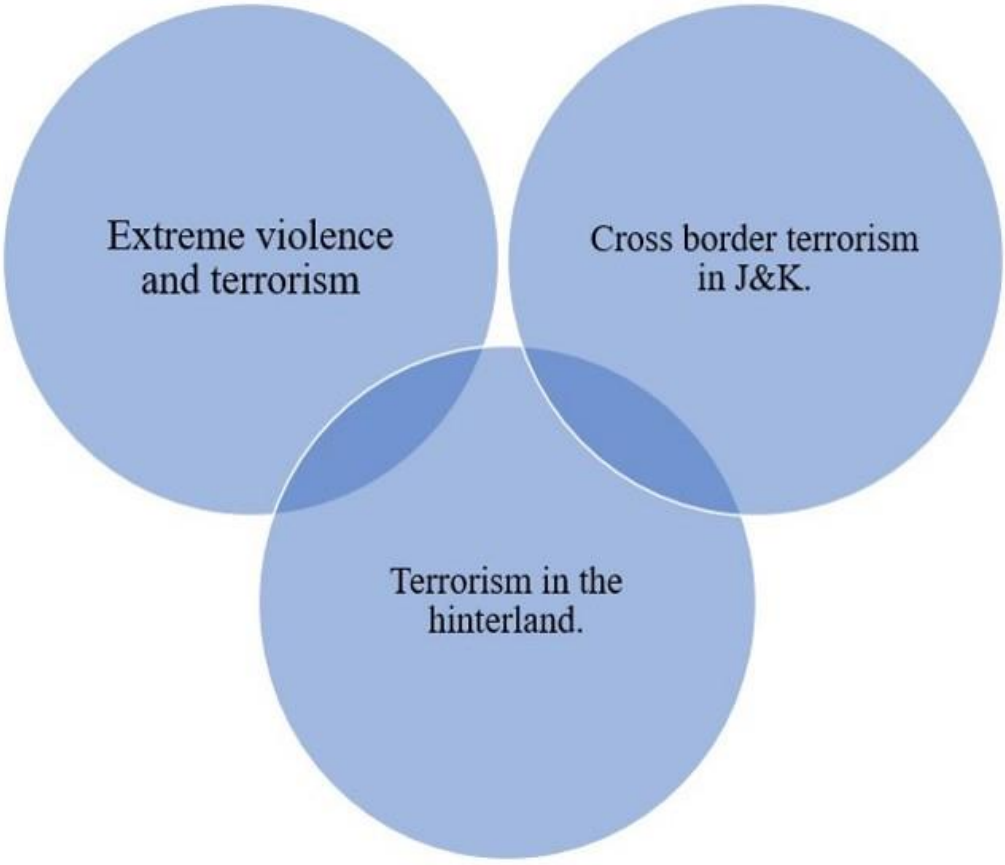

Figure 2: Pattern of terrorism in India

Other factors accounting for terrorism:

The modus operandi of terrorism is dynamic to achieve its goals [Figure 3]. They identify with vast cultural groups, tribes, ethnicities, religions, nations, and ancestries. Many a time incidents relating to a particular religious or ethnic group act as catalysts. The youths are also radicalized by 'hate speeches' and contextual manipulation of specific events. Politics is used to advance their interests. As in the past, their behavior is shaped by the pursuit of power and wealth.

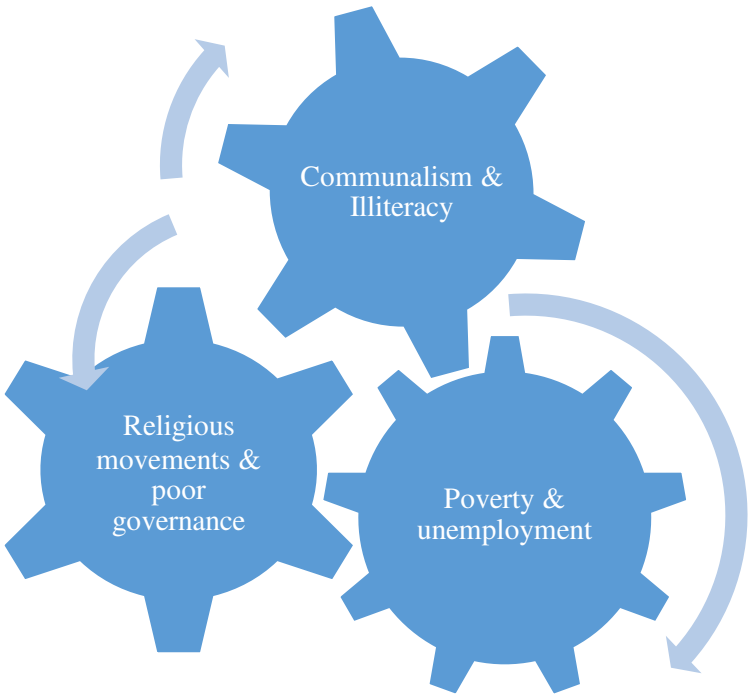

Figure 3: Showing various factors responsible for terrorism

There are various forms of terrorist attacks such as hijacking and blowing up of aircrafts, sabotaging railway tracks, kidnapping hostages for political demands, suicide attacks, attacks on places of worship and financial hubs, and communal riots are the most common modus operandi.

Challenges of Terrorism

- Lack of global definition of terrorism: The classification of any terrorist activity becomes difficult in different regions of the world as there is no universally accepted definition of terrorism,
- Networking of Terrorism: Terrorists can disseminate propaganda through limitless websites and social media platforms due to increased accessibility and attract new recruits to join these organizations.
- Terror Financing: Huge funds get disbursed in terrorism. According to the International Monetary Fund (IMF) and World Bank survey, it was found that criminals stacked about two to four trillion dollars each year through charities or other alternatives.
- Bio-Terrorism: Biotechnology poses a threat as biotic agents can be transported and discharged in small amounts into vulnerable populations in a concealed pattern.

- Tropical agricultural pathogens or pests can also be used to damage crops to hamper food security and get the nation to the step of starvation.
- Cyber Attack: The world is now influenced by the high tides of cyberspace and terrorists use this space for unlawful attacks in a country to coerce a government or its people.

Impact on Mental health

Terrorism can have widespread mental health effects. The main effects are short-lived but victims may continue to experience both clinical and subclinical symptoms. Whalley & Brewin estimated that 30-40% of people develop post-traumatic stress disorder (PTSD), and at least 20% may be experiencing these symptoms two years later. Less is known about the mental health impact on children. Rescue workers are at risk of developing these disorders. [8-10] However, their prevalence rate differs across the population.[11,12] Lowell and colleagues analyzed victims of 9/11 and reported PTSD to be the most common mental disorder even over a period of 15 years. There are various psychological responses exhibited such as acute stress disorder, PTSD, generalized anxiety disorder, major depression, and substance use disorder.[13,14] Researchers have shown the association between cultural, and socio-economic characteristics, and the prevalence of trauma-related disorders with suicide. [15] The socio-economic association has been confirmed for general anxiety disorder and adult ADHD.[16]

Identification and Intervention

A thorough investigation of victims of terrorist attacks will help in identifying at-risk populations. It is extremely difficult to conduct research on the psychological consequences of terrorism in these chaotic settings of unpredictability. The initial approaches to mitigate the mental health consequences of terrorism involve patient education and support, referral for formal psychiatric evaluation and counseling, and pharmacological intervention. Finally, the incorporation of an integrated model of assimilating various communal, cultural, spiritual, and religious healing practices is helpful.[17-18]

Figure 4 represents a Pyramid model. The top focuses on specialized clinical mental healthcare services for a smaller population whereas base-level services are for the general need of the communities etc.

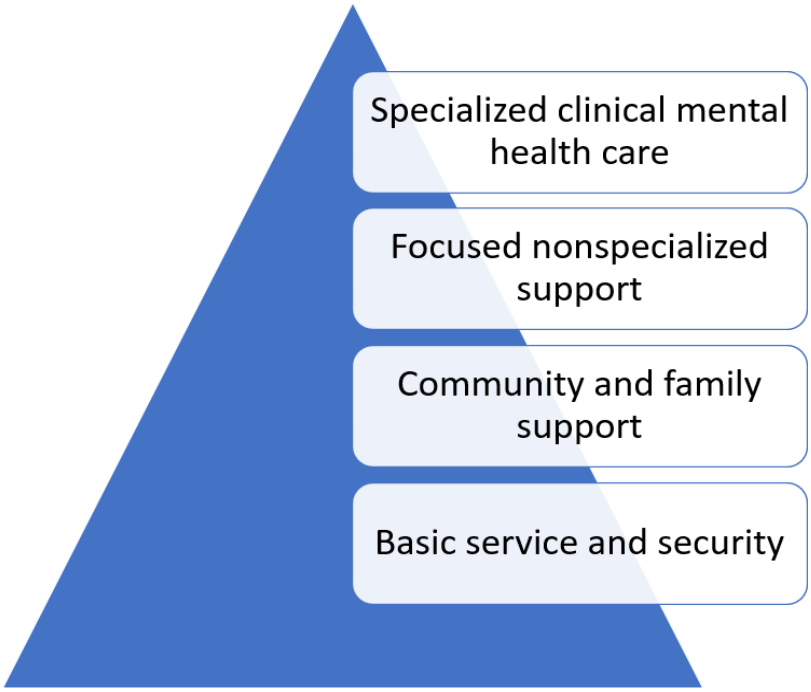

Figure 4: Intervention strategy for terrorism affected people

Strategies to Combat the Threat of Terrorism

Various International Initiatives were developed to counter Terrorism i.e., the United Nations Office of Counter-Terrorism (UNOCT), the Terrorism Prevention Branch (TPB) of the United Nations Office on Drugs and Crime (UNODC), the Financial Action Task Force (FATF), and India's Annual Resolution on Counter-Terrorism.

After the 26/11 terrorist attack in January 2009, the National Investigation Agency (NIA) was established to tackle terrorism in the nation.

In India, the Unlawful Activities (Prevention) Amendment (UAPA), Act is the primary anti-terrorism law.

National Intelligence Grid (NATGRID) has been established for collecting security-related information.

To ensure a rapid response to terrorist attacks, an operational hub has been created for the National Security Guard (NSG).

The pathway to violence and strategies to prevent and/or behaviourally intervene has been explained in various stages. [19-20]

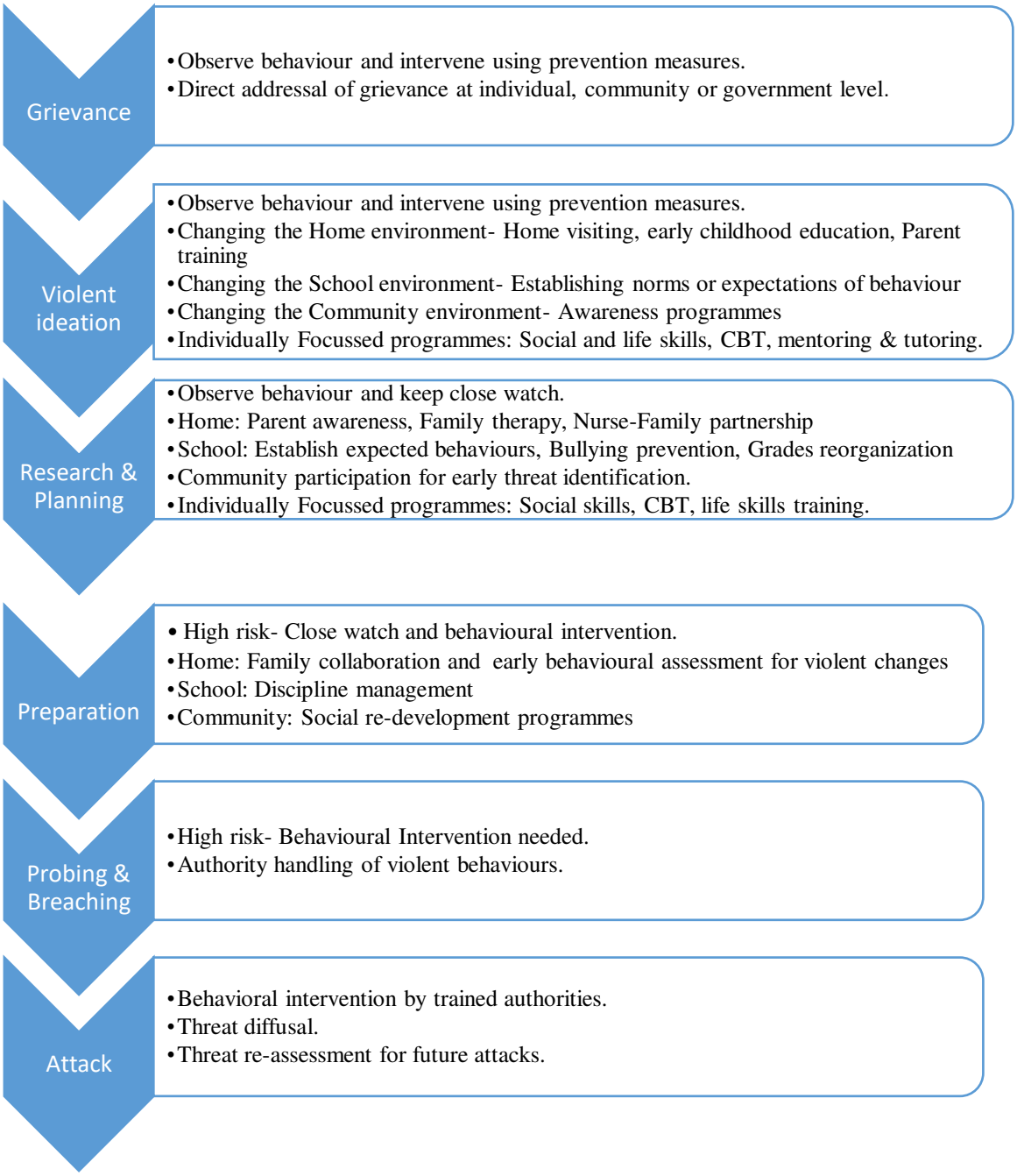

Figure 5: Pathway to violence and strategies to tackle.

The role of 'Resilience'

Defined as the ability to engage in healthy functioning in an unhealthy setting or as the maintenance of mastery under stress. It has been studied as both a personality trait as well as a survival pattern in highly stressful environments.

Levels of resilience

1. Individual-level- Positive internal resources: Temperament, cognitive functioning, self-efficacy, shyness, and intelligence.
2. Community level- Social and family system functioning, belongingness to a geographical region.
3. Characteristics of a dramatic incident- The degree or dose of the incident. A more catastrophic event will test a person's resilience even more. [21]

Various studies show that the developmental timing of adverse experiences in young minds has important implications for the nature of exposure, mediating processes, protective factors, and resilience. Despite the shortage of data, pre- and post-disaster interventions, the promotion of resilience in young people and families is the top priority. Consensus guidelines promote individual, family, and community-based intervention to enhance the same, however, a holistic approach is required nonetheless. [22] Considering resilience at an administrative level, Canada's framework of 'Building Resilience Against Terrorism' is depicted in Figure 6. [23]

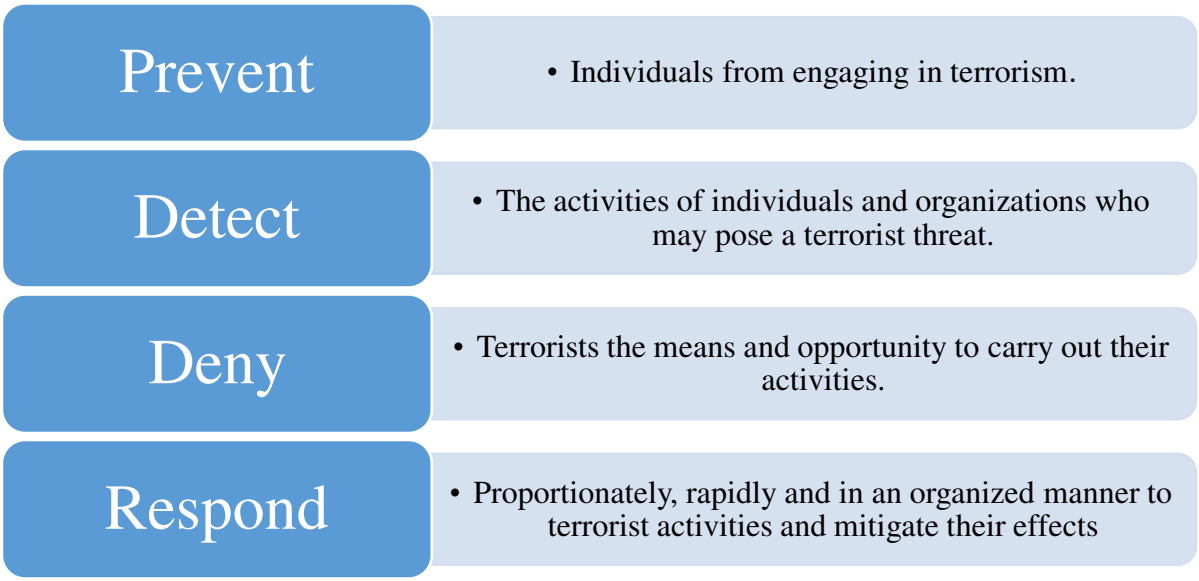

Figure 6: Building resilience against terrorism

Novel strategies for Terror survivors:

Memory Modification Techniques (MMTs): Conditioning to and consolidating of fear memories has been one of the core etiology of stress-induced psychiatric disorders like PTSD. However, recent research shows that these memories may be weakened at the time of their re-experiencing using drugs hacking the proteins responsible for memory consolidation-

reconsolidation. These include beta-blockers like Propranolol, opioids like morphine, and psychedelics like MDMA (3,4-Methylene-dioxy-meth-amphetamine). Alteration to memory may also be achieved using neuro-modulation via somatic therapies. Of the invasive ones and somewhat effective are Deep Brain Stimulation (DBS) of Hippocampal areas including the CA1, CA3, CA4, hippocampus-amygdala transition area, and the entorhinal cortex. The Nucleus Basalis of Meynert (NBM), having high cholinergic innervation has also been the target. Non-invasive therapies include repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS), their major targets being the dorsolateral prefrontal cortices (dlPFC). For rTMS, low-frequency rTMS (≤1 Hz), i.e. inhibitory impulse is applied to the right (100 impulses for at least 10 days), while high-frequency rTMS (>5 Hz; 10 Hz for PTSD) is applied to the left dlPFC (200 impulses for at least 10 days). In tDCS, the anode (excitatory) is placed over left dlPFC/F3 (10-20 EEG system), while the cathode is placed over another cephalic location like right dlPFC/F4, right supraorbital/Fp2 or extracephalic region like the shoulder. A dose of 0.08 mA/cm^2 current is given for at least 20-30 minutes for a total of 10 sessions (once or twice a day). Studies have shown that using these drugs may even prevent the development of PTSD if used early after trauma. [24-29] Further, although pending research trials, it may be hypothesized that if MMTs can be used on patients to relieve painful memories, the same may help in deradicalization. Since torture and or 'brainwashing' were coercive techniques employed to radicalize techniques must be explored to deradicalize, albeit in a humanitarian way. [30] Enhancing readiness to change using MDMA-assisted motivational interviewing, [31] neuromodulation techniques and narco-analysis as a forensic psychological technique are some ways proposed for future research. Recently, the role of serotonergic receptors, specifically the 5HT2A receptor has been cited to induce 'Pivotal Mental States' under stress. These states are defined as hyper-plastic states aiding in deep learning and psychological transformation. Moreover, serotonergic psychedelics like psilocybin, LSD, mescaline, etc. may induce a positive pivotal mental state and cause a reversal in a radicalized mind. [32]

The Way Forward

Cyber-Defence Mechanisms development is mandatory in conducting cyber search operations or extending the scope of countermeasures against cyber-attacks and secure cyber ecosystem.

Global Counter-Terrorism Measures: The international community should rise above political differences and Terrorism should be condemned bitterly.

Capacity building for the fight against cross-border terrorism.

Enhancing the National Criminal Justice system.

Curbing terror financing and regulating crypto-currency.

Reducing Youth's Exposure to Terrorism by promoting the values of non-violence, peaceful co-existence, and tolerance in counter-radicalization programs.

Tackling of economic and social inequalities.

Conclusions

In the modern era due to advancements in technology, social media, and telecommunications, terrorism has spread beyond territorial boundaries. However, resilience and deradicalization can reduce its impact. Therefore, coordinated global strategies (wisdom of the crowd) are the way (Tao) forward to combat terrorism.

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Chapter: 3
Effect of aging on physiological and pathological ocular conditions

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Abstract: Aging of the eye affects all ocular structures. It undergoes a variety of structural and physiologic changes that can impair vision and cause functional disability. Preventive care at all ages may help forestall ocular changes and their subsequent morbidity and mortality. So this chapter focuses on age-related changes in the eye that can result in ophthalmological diseases.

Keywords: Aging, Presbyopia, Cataract, Age-related macular degeneration

Introduction

Aging is progressive physiological changes in an organism that lead to senescence, or a decline of biological functions and of the organism's ability to adapt to metabolic stress. Aging takes place in a cell, an organ, or the total organism with the passage of time.[1] Aging shows its impact on the whole body of a human being. The ocular structures starting from outside the eyes such as the skin to the inner structures get affected by aging. A few changes which happen in the eyes are physiological but the maximum is pathological. So this chapter will highlight these changes, their impact on the functioning of the eyes, and their treatment modalities.

Various theories of Aging

Biological theories of aging[2]

Aging has many aspects which are explained by a number of theories.

The genetic theory of aging

The focal point of the genetic hypothesis of aging is telomeres, which are repeating DNA (deoxyribonucleic acid) segments found at the ends of chromosomes. With each division of cells, numerous repeats are lost and the number of repeats in a telomere defines the maximum

life span of a cell. The shortening of telomeres leads to the collapse of cell structure and further senescence or apoptosis which perishes the cell.[3]

In humans, variations in a gene known as telomerase RNA (TERC [ribonucleic acid] component), which encodes an RNA segment of an enzyme known as telomerase, have been associated with decreased telomere length and an increased biological aging rate. The length of telomere can be affected by the gene mutation which further supports the genetic theory of aging.

Nongenetic theories

There are various other factors that can influence the expression of a genetically determined "program." These theories attempt to explain aging in terms of cellular and molecular changes.

Wear-and-tear theory

This theory assumes that with the passage of time, animals and cells wear out like machines. Animals have some ability to repair themselves unlike machines so this theory does not completely explain the facts of a biological system.

Cross-linking theory

With increasing age, there is the development of cross-links between or within the molecules of collagen. This structural alteration leads to changes in the shape and structure of the enzyme molecules, preventing them from performing their intended roles in the cells. Even the tendons, skin, and blood vessels also lose elasticity.

Autoimmune theory

Antibody-produced by immune systems loses their capacity to discriminate between "self" and foreign proteins.

Oxidative damage theory

Oxidation of proteins and other cellular molecules happens within the cells. Oxidative damage (oxidative stress) accumulates with age giving rise to the free radicals, which is

concerned in particular with molecules known as reactive oxygen species (ROS). ROS acts as a contributing factor to much age-associated pathology.

Psychosociological theory

It states the behaviour and social interactions of people changes as they grow older, and the even the activities in which they engage also change. Advancements in modern medicine have contributed to a marked increase in average life expectancy (lifespan) in recent decades. The prevalence of age-related illnesses is quickly rising in line with this trend. The eye is no exception to this rule. Aging affects ocular structures in various ways, and these sequelae have been well-defined as distinct clinical entities.

Pathological and Physiological changes in the eye due to aging:

Functional changes

- Aging has a variety of effects on vision. A notable feature is a presbyopia. It is the irreversible loss of the accommodative ability of the eye. [4] According to Helmholtz's classical theory of accommodation, the ciliary muscle contracts and moves anteriorly and inwardly during accommodation. This lessens the tension on the zonular fibres, which increases the curvature of the elastic lens and boosts focusing power. With aging lens tissue hardens which leads to decreased flexibility and hence, decreased lens distortion during accommodation. Presbyopia frequently manifests as gradual blurring of near vision. Prescription of glasses, whether they be a separate pair of reading glasses, contact lenses, bifocals, or progressive lenses, are the safest and least invasive way to treat presbyopia.
- As media opacities increase, contrast sensitivity gradually decreases. Reduced contrast sensitivity affects an aged person's perception of depth as well.
- It's necessary to keep in mind while assessing the visual fields of glaucoma suspects that a reduction in the visual field is typical with aging.
- A decrease in cone density at the fovea results in an overall decline in colour perception. Reds and yellows are easier for people of all ages to distinguish from one another than blues and greens.
- Elderly persons have a tough time adjusting to strong light, darkness, and glare.

Ageing changes of eyelids

Loss of adnexal structural support of tarsus, canthal tendons, and orbicularis muscle with thinned skin leads to orbital fat prolapse, eyelid malposition, blepharoptosis, and tearing.[5]

- Horizontal lid laxity in the lower eyelid is also the sign of aging. The pinch test, which measures how far the eyelids can be pulled away from the globe and the length of time it takes for them to snap back into place, can be used to identify it. The more distance of the lid pinch and the more time it takes is indicative of the same.
- The orbital fat decreases with age causing the eyes to "sink in" and highlighting the laxity of the lids.
- Progressive laxity can lead to punctual eversion, following ectropion, which results in signs of a watery eye.
- Generalized midface drop as a result of aging also aids in the development of ectropion.
- The inversion of the eyelid (entropion), causes eyelashes to rub against the cornea and irritation if the pretarsal orbicularis muscle is somewhat strong. [Figure 1]
- Involutional ptosis may be brought on by the disinsertion or attenuation of the levator muscle in the upper lids.
- The brow ptosis, which is caused by age-related brow decline, also plays a role in the development of ptosis. Dermatochalasis is caused by excess upper eyelid skin and anterior migration of the preaponeurotic fat pads.
- "Crow's feet" are caused by the expression lines becoming deeper, particularly at the lateral lid edges.

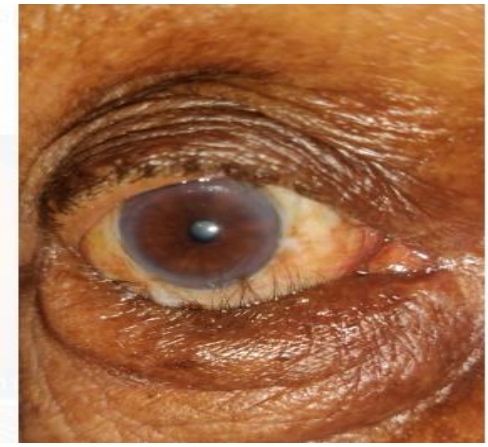

Figure 1 showing Entropion

Dry Eye

A common ailment called dry eye causes severe ocular pain and impaired vision. From 8.4% of people under the age of 60 to 19% of people over the age of 80, the prevalence of dry eyes considerably rises with age. Women are more affected than men. Generally speaking, dry eye is a multifactorial disease of the tears and ocular surface. [6]

The two main types of dry eye disease are evaporative, which involves excessive water loss from the exposed ocular surface and aqueous deficient, which is caused by diminished tear secretion from the lacrimal gland.

The most common cause of dry eye linked to ageing is meibomian gland dysfunction (MGD). The proposed mechanisms of MGD is that with aging there is considerable structural changes and reduction in number of meibomian glands which have an impact on lipid release.

Dry eye can also be caused by lacrimal gland pathologies. Variety of drugs taken by adults can worsen dry eye.

Although eyelid misalignment is the primary cause of watery eyes in the elderly, lacrimal blockage can occasionally occur. Dacryocystorhinostomy can be used to treat nasolacrimal duct obstructions. Artificial tears or punctual plugs are used to treat dry eyes caused by decrease tear production.

Corneal changes

In older people, changes in corneal curvature lead to changes in refraction, typically a shift from "with the rule" to "against the rule" astigmatism. Therefore, regular refraction check-ups are indicated for the elderly. [7]

- Other corneal changes include an increase in corneal fragility, a decrease in corneal lustre and sensitivity.
- The endothelium, stroma, and corneal epithelium all experience age-related degenerative changes.

i. The Hudson-Stahli line, a pigmented line of iron deposition visible at the intersection of the middle and lower thirds of the cornea is due to tear film deposition over the opposing lower lid edge.

ii. The most noticeable and prevalent ageing change is arcus senilis. These are asymptomatic bilateral yellow-white deposits made up of neutral glycerides, cholesterol, and cholesterol esters develop in an annular opacity on the peripheral corneal stroma separated from the limbus by a thin band of clear cornea.

iii. Hassall-Henle bodies are discrete thickenings in endothelium. The term "cornea guttata" refers to these descemet membrane excrescences that develop axially in the corneal endothelium.

iv. With aging, uveal pigment is deposited on the corneal endothelium, resulting in the Kruckenberg spindle.

None of the aforementioned modifications interfere with vision.

- As the corneal endothelium cannot regenerate, endothelial cell density declines with aging. A further decline in endothelial cell count due to surgery may cause corneal thickening, which will lead to opacity and a reduction in visual quality. Penetrating keratoplasty is a possibility if visual acuity is compromised.

Uveal and Trabecular meshwork changes

Gonioscopy shows increased pigmentation of the trabecular meshwork. The resistance to aqueous humour outflow brought on by ageing may cause glaucoma. The most common cause of permanent blindness in the world is glaucoma. The two main types of glaucoma are open-angle, which is the most prevalent form, and closed angle. People who are affected typically lose their peripheral vision but their core vision is retained, hence the name "tunnel vision." Treatment options include laser trabeculoplasty, canaloplasty, and trabeculectomy as well as drugs that lower intraocular pressure, such as prostaglandin analogues. [8]

- With age, the pupil tends to become smaller, the iris becomes less responsive, and pharmacological dilation becomes more challenging.

- Presbyopia is caused by a decrease in the amplitude of accommodation as a result of changes in the form and tone of the ciliary body.

Crystalline lens changes

- As we become older, the lens accumulates more yellow pigments, which causes it to selectively absorb more blue light (410 nm). This decline in blue light transmission results in a relative "blue blindness" as people age. The crystalline lens loses its transparency and becomes pearly white and blocks the transmission of the light to retina and hence reduces the vision remarkably. [Figure 2]

- A cataract develops when the lens loses some of its transparency to light.[9] With time, lens proteins have a propensity to aggregate into microscopic clumps. This hinders the transfer of light and degrades eyesight in general. Cataracts can be treated by switching to an artificial lens (IOL). There are several ways to accomplish this; the most popular is phacoemulsification, which entails employing high frequency ultrasonic waves to emulsify and fragment the lens before extracting it through a small corneal side incision.

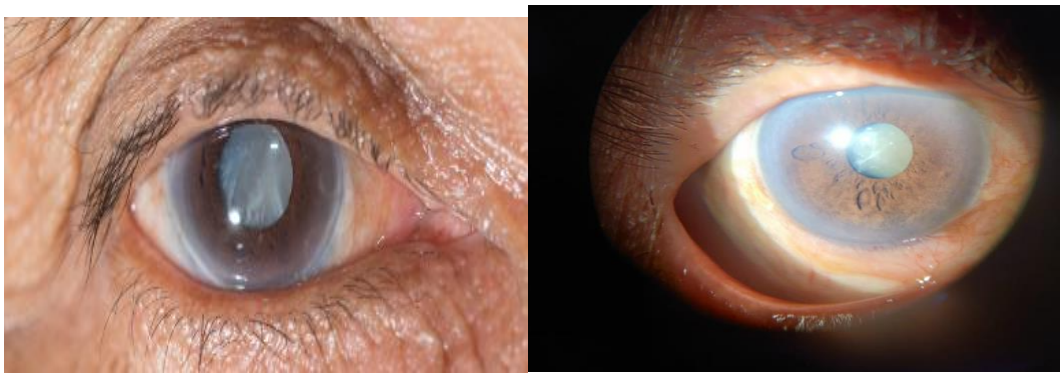

Figure 2a &b showing mature pearly white cataract

Vitreous changes

The vitreous ages irreversibly, changing the collagen fibrils and hyaluronic acid components, this causes the innocuous floaters. When the vitreous liquefaction reaches around 50%, the vitreous body begins to shrink away from the retina, which leads to posterior vitreous detachment. Patients report a spider-like floater in front of the eye that travels in the direction of look.

A retinal tear can occasionally occur during acute PVD if there is substantial vitreoretinal adhesion in the peripheral retina. Therefore, patients who experience sudden onset flashes, floaters and the onset of a curtain-like shadow in the field of vision may actually indicate a retinal detachment that requires surgical intervention.

Retinal changes

Diabetic Retinopathy

The most common reason for blindness is diabetic retinopathy. It has an impact on the retina's microvasculature, which expands and leaks as a result of the changes that elevated glucose levels create in their cell walls. When the retina lacks vasculature in some regions, aberrant new small vessels might develop. Retinal haemorrhage may occur as a result of the irregular form and fragility of these veins. [10]

It ranges from non-proliferative diabetic retinopathy (NPDR) and its stages to proliferative diabetic retinopathy (PDR). As the disease progresses, associated diabetic macular edema (DME) may also become apparent. Additionally, diabetes itself is a risk factor for glaucoma and cataract development. To delay the disease's progression, strict glycaemic management and routine eye exams are advised.

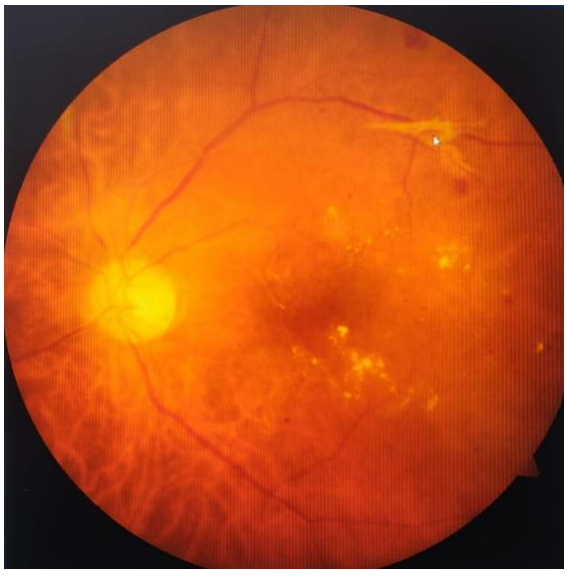

Figure 3 shows severe NPDR along with CSME

Changes at macula

Age related macular degeneration (ARMD)

Bruch's membrane present between RPE and choriocapillaries controls the flow of oxygen, nutrients, and metabolic waste products. As eye ages it becomes thicker, more calcified and less elastic due to accumulation of cellular waste and lipids that may precede drusen formation leading to ARMD. [11]

Drusen are the specks of yellowish white material under the retina. Drusen can be either hard drusen or soft drusen. Drusen by themselves do not usually cause visual disturbances and cannot be treated, but can progress. Hard drusen can progress to dry ARMD (atrophic) causing gradual distortion of vision and progressive central visual deterioration. Dry ARMD accounts for nearly 90% of all ARMD. They are associated with pigmentary maculopathy and in severe cases geographical atrophy.

Soft drusen are more susceptible to undergo wet AMD (neovascular/exudative) leading to formation of subretinal neovascular membrane (SRNVM). This SRNVM can leak causing central distortion and bleed causing a sudden drop in central visual acuity and exudative maculopathy. Even while wet ARMD accounts for approximately 10% to 15% of all cases of the illness, it causes more than 80% of severe vision loss or legal blindness.

Early-stage ARMD symptoms include visual scotomas and blurred vision (blind spots in the central vision leading to difficulty with recognising faces and reading small print).

Ageing, smoking, family history, and genetic factors are all significant risk factors for ARMD. Exposure to sunlight, particularly blue light, hypertension, cardiovascular risk factors, female sex, non-Hispanic white persons, and hyperopia (farsightedness) are potential risk factors.

In patients at high risk of developing ARMD, recommendations have been made about diet, particularly green leafy vegetables and fruits, quitting smoking, taking certain multivitamins (AREDS trial), and self-monitoring with an amsler chart. A high dose combination of vitamin C, vitamin E, beta-carotene (in AREDS 2 instead of beta carotene lutein and zeaxanthin are given) and zinc reduced the likelihood of advanced stages of ARMD in patients at high risk of getting it by nearly 25%. [12]

Photodynamic therapy (PDT) and intravitreal anti-VEGF injections are two recent advancements in treatment for the wet type of ARMD.

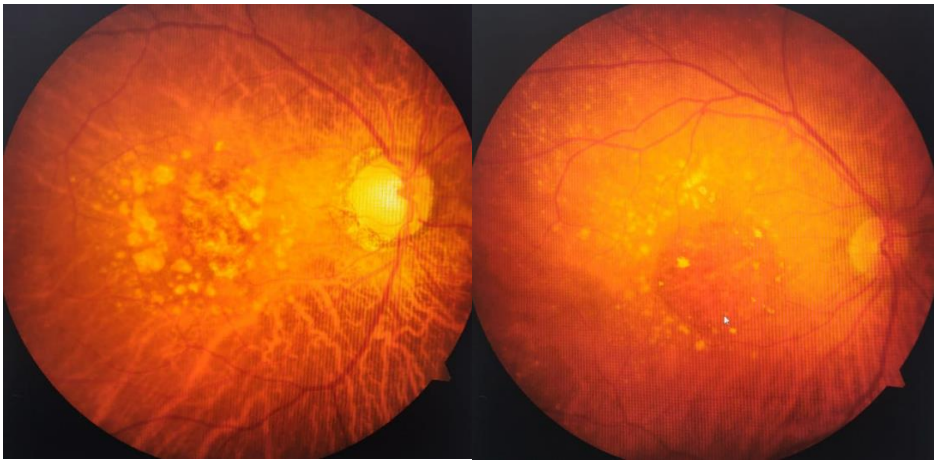

Figure 4 Demonstrates dry and wet ARMD

Other changes in fundus

The number of optic nerve axons declines with age, while the connective tissue of the optic nerve thickens and the elastic fibres increase.

Age-related clinically visible fundal alterations include peripapillary atrophy, peripheral retinal degenerations and increased visibility of bigger choroidal veins (senile tigroid fundus).

Circadian rhythms: the eye's role in the body's clock

The eye has a crucial role in regulating circadian rhythms thereby regulates broad physiological processes, such as metabolism. The intrinsically photosensitive RGCs (ipRGCs) transfer nonvisual information to the suprachiasmatic nucleus of the hypothalamus, which is the master controller of the body's circadian rhythms. Aging also affects the ability of the eye to set the body's clock.

Prevention measures and follow-ups

Unfortunately, we are unable to stop the aging process. We can definitely lessen how much aging affects eyesight, and most significantly, we can lower the risk factors. It has unquestionable benefits to maintain a healthy lifestyle, including eating right and exercising.

For people 60 and older, the NHS (National Health Service) currently suggests a regular checkup every two years. Regular eye exams and follow-up visits to ophthalmologists can aid to identify early changes in the structure of the eyes and possibly halt the progression of vision loss.

Conclusions

Aging affects the ocular structures significantly which further produces various pathologies which directly affect vision such as presbyopia, glaucoma, cataract, ARMD and retinal pathologies as diabetic or hypertensive retinopathies. Aging is inevitable but proper management of these ocular changes can assist in maintaining the visual function of the patients.

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Chapter: 4
Menopause and Quality of Life

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Menopause is a normal physiological phenomenon in which women stop menstruating for at least 12 months as ovarian hormone production declines. As per the WHO, premenopausal females had regular monthly flow within a preceding 12 months, Periods were irregular or no menstruation for more than three months but less than a year for perimenopausal women whereas no menstruation for more than a year was seen in postmenopausal women. Menopause happens naturally between the ages of 45 and 50. [1]

From the perspective of the value and culture system where they reside, quality of life refers to people's views of their living status in respect to their objectives, ambitions, interests and ethics. One needs to understand that, the attitude of women toward menopause and their quality of life are linked. Those who had a negative attitude about menopause reported greater symptoms than women who had a good attitude. Women's views regarding menopause should be understood by healthcare providers in order to provide the best information and assist women in developing good attitudes and healthy perspectives of this stage of life.[2]

Menopausal symptoms, their incidence and intensity, and its influence on QOL within females at in Riyadh attending primary care hospitals, Saudi Arabia. Counted as total of 119 females between the ages of 45 and 60 were questioned at random using a questionnaire. Subjects had divided into 3 groups: pre, peri and post-menopausal (n = 31, n = 49 and n = 39) respectively. The pain specifically at the joint and muscular (80.7 percent), mental with the physical tiredness (64.7 percent), then sweating and hot flushes has been the most often reported symptoms (47.1 percent). Females in their menopause reported more physical and psychological complaints than other groups. Although the symptoms were low in intensity, according to the overall MRS score, perimenopausal women had a greater overall quality-of-life score (MRS 9). Menopausal symptoms were more common in Asian females than in Western females, menopausal symptoms including hot flashes with nocturnal sweats, noted to

be however, less common than in Western research. Saudi women scored lower on the MRS, showing that their symptoms were less severe and thatthey were better equipped to cope with climacteric symptoms.[3]

The modified Kupperman menopausal index (mkmi) had utilized to determine how severe symptoms of menopausal between Chinese middle-aged females and to learn more about the factors that influence their perimenopausal healthcare seeking behaviour. All of the participants were 51 years old on average. Premenopausal women made up 33.13 percent of the participants, perimenopausal women 14.52 percent, and postmenopausal women 52.35 percent. Menopausal symptoms were present in 73.8 percent of women, with perimenopausal females experiencing a highest symptom (81.70 percent). The main three symptoms stated has been fatigue (38.08 percent), hot flushes and sweating (33.65 percent), with joint discomfort (28.81 percent). Premenopausal women scored lower on the mkmi than perimenopausal and postmenopausal women. 25.97 percent of the women with symptoms had sought medical help. Employment, menstrual status, and the mkmi were all shown to be strongly linked with healthcare-seeking behaviours in a logistic regression model. Menopausal symptoms were common in middle-aged females, with perimenopausal females experiencing a most. Only a tiny fraction of those whotook part needed medical assistance.[4]

In India, symptoms of menopausal with their influence on QOL were observed to affect 87.7% of rural middle-aged females in Haryana 40–60 years of aged. The study found that anxiety was the most prevalent symptom, occurring in 80% of cases. After it, there has physical along with mental tiredness (71.5 percent), trouble sleeping (61.2 percent), irritability (60.7 percent), joint and muscle pain (56 percent), and heart abnormalities (54 percent). Hot flushes, considered to be a menopause's important symptoms, were experienced by 36.7 percent of women. The mean age of menopause has 47.53 ± 4.5 years of standard deviation. Some noticeable symptoms mean score like, such as hot flushes, sweating, and joint and muscle soreness, was statistically significant between thepost and peri-menopausal groups. 70.2 percent of research participants had a poor quality of life. 70.8 percent of the low QOL has been ascribed to psychological problems. A comprehensive strategy in the form of lifestyle and behavioural adjustment is necessary to increase QOL and reduce menopausalsymptoms in these women.[5]

Menopause, sometimes known as menstrual menopause, is a scientific link between reproductive to non-reproductive stages at the physiological level of life that affects all

women. Women have physical, psychological, and urogenital morbidities as a result of a drop in oestrogen levels, which impacts their quality of life. All joints with muscular discomfort (92.27 percent), anxiety(72.72 percent), hot flushes along with physical mental tiredness (71 percent), bladder illness (67.2 percent), sleep issues (62.27 percent), heart discomfort with irritability (57 percent), depression (55.9 percent), sexual delinquent (56.36 percent), and dryness of vagina had been the most common perceived symptoms among perimenopausal women in the age group 51-55 years (55 percent). Perimenopausal women reported significant levels of depression and physical and mental weariness. In the somatic and urogenital subscales, postmenopausal women had more severe morbidities. In the slum population, illiteracy and a significant concentration of low-income people made menopausal quality of life poorer. "Depression (55.9%), sexual problem (56.36%) and vaginal dryness (55%). Depression and physical and mental exhaustion complaints were high among perimenopausal women. The severity of morbidities was higher among postmenopausal women in somatic and urogenital subscales, Illiteracy and the high proportion of low SES made the menopausal quality of life worse in slum population".[6]

According to self-reported research, 50–75 percent of women suffer symptoms throughout menopause. In the year after the index, Comorbid disorders (depression, anxiety, osteoporosis, and sleeplessness) found more common in Israeli females with menopausal symptoms. The usage of hypnotic, SSRI (selective serotonin reuptake inhibitors) and SARI (serotonin norepinephrine reuptake inhibitors) medications, as well as hospitalization, primary care visits, gynecologist appointments, and hysterectomy surgeries, was significantly higher among symptomatic women. Medically verified menopausal symptoms are linked to higher disease burden, healthcare consumption, and a higher risk of hysterectomy within a year of diagnosis. As more people becomeaware of and accept peri- and postmenopausal symptoms, the burden is projectedto grow.[7]

Brown WJ (2002) conducted carried out cohort research on physical symptom changes throughout the menopausal transition. This article examines the physical symptoms experienced by middle-aged Australian females throughout different stages of the menopausal transition. Headaches, fatigue, back pain, stiff joints, and sleeping problems has been the most often reported symptoms in Survey 1. These symptoms are more common in perimenopausal females than in premenopausal or postmenopausal females. In postmenopausal females, hot flushes and nocturnal sweats were more prevalent. At Survey 2, female in the initial phases of menopause or perimenopause has more likely than

premenopausal female to experience fatigue, stiff joints, sleeping problems, and hot flushes. Back pain and urine incontinence were also more common in perimenopausal female. The chances ratios for night sweats increased as women progressed through the menopause transition, and these odds ratios remained high in postmenopausal female.[8]

The investigator interviewed few women to know their knowledge regarding care during menopause and found that firstly many responded that it is natural. Secondly women in their midlife have responsibility of family and they don't have time to maintain quality of life. The investigator interacted with the health officer at health centers and community health nurses. They stated that women above the age of forty years. Reported with body aches, hot flushes, night sweating, palpation, irregular menstrual flow etc. but few are aware that these are menopausal symptom. The gynecologist told the investigator that few women approach them directly for menopausal symptom though the percentage of menopausal discomfort is high. There is lack of awareness regarding self-care among women during this transitional phase.

If the women are given information on care during menopause it will help them to make informed health decisions, clear of the confusion they may be experiencing about menopause and take measures to promote her health. The nurse is the primary source of information to the perimenopausal women. She is there with them in all phase like prevention, cure and rehabilitation. Sheprovides health education as an integral part of nursing care, which brings about change in the health status of the client. The need of information is universal and the transitional phase in life such as menopause increases the need for additional information .These needs can be met through learning. The BASNEF model is an acronym for the component parts: Belifs, Attitude, Subjective Norms and Enabling factors). This model was developed by J Hubley, Department of Health and Community Studies UK in 1988.It is helpful to understand behavior and to modify existing behavior into new one.[9]

Some important behaviors includes in this model are –

1. Adoption of health-promoting behaviours.
2. Reduction of health damaging behaviours.
3. Utilization of health services.
4. Recognition of early symptoms and prompt self-referral treatment.
5. Following of drug regimes.
6. Measures to aid recovery and reduce the risk of future impairment.
7. Individual and collective actions to alter and enhance their environment.

In this study, the author finds need for education programe based on BASNEF model (Knowledge, Belief, Attitude, Subjective Norms and Enabling Factors) which will help to make awareness and knowledge regarding care during perimenopause and to prevent complications in menopause to improve quality of life among perimenopausal women. An educational teaching programme can be an effective and economical teaching aid. Considering all the above aspect the investigator felt the need to educational teaching programme on care during perimenopausal to menopausal women and study to its efficacyon the level of depression and quality of life. So Investigator decided to undertake this study.

Chapter: 5
Vaccines and Drug development in the treatment of Ebola

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Abstract: Ebola virus (EBOV), is responsible for Ebola virus disease (EVD) (formerly named Ebola hemorrhagic fever). This is a severe, frequently fatal illness, with human fatality rates ranging from 50 to 90%. Although the virus and accompanying sickness have been known since 1976, it was not until the latest epidemic of EBOV in 2014-2016 that the danger and global impact of this virus became clear, prompting the development of effective vacines and medications to combat its pandemic threat. Although no commercial vaccination against EBOV is currently available, a few vaccine candidates are being evaluated and tested in clinical studies to determine their preventive efficacy. Recombinant viral vectors (recombinant vesicular stomatitis virus vector, chimp adenovirus type 3-vector, and modified vaccinia Ankara virus), Ebola virus-like particles, virus-like replicon particles, DNA, and plant-based vaccines are examples of these. Epitope-targeted vaccinations have risen to prominence as a result of advancements in genomics and proteomics. Several therapeutics, including immunoglobulins against specific viral components and small cell-penetrating anti body fragments that target internal EBOV proteins, has been developed in response. Small interfering RNAs and oligomer-mediated inhibition have also been demonstrated to be effective for EVD treatment. Viral entrance inhibitors, transfusion of convalescent blood/serum, neutralizing antibodies, and gene expression inhibitors are among the other therapy options. Repurposed medicines with validated safety profiles can be repurposed for EVD treatment after high-throughput screening for efficacy and potency. Herbal and other natural products are also being investigated for the treatment of EVD. Further research into the pathophysiology and antigenic structures of the virus can aid in the development of a successful vaccination and the identification of relevant antiviral targets. This review summarizes current achievements in the design and development of vaccines, drugs to combat the EBOV threat.

Keywords - Clinical trials, Drug development, Ebola, Pathogenesis, Vaccine development

Introduction

Ebola virus

Ebola virus disease formerly called Ebola hemorrhagic fever, for which Ebola virus (EBOV) is responsible which cause severe hemorrhagic fever.

Structure

A peak-infectivity virion often has a length of 1200 nm, and EBOVs frequently have a thread-like shape with uniform diameters of 80 nm and lengths of up to 14 meters. Trimeric glycoprotein (GP1,2) spikes that are part of the envelope's decoration allow the virus to enter target cells (GP1) and viral ribonucleoprotein are release for replication from endosomes into the cytoplasm (GP2), respectively.(1,2). The Democratic Republic of the Congo's Northern Zaire first reported it in 1976. (1)

The largest, most challenging most severe, and Ebola outbreak is currently occurring in West Africa, more specifically in Liberia, Sierra Leone and Guinea.(2)

Taxonomy

The five ebolavirus species are the following: Bundibugyo ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus and Zaire ebolavirus. Ebolavirus and the closely related Marburg viruses. (3)

Transmission

The sole route for Ebola viruses to spread is by direct contact with infectious bodily fluids such as saliva, sweat, blood, and tears from EVD patients or wild animal carriers. The incubation period for Ebola viruses is 2–21 days.(2)

Pathogenesis

Following a 3–21-day incubation, the sickness (4,5)quickly progresses to fever, acute tiredness, diarrhoea, abdominal pain, anorexia, myalgia, hiccups, disorientation, vomiting and conjunctivitis that may cause visual loss.

EBOV can spread through semen to females from males, as well as from mothers to foetuses and neonates during pregnancy and lactation, respectively. The male genital organ is the virus' preferred location for replication, as evidenced by the fact that a patient with EBOV had an increased concentration of Ebola viral RNA in semen throughout the recovery phase

than in blood during the height of the infection (18). As the human immune system launches an offensive against pathogenic microorganisms, a number of pathogen-recognition receptors typically recognize the pathogen-associated molecular patterns. However, in the case of EBOV, immunosuppressive viral proteins like VP24 and VP35 weaken innate immunity, and lymphocytes are decreased as a result of unfavorable DC-T cell interactions that encourage death.(1)

Symptoms

Early symptoms of EVD often include fever, extreme weakness, headaches, and muscle pain. As the illness gets worse, bleeding from the inside and outside as well as issues with the kidneys and liver will start to show up.(2)

Mode of Transmission

Ebolaviruses are typically transmitted by close contact with infected people, especially through their bodily liquids

Due to inadequate infection control procedures, nosocomial transmission has also been a significant contributor to a number of epidemics. (6)

Person to person EBOV transfer happens when the virus is injected into the bloodstream or when nonintact skin or mucous membranes come into contact with contaminated body fluids or tissues. There is a dramatically higher risk of infection following direct contact with infectious material. It is possible for previously contaminated fomites to act as active sources of infection since infectious virus particles in proteinaceous material can stay on inanimate objects for days, weeks, or even months in certain conditions. All hospital transmission of EBOV in 1976 was mostly attributed to infected needles or syringes. About 5% of people had infections that could only be explained by extremely close contact with sick people. Infections in 5% of the population could only have been explained by very close contact with ill patients. These people most likely contracted the illness through skin breaches or mucosal inoculation diagnostic procedures of filovirus identification, even in field operations. (7)

Ebolavirus ecology

There have been theories that ebolaviruses may exist naturally in fruit bats and that wildlife, particularly great apes, contract diseases via bats. Significant ape die-offs have occurred in some cases, and ebolavirus infection is thought to be the cause. Every year since 1994, there

has been an average of one EHF outbreak, and they have all originated or occurred in central Africa. In 1978, the first reports of human EHF epidemics were made. Some epidemics are thought to have started after people came into touch with infected NHPs, and killing or shooting these animals is a risk factor for getting EHF. Direct human-to-bat transfer has been proposed as a second probable mode of transmission, albeit.

Bats are the most likely candidate for the REBOV natural reservoir despite the fact that they have been shown to be seropositive for the virus. (6)

Drug development

Early Steps in Compound Discovery for Ebola Virus Treatment

Targets for Treating EVD Biologically

Identification of biological elements that will constitute good drug targets is necessary for the development of therapies.

Drug targets are often generated from the host or the pathogen and are discovered and verified by combining biochemical, genetic, structural, and computational methods. Since the virus can be directly targeted, host factors can be changed, the immune system can be affected, and clinical sickness can be managed, there are four main types of therapy techniques to combat EBOV.

Antivirals that specifically target viral life cycle stages make up one of the most widely used EBOV treatment approaches. There are numerous EBOV antiviral agents on the market, such as small compounds, antisense therapies, and immunotherapeutic. The most cutting-edge medicines now under testing contain a disproportionately large amount of small molecules that target the virus replication enzyme L, an RNA-dependent RNA polymerase. The active nucleoside triphosphate is synthesized intracellularly by BCX4430, GS5734, and favipiravir (T-705) or an amino acid. Small-interfering RNAs (siRNAs), which encourage the destruction of mRNA transcripts, and phosphorodiamidate morpholino oligomers (PMOs), which obstruct translation, are the two main groups of antisense drugs. TKM-100802 (TKM-Ebola) and TKM-130803 are combinations of three siRNAs that target several viral sites and were created to increase targeting of the West African strain of EBOV (L, VP35, and VP24). The PMOs AVI-7537 and AVI-6002 (which combine AVI -7537 and AVI- 7539) both target VP24 and VP24/VP35, respectively. IN vitro research is currently being done on additional

viral proteins such VP35, VP24, and VP40 in order to identify potential new targets for EBOV drugs. Direct antivirals also include a large number of immune therapeutics in development that bind to the virus and prevent entrance.

Therapeutic usually target GP since it is the only surface-expressed protein of EBOV. The ZMapp cocktail is made up of three neutralizing monoclonal chimeric antibodies that target the GP base and glycan cap. Other immunotherapeutic that target GP include lectins such as mannose binding lectin (MBL), which have demonstrated efficacy in in vitro and animal experiments.

In recent years, host factor modulators have drawn increased attention in EBOV research. Like many other viruses with tiny genomes, EBOV exploits the host proteins to enter the body and start reproducing. Both VP24 and VP24/VP35 are targeted by the PMOs AVI-7537 and AVI-6002 (which combine AVI-7537 and AVI-7539). Additional viral proteins including VP35, VP24, and VP40 are presently the subject of in vitro research to find possible new EBOV therapeutic target. Numerous immune therapeutics is being developed as direct antivirals as well; these attach to the virus and block entry.

Since GP is the only surface-expressed protein of EBOV, therapeutic antibodies like the ZMapp antibody cocktail, monoclonal antibodies, and polyclonal antibodies typically target it. Three monoclonal chimeric antibodies with neutralizing activity that target the GP base and glycan cap make up the ZMapp cocktail.

GP is the target of other immune therapeutics such as lectins like mannose binding lectin (MBL), which have demonstrated efficacy in in vitro and animal testing. Host factor modulators have received more interest recently in EBOV studies. The host proteins are used by EBOV, like many other viruses with small genomes, to enter the body and begin reproduction. Tests have been conducted on numerous host proteins implicated in EBOV entry, including cathepsins, Niemann-Pick C1 (NPC1), T-cell immunoglobulin, and mucin 1. Before fusion and entrance, the EBOV GP is broken by the endosomal cysteine proteases known as catharsis, which include CatB and CatL. Although in vitro tests against EBOV showed that protease and cathepsin inhibitors were effective, it is yet unknown if cathepsins in particular could be specifically targeted for therapeutic purposes because of potential compensatory mechanisms It has been established that after cathepsin-mediated cleavage, Niemann-Pick C1 protein (NPC1), a cholesterol transport protein, can bind to GP. According to in vitro tests, the small compounds MBX2254 and MBX2270 are thought to prevent

EBOV GP from binding to NPC1, hence preventing infection. It has been demonstrated that TIM-1 may bind to GP and serve as a receptor for EBOV and other filoviruses. The inhibition of EBOV infection when cells were treated with the TIM-1 antibody ARD5 suggested that TIM-1 would be a good target for EBOV therapy. Another technique being researched for the treatment of EVD is immune system modulation. Cytokines, chemokines, and other proteins, which are immunomodulators for EBOV infection, may strengthen the immune response and hence promote viral clearance. Alternately, they might reduce unfavourable immunological reactions, like the excessive release of inflammatory cytokines linked to EBOV It has been established that after cathepsin-mediated cleavage, Niemann-Pick C1 protein (NPC1), a cholesterol transport protein, can bind to GP. According to in vitro tests, the small compounds MBX2254 and MBX2270 are thought to prevent EBOV GP from binding to NPC1, hence preventing infection. It has been demonstrated that TIM-1 may bind to GP and serve as a receptor for EBOV and other filoviruses Extended time to death was the effect of similar interferon- therapy in NHPs.

Treatment of the hemorrhagic and coagulation abnormalities that characterise the clinical signs of EVD is the aim of management therapy. Recombinant nematode anticoagulant protein C2 and recombinant human activated protein C (rhAPC) (rNAPc2) are two examples of anticoagulants that have been the subject of research. In an effort to limit arterial leakage during the epidemic, patients were given FX06, a fibrin derived peptide being researched as a treatment for vascular leak syndrome.(8)

Data on EBOV Therapeutics' in vitro effectiveness (drug-target interaction)

A wide range of cell-culture based assays, some of which have high throughput capability to aid in the screening of huge chemical libraries, have been used to find hits for potential EBOV therapeutics. The two most popular ones are replication tests using infectious EBOV, which can only be carried out in BSL-4 laboratories, and pseudo typed-virus assays, which may be carried out in BSL-2 facilities. Pseudo typed virus experiments, in which EBOV GP is expressed on a viral backbone such as HIV or VSV, are helpful for determining whether the drug also overcomes biosafety limitations. With the help of this knowledge, the target or method of action of drugs identified through phenotypic screens may be more precisely defined. Cytotoxic effects reduced viral replication, or both PCR or fluorescence imaging are used to evaluate. The usage a variety of tests to evaluate the effectiveness of medicines that block EBOV could make it challenging to comparing outcomes from various platforms

methodologies. All is clear when a substance produces distinct EC50/IC50 values for each assay when tested simultaneously against pseudo typed and wild-type viruses. It's possible that the discrepancy results from different GP expression in the two different viral particle types. It has also been discovered that lead optimization programmes and the screening of new chemical libraries, in addition to commercial medications originally developed for diseases are effective against EBOV. Toremiphene, clomipheme, azithromycin, and chloroquine are a few of these, the majority of which are classified as cationic amphiphilic drugs (CADs). The anti-EBOV mechanisms of several of these drugs are unknown. action. Other viral targets like VP24 have also been hit during screening for medication repurposing initiatives (8)

EBOV Pharmacokinetics and Tolerability to Commercial drugs

Drug tolerance is especially important because survival is seen as a critical effectiveness indicator in preclinical EBOV treatment trials. In general, when a dose lowers than the maximum tolerable dose is used. Free drug concentrations should be kept above EBOV EC50 values at the target location (MTD). This brings up an essential question: What is the definition of "target site"?

The most popular comparison between the corresponding and plasma PK curves is made by researchers. To determine a dose schedule and/or if a chemical can deliver enough exposure to support effectiveness trials, use the EBOV EC50 (or EC90) value. On the other hand, by Day 2 post infection, Dendritic cells, monocytes, and macrophages all harbor the EBOV virus. By day 5, it can be found in tubular epithelium, fibroblasts, polymorphonuclear cells, tonsillar epithelium, Kupffer cells, endothelial cells, adrenal cortical cells, and stromal cells. EBOV is still present in the semen and eyes of EBOV survivors, it has been discovered. As a result, effective EBOV therapies may not need to be highly selective for any one cell or tissue, but rather may need to be widely dispersed (for example, high volume of distribution, Vd). When developing new medications, researchers frequently have to decide whether to invest in more thorough PK investigations that define the drug's distribution in cells and tissues or to rely solely on plasma to gauge proper drug exposure.

This is crucial for nucleosides in particular because of how quickly they can enter cells and then convert there to the appropriate nucleoside triphosphate (TP), where they may persist. Their plasma half-life is typically quite short as a result (longer half-life). For instance, BCX4430 has a half-life of 10 minutes in the mouse's plasma but 4.3 hours in the liver's TP.

The finding that this conversion was higher in mouse hepatocytes than in human hepatocytes brought attention to the significance of interspecies translation. Notably, liver TP levels at the mouse's effective dose (150 mg/kg, IM) were 2.5 times greater than the EBOV EC50. A different nucleoside, GS-5734, indicated quick absorption by monkey PBMCs and triphosphate levels that stayed above the EBOV EC50 for 24 hours at an efficient dose (10 mg/kg) that completely protected NHPs. Maximum unbound drug concentrations in human plasma at the highest doses of medication that have received FDA approval are usually substantially lower than the EBOV EC50 values . With the exception of azithromycin (50 mg/kg, PO), for which mice PK data are available (chloroquine, toremiphene, azithromycin, sertraline), unbound plasma levels appear insufficient. It is surprising that oral azithromycin delivery to mice did not increase survival, especially given adequate plasma and tissue exposures were probably attained at the 100 mg/kg dose. This finding indicates that treating EVD using the CAD mechanism is ineffective. (8)

Animal Models for Preclinical Efficacy

After the discovery of active leads and the subsequent evaluation of their PK and tolerability, promising therapeutic compounds are advanced into preclinical studies in order to gather information that will direct the design of upcoming clinical trials and the creation of a potential therapeutic candidate into a secure and marketable product. This includes employing animal models of the disease or condition to examine the efficacy of treatments in vivo. To research prospective EVD treatments, lethal EBOV models in mice, guinea pigs, or nonhuman primates are used (NHPs). Initially, mice and/or guinea pigs are used to evaluate a number of EBOV treatments because they are cheaper, lower risk, and more convenient than other small animal and rodent models.

Adult immunocompetent mice and guinea pigs are not killed by wild type EBOV, however both models require the use of modified virus created through repetitive serial transmission.

Both models lack critical components of EVD in humans, such as alterations in immune cell populations in guinea pigs and hemorrhagic and coagulation issues in mice. Survival is used to gauge effectiveness in both the rodent and guinea pig models.

Survival is used to gauge effectiveness in both the rodent and guinea pig models.

The NHP model is the most accurate surrogate for human EVD since the clinical picture in NHPs is quite comparable to that of humans in terms of hemorrhagic symptoms,

coagulopathy, and pathology. Candidates may proceed into this model if they perform well in the mouse or guinea pig models. Effectiveness in the NHP model is normally measured by survival; however, viral load reduction and delayed time to death have also been used. For instance, interferon treatment increases macaque survival after EBOV. The effectiveness of the rodent model is not always translated by the NHP model. This could be partially accounted for by the fact that EBOV manifests differently in mice than it does in NHPs. Alternatively, the protection threshold for a mouse may be lower than that of an NHP P. The limitations associated with distinct species can occasionally influence the type of animal chosen. It can be challenging to assess brincidofovir in the NHP model, for example, because of the drug's primate metabolism. NHPs are far less successful at converting brincidofovir into its active form compared to those of other species like mice and humans, which lowers systemic exposure. Therefore, investigations on humans will be necessary to show that brincidofovir is effective. Though their translation from mice to people is disputed, some host-modulating medications rely on the inflammatory response.(8)

Observational studies and clinical trials for EBOV therapeutics

In response to the West African epidemic that occurred between 2014 and 2016, numerous clinical trials for lead candidates that had already shown efficacy against EBOV in animal models were started. The goals and scope of phases I, II, and III of clinical trials are distinct from one another. Clinical investigations carried out during the outbreak lacked proper controls and/or statistical power because of the urgency and severity of the sickness but also because the outbreak was very temporary. Only Phase I and Phase II studies have been used to assess the safety and efficacy of the EBOV treatments that are in advanced development. The Phase I studies for two further recent EBOV medication candidates, GS- 5734 and BCX4430, have been completed; the of EBOV male survivors. The first part of the project has been completed by AVI-6002 and AVI-7537.

Despite positive safety, tolerability, and PK data in humans as well as preclinical efficacy evidence in three species, the company is not undertaking I studies. Ability of the former to lower viral burden in the semen is currently being assessed. Phase I studies are not being developed by the company in spite of encouraging evidence for safety, tolerability, and PK in humans as well as three species' preclinical effectiveness data. Several of the treatment strategies listed in the 2014–2016 outbreak have safety concerns, despite many of them having positive Phase I findings.

TKM-100802, which was tested in a Phase I trial in January 2014 on healthy volunteers, is one illustration. Experiencing flu-like symptoms in patients receiving treatment, which was ultimately connected to The FDA made the decision to stop the trial because the devcytokine release brought up by the siRNA's effect generated safety concerns. If the hold was eventually lifted, the experiment might restart at a lower dose than the one that was first examined, allowing for greater access for EVD patients throughout the outbreak. The goal of phase II/III trials is to evaluate effectiveness, with the randomized controlled trial serving as the gold standard and randomly assigning patients to the treatment or placebo arm. Although the primary end point in these trials is a decrease in mortality, other endpoints such a decrease in viral loads are also monitored. Prior to the trial's start, its goals are laid out. The study may be terminated early on the grounds of "futility" if an analysis of the preliminary data indicates that the objectives are unlikely to be attained. After its Phase I trial was successfully restarted and finished in March 2015, TKM -130803 commenced a single-arm Phase II trial there. The trial was terminated early due to a lack of sufficient effectiveness data. The creator has put a stop to the TKM-continued Ebola outbreak. Clinical trials must be powered adequately in order to show a statistically meaningful benefit for the therapy. Which means they must have a minimum number of participants. It might be difficult to enrol enough patients for clinical trials, which can affect whether the study is successful or unsuccessful. Low enrolment may be caused by things like cultural ideologies, difficulty accessing trial sites, and communication problems. Due to the low enrolment numbers. Similar to this, after one month, enrollment was halted in the Phase II research of brincidofovir to evaluate its safety, tolerability, and effectiveness.

There are presently no plans to advance brincidofovir as an EBOV treatment. In addition to statistical power, a well-designed study must also have other essential components. In 2014, the JIKI experiment, a multicenter proof-of-concept non-comparative trial, evaluated the effectiveness of favipiravir in four Ebola treatment centres in Guinea. Design of the study, which was dependent on applying historical controls and was not randomized, was highly criticized. Because of this, many people believed it was challenging to accurately understand the study's findings. Favipiravir's most recent efficacy findings are inconclusive and point to the.

There is a chance that it might only be helpful for treating people with low to moderate virus loads (CT values 9 to 20). Similar to that, convalescent plasma was evaluated in a non-randomized, historically controlled Ebola investigation. Tx experiment in Guinea; it did not

appear to show a benefit in survival. Several EBOV therapies' inability to show benefit in Phase II research, as well as the irregular difficulties in evaluating such clinical data underline the need of properly-designed research. However, the design of these trials may raise ethical concerns when dealing with diseases that have a high fatality rate, like EBOV. However, it is immoral to offer no therapy for a disease with a high fatality rate like EBOV. However, it is immoral to provide no treatment for a condition like EBOV that has a high mortality rate Many studies have contrasted supportive care, which served as the control arm, with experimental therapy in an effort to address this issue and ascertain whether the experimental therapy boosts survival. Patients with EBOV infection were also given a variety of drugs that had undergone efficacy testing in clinical trials and were given to them with expanded access or emergency use authorization. In these circumstances, critical patients may get experimental medications or medications approved for use in other situations. Under such conditions, brincidofovir was administered to many patients throughout the outbreak, one of whom lived after receiving brincidofovir together with convalescent plasma and supportive care. However, it didn't seem like any of these medications had statistically significant effectiveness against EBOV. The fact that these individuals frequently received multiple experimental treatments in tandem contributes to the challenge in evaluating such data. It can be challenging to determine which medication caused the therapeutic effect in such circumstances.

Developing Drugs to Treat the Ebola Virus

EBOV Drug Discovery and Development Challenges

There is still no FDA-approved treatment for EVD, despite the fact that numerous treatments have started to go through the clinical trial pipeline.

Since the 2014-2016 outbreak is over, EBOV can once more take the lead in intermittent, localized outbreaks. Due to this and the unexpected nature of such outbreaks, conducting Phase II/III clinical trials to assess efficacy is currently challenging. Phase I studies can still be used to assess safety, dose ranges, and adverse events, however the majority of early trials are frequently carried out in American research facilities.

However, the areas where safety is initially assessed frequently diverge from those where epidemics actually take place. Before obtaining more safety information in diverse populations, care should be exercised when interpreting Phase I safety findings because of

genetic and immunological variations among various patient populations phase three Malaria can cause symptoms that are comparable to those of other illnesses and treatment with an antimalarial drug can result in drug interactions that could have an impact on phase II/III results in the patient populations in the areas where previous outbreaks have occurred. The FDA Animal Rule has been suggested as a practical procedure for EBOV drug approval. V. The purpose of the Animal Rule was the patient populations in the regions where previous outbreaks occurred are also susceptible to malaria, which can cause symptoms that

are similar to those of other diseases (such as fever, Drug interactions that potentially influence phase II/III outcomes include taking an antimalarial drug concurrently with other medications for symptoms like headache, muscle pain, weariness, diarrhoea, and vomiting.

One practical remedy for EBOV has been proposed: the FDA Animal Rule.

Effectiveness must be proven in at least one animal model that accurately mimics a human disease in order to be approved under the Animal Rule.

It is also necessary to describe the drug's mode of action. Sometimes drugs work against EBOV without having a specific target or mechanism of action. One well-known example is brincidofovir, which was investigated as a therapy for adenovirus, smallpox, and cytomegalovirus. How the chemical prevents an RNA virus like EBOV is not yet known because it only inhibits dsDNA viruses by way of its method of action. Some of the treatments

The antibodies used in the ZMapp mixture are made by tobacco plants (Nicotiana benthamiana). Due of the limitations on antibody production, there were issues with drug supplies during the epidemic It is possible to quickly develop the best EBOV treatment option in huge quantities so that it is always available when an outbreak occurs.

Obtaining large quantities of convalescent plasma or serum could be difficult. Because they require samples from affected individuals. Because of the rapidity and severity of the 2014-2016 outbreak, as well as the difficulties connected with the pharmaceutical research and development process, it was critical to investigate other options. Repurposing medications was one of these strategies, which aimed to quicken the procedure so that those in need could more rapidly access an approved therapy. Drug repurposing is the process of using chemicals or medications that have already received approval for new uses

Their primary advantage is the use of drugs that the FDA has already approved for various reasons.

Each FDA approval comes with a recognised safety profile that includes details on toxicity, pharmacokinetics, pharmacodynamics, and dose. Furthermore, figuring out how these agents attack EBOV may be difficult. In contrast to Every FDA approval is accompanied by a well-known safety 1 1 5 profile that provides information on toxicity, pharmacokinetics, pharmacodynamics, and dosage. Furthermore, it can be challenging to understand how these agents target EBOV as opposed ton. The EBOV life cycle may be better understood by investigations into the mode of action of these chemicals. Additional information EBOV may continue to persist in body fluids like semen for months after sickness recovery, as evidenced by data from the 2014–2016 outbreak. Some studies have linked EBOV sexual transmission from survivors to their spouses to viral persistence in the semen. As a result, research is being done on the creation of medicines that may remove EBOV from human fluids. To find out if GS- 5734 can remove residual viral RNA in survivors' semen, the PREVAIL IV experiment is now running (NCT02818582) (8)

Vaccines

Ebolavirus vaccines types

In general, non-producing vaccines against the Ebola virus indefinitely virus can be separated with the former further subdivided into vector-based vaccinations, inactivated vaccines, and vaccines against single units. (6)

1 Non-replicating ebolavirus vaccines

a) Inactivated Vaccines

Numerous strategies have been continually researched producing something reliable and efficient non replicating vaccine candidates to treat EBOV infection, despite the fact that inactivated vaccines have the issue of inadequate viral inactivation leading to a rebound to virulence. In a guinea pig, it was discovered that EBOV that had been inactivated by heat and formalin was protective against EBOV infection model. The use of immunological plasma, interferon (IFN), and inactivated vaccination with EBOV E-178 spared a researcher on EBOV.

Liposome-encapsulated radioactive EBOV was proven to be 100 percent effective at protecting mice when in a mouse model for testing. These viral particles, however, were unable to shield NHPs. Therefore, the mouse model is very useful for evaluating the effectiveness of vaccines. Because the extent of protection may vary between species, immunizations must first be studied in NHPs before being put through clinical trials on people. It has been established that EBOV vaccines that have been destroyed by heat, formalin, or gamma radiation are useless at preventing EBOV disease. (1)

b) Replicons

Alphavirus replicants were a part of a different early attempt at a vaccination. This was achieved by introducing ZEBOV GP in place of the structural genes of the Venezuelan equine encephalitis virus (VEEV).

The replicon was then generated from an RNA expression vector and packaged into VLPs by delivering the structural VEEV proteins in trans.) When replicon-containing VLPs were given to animals as a vaccination

The replicon's nonstructural VEEV proteins caused ZEBOV GP to replicate and express strongly in the mice. Due to the lack of expressed structural VEEV proteins in animals exposed to the vaccination,

VLPs carrying the VEEV replicant can only survive for one infectious cycle. These vaccines failed to protect NHPs despite being extremely protective in mice after two vaccinations and in guinea pigs after three vaccinations. According to the vaccination dosage and immunogen employed, a similar strategy was previously applied to Kunjin virus replicons, and it shielded between 25 and 86% of guinea pigs challenged with ZEBOV. It is unknown whether the Kunjin virus replicon will be protective in its present state, despite the fact that this immunization has not been tested in NHPs. Resulting from the VEEV replicon, which completely protected guinea pigs,(6)

c) DNA vaccines

DNA ebolavirus vaccines have been shown to protect rats, mice, and guinea pigs in studies. Increasing the dose resulted in 100% survival after two shots in mice and 100% survival after three vaccinations in guinea pigs. Previously, 100% protection in mice took four to five

injections. DNA vaccinations with a boost using a recombinant, replication-deficient adenovirus expressing ZEBOV GPhave been evaluated in NHPs.

This was the first tactic to successfully defend all NHPs against a challenge that would be fatal if not. However, given that the recombinant adenovirus alone can provide 100% protection, it is unclear how much the DNA component of this method contributed to this success. But in a preliminary Phase I clinical experiment, a DNA vaccine has been shown to be secure and to trigger T-cell and antibody responses in humans after three doses.

d) Artificially generated adenoviruses

The first application of recombinant adenoviruses was as a booster with DNA vaccinations. Although all of the challenged NHPs were totally protected by this immunisation method, it took longer than six months to finish the immunisations. However, even though antibody titers were lower than when utilising the DNA/adenovirus combination approach, the recombinant adenovirus alone offered 100% protection in just 4 weeks. It has been proven that the vaccine dose is crucial for its efficacy, with NHPs requiring at least 1 1010 virus particles for complete immunity. Although successful in mice, attempts to reduce this dose by employing optimized immunogen expression casettes have not yet been tested in NHP models. Multiple ebolavirus strains have been protected against using adenovirus-based vaccinations. After a single vaccination, NHPs were protected against challenge with either virus by a recombinant adenovirus that expressed the GP of SEBOV and ZEBOV.

In addition, a mixed vaccine including Cross protection against BEBOV, an ebolavirus strain not covered by the immunisation, was brought on by adenoviruses expressing either ZEBOV GP or SEBOV GP and administered as a component of a combined DNA/adenovirus vaccination strategy. This suggests that it ought to be able to develop a robust immune system to defend against ebolaviruses, including newly discovered species.

The adenovirus vaccine was assessed in a Phase I clinical trial and shown to be safe for all participants, similar to DNA immunisation.

GP-specific T-cell responses, which have been proven to be the primary predictor of protection for the adenovirus vaccine in NHPs , were detected in 25-45% of vaccinees, depending on the vaccination dose and species from which the GP gene was derived. Obtained Pre-existing immunity is a major issue for the viral vaccination platform.

According to their country of origin, between 60 and 90% of people are seropositive for adenovirus serotype 5 (Ad5), the basis of the first recombinant adenovirus vaccination. Pre-existing immunity to Ad5 has significantly decreased the Ad5 vaccine's efficacy in mouse and NHP models. Ad5 seropositive individuals exhibited considerably reduced antibody response rates and antibody response magnitudes following immunization in the Ad5 vaccination clinical study.

To solve this issue, a number of strategies have been explored, including the use of various adenovirus serotypes as vectors, modifications to the vaccine delivery method, and adjustments to the frequency of injections. This suggests that it ought to be able to develop a robust immune system to defend against ebolaviruses, including newly discovered species. The adenovirus vaccine was assessed in a Phase I clinical trial and shown to be safe for all participants, similar to DNA immunisation. T-cell responses to the GP gene were observed in 25-45% of vaccination recipients, depending on the immunization dose and the species from which the GP gene was taken. These responses have been proven to be the primary correlate of protection for the adenovirus vaccine in NHPs. Pre-existing immunity is a major concern for the viral vaccination strategy. The effectiveness of the Ad5 vaccine has been severely reduced in mouse and NHP models due to pre-existing immunity to Ad5. In the clinical trial of the Ad5 vaccine, Ad5 seropositive individuals showed a noticeably lower antibody response rate and antibody response magnitude after immunisation. The use of alternative adenovirus serotypes as vectors, modifications to the vaccine administration method, and adjustments to the frequency of injections are only a few of the strategies that have been explored to address this issue. It has been demonstrated that preexisting immunity to Ad5 can be overcome in the NHP model by increasing the number of Ad5 vaccines to two. It has also been demonstrated that vaccines based on Ad26 and Ad35, whose seroprevalence is significantly lower, offer 100 percent protection against a ZEBOV challenge, but only after two doses. To solve this issue, a number of strategies have been explored, including the use of various adenovirus serotypes as vectors, modifications to the vaccine delivery method, and adjustments to the frequency of injections. By increasing the quantity of Ad5 vaccines to two, it has been shown that preexisting immunity to Ad5 can be overcome in the NHP model.

A ZEBOV challenge has also been demonstrated to be completely protected against by vaccines based on Ad26 and Ad35, whose seroprevalence is substantially lower, but only after two doses. (6)

e) Subunit vaccines

Traditional subunit vaccines for ebolaviruses use VLPs and pure, recombinantly produced viral proteins as its subunits. Use of traditional subunit vaccines against

ebolaviruses have only been attempted in a small number of studies. In guinea pigs, GP derived from a baculovirus offered. After three injections, there is 50% protection. A component vaccination that protects 83% of challenged mice after four injections purifies the ZEBOV GP ectodomain by fused it to a human Fc fragment.

Immunocomplexes' efficiency as vaccinations was also examined in one study. Plants that adopt this approach must produce GP1 coupled to an anti-GP antibody.

Eighty percent of mice were demonstrated to be protected against challenge by the resulting immunocomplexes after four immunisations. However, these conventional subunit vaccines currently lack the protective efficacy of alternative immunisation strategies, and further advancements are required before the need for NHP research can be justified. The more sophisticated VLP-based vaccinations, however, hold great potential. VLPs bloom when the matrix protein VP40 is expressed in mammalian cells. When coexpressed, these particles contain additional viral proteins, and this characteristic has been utilized to create VLPs that contain VP40, GP, and additional viral proteins. Furthermore, NP. Rodents and an NHP model where they were protected against challenge after three vaccinations have demonstrated the protective effects of these VLPs. The efficiency of vaccination has been shown to be dosage dependent, at least in mice. Yet it may be challenging to synthesize sufficient amounts of VLPs using 293T cells, which are often utilized for VLP production, to immunize humans. Recent research have demonstrated that VLPs can also be created in insect cells using the baculovirus expression system, which is more suitable to large-scale manufacture under good manufacturing production (GMP) standards, albeit they have not yet been tested in NHPs. They have also shown that they protect mice. As they have not yet been tested in, this issue needs to be addressed. (6)

f) Replication-deficient ebolaviruses

It is now possible to genetically alter ebolaviruses thanks to reverse genetics causing this ability, the rEBOVDVP30 virus was produced, which is deficient in the gene encoding the transcriptional activator VP30. While the generated rEBOVDVP30 can infect target cells, it is only capable of undergoing one infectious cycle before ceasing to create infectious

offspring in the absence of VP30. VP30 must be provided in trans in order to grow this virus (for example, by a cell line that was developed specifically for this purpose and stably expresses VP30). As a result, STAT1-KO mice have demonstrated that this virus is not harmful to them. Despite this, 100% of mice and guinea pigs were protected by rEBOVDVP30 after two vaccinations against a challenge that would usually be deadly. Due to There are significant worries about the safety of vaccinations due to the recombinant nature of rEBOVDVP30 and the fact that its genome still maintains more than 95% of the original ZEBOV genome. This is especially true given the emergence of viruses with VP30 reintegrated into their genomes. Sequential passage in Vero cells that produce VP30, however, has demonstrated that there are no recombination events. It could result in VP30 being reintegrated into the genome over the course of at least seven passes. Furthermore, based on what we now know about the biology of filoviruses, such recombination events are not likely to occur.(6)

2 Replicating ebolavirus vaccines

a) Recombinant VSV

NHPs revealed protective benefits from the first replicating ebolavirus vaccine based on a recombinant VSV (rVSV). The VSV glycoprotein of this virus was altered to become ZEBOV GP, and the resulting strain (rVSV/DG/GP) was completely protective in NHPs following a single vaccination.was the outcome

No ZEBOV was detected after a challenge in vaccinated NHPs.

Vaccinated animals showed signs of replication as identified using reverse transcriptase polymerase chain reaction or viral isolation (RT-PCR), and no symptoms of ill health. The dose for 100% in mouse studies It's possible that only two PFU are needed for a successful vaccination because since rVSV/DG/GP is replication-competent, it requires fewer recombinant viruses (1 107 PFU of rVSV/DG/GP vs. 1010 Ad5 particles/GP) for successful immunisation than adenoviruses, which have a weak replication platform. Nevertheless, the rVSV/DG/GP or comparable Using the same platform, relevant vaccinations were given to more than 100 NHPs,no negative effects were seen despite the possibility of a transitory rVSV viremia in vaccinated animals . NHPs intrathalamically infected with rVSV/DG/GP do not exhibit neurovirulence, which is a possible issue following infection with wildtype VSV [82]. Furthermore, rVSV/DG/GP was tested in NHPs with SHIV infection, and despite their

immunocompromised state, the vaccine had no adverse effects in the form of local responses at the immunisation site, a fever, or clinical sickness. Animals with immunodeficiencies had lower and shorter rVSV viremia levels than mice with immunocompetence. Despite having underlying SHIV infections, the vaccine provided protection for four out of six NHPs, with the two infected animals having the lowest CD4+ cell counts. Not only does this study establish the safety of rVSV/DG/GP, but it also highlights the high prevalence of HIV in areas where ebolavirus epidemics are happening. NHPs were discovered to be totally protected against both after receiving the rVSV vaccine by oral or intranasal mucosal administration. According to experts, the most plausible scenario for a bioterrorist strike is a ZEBOV aerosol challenge. The ebolaviruses SEBOV, ZEBOV, and Marburg were able to protect against challenge 2 2 2 with any of those viruses as well as challenge with CIEBOV in recent research seeking to generate vaccines that provide protection against diverse ebolavirus species. Unexpectedly, post-exposure vaccination using the rVSV platform has showed potential rVSV/DG/GP immunisation can still completely protect mice and hamsters up to 24 hours after challenge. The survival rates This duration may potentially be longer for humans because EHF seems to be less harmful in people than it is in NHPs. In actuality, 48 hours following the researcher underwent rVSV/DG/GP treatment after incidental exposure to ZEBOV at a facility with a level 4 biosafety. On Days 1 and 2 of the post-immunization periods, the patient had fever and myalgia.

RTPCRs against ZEBOV L remained negative, and no more adverse effects were noticed. The initial proof that the rVSV vaccination platform is safe for use in humans. Despite the fact that several studies have demonstrated this platform's safety in NHPs, a perceived safety risk persists for it. Additionally, neither the correlates of protection nor the post-exposure vaccine's mode of action are understood. (6)

b) Recombinant human parainfluenza virus type 3

Another negative-sense RNA virus, human parainfluenza virus type 3, has been successfully used as a platform for an ebolavirus vaccine (HPIV3). HPIV3, a common human respiratory virus, was selected to test immunization through the respiratory pathway. Between the P and M genes of HPIV3, a transcription casette expressing the GP gene was introduced, resulting in a recombinant HPIV3 virus (rHPIV3/GP).that carried ZEBOV GP in addition to its own surface proteins

In guinea pigs, this virus was completely protective after a single vaccination and in NHPs, it was completely protective these animals showed no symptoms of EHF illness or viremia after receiving two vaccines. HPIV3 has a high seroprevalence among people, similar to adenoviruses, which may cause concerns with innate immunity. By removing the ZEBOV glycoprotein in place of the genes encoding the HPIV3 surface proteins HN and Fa second-generation rHPIV3 vaccine (rHPIV/DHN F/GP) was developed to solve these problems.

Despite being greatly attenuated in vivo and not spreading past the guinea pig respiratory tract, this virus totally protected all challenged guinea pigs 2after a single vaccination. Although both HPIV3 seropositive and seronegative animals' NHPs responded equally to this vaccine in terms of its immunogenicity.(6)

Vaccination progress

Preclinical Efficacy and Vaccine Platform Vaccination is one of the key strategies for protecting people from infectious diseases. Therefore, it should not be surprising that the first EBOV vaccination attempts started soon after the virus was discovered in the late 1970s. Immunological response or the life cycle

Inactivated virus served as the first EBOV vaccination and shields guinea pigs against the fatal disease. Since then, a range of vaccines against EBOV have been under preclinical development. Recombinant proteins, DNA, virus-like particles (VLPs), and viral vectors make up these vaccines. Plasmids encoding sGP and GP were used to create the first DNA vaccine for EBOV, inducing humoral and T cell responses. Compared to live attenuated vaccines, DNA vaccines have a number of advantages. They are simple to make and safe to use. The DNA itself causes immunological stimulatory reactions, whereas host-cell protein synthesis allows the antigen to be presented internally. The first successful EBOV immunization strategy using a DNA vaccine was four doses of either a DNA vaccine encoding EBOV GP or EBOV NP, which was revealed in 1998 and shown that 100% of mice were protected from lethal EBOV challenge. Ebola VLPs, which morphologically mirror infectious EBOV particles, have also being examined as vaccine candidates. These preparations are the consequence of the co-expression of EBOV GP and VP40 in transfected cells; EBOV NP may also be present but is not essential for these preparations' protective effect. In transfected cells, GP and VP40 self-assemble to create VLPs. Nk cells, which are crucial for innate immune defence against the devastating EBOV infection, are stimulated more by the VLP vaccine. Additionally, VLP vaccination triggers early innate immune

responses that are protective through the host's the production of potent T cell responses and antibodies specific for the GP of the EBOV. A lethal EBOV challenge was overcome by all immunized NHPs without any of them displaying any clinical signs. (9)

Vaccines in Human Clinical Trials

All immunized NHPs survived a deadly EBOV challenge without exhibiting any symptoms, and immunisation with these VLPs RIBI adjuvant additionally generated EBOV GP-specific antibodies and strong T cell responses. Due to the pharmaceutical industry's and other institutions' lack of interest in licencing such products given that there have only been. Despite a few occurrences of human since 1976, the majority of vaccine candidates are still in the preclinical stage.despite these efforts. All four of the nation's phase 1 EBOV vaccination studies, which assessed either the DNA- or rAd5-based vaccines, were handled by the National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases. Clinical investigations for EBOV vaccines were accelerated during the EBOV outbreak in west Africa from 2013 to 2016, resulting in the registration of more than 60 trials on https://ClinicalTrials.gov or the Pan African Clinical Trials Registry. In the majority of trials, vaccination candidates for chAd3, Ad5, DNA, HPIV3, subunit, Ad26- EBOV mixed with MVA-BN Filo, VSV-EBOV, or VSV-EBOV combined with Ad5-EBOV were assessed for their safety, immunogenicity, and effectiveness. Phase 1-3 clinical trials investigated Ad26-EBOV in combination with MVA-BN Filo, VSV-EBOV, and VSV-EBOV in combination with Ad5-EBOV.Countless nations, including the United States, the United Kingdom, and several in Africa, have clinical trials registries. The Ad26-EBOV and MVA-BN Filo vaccines have been the subject of seven phase 1 clinical trials in African nations, which are either ongoing or completed (https://ClinicalTrials.gov; NCT02325050, NCT02313077, NCT02376400, NCT02891980, NCT02376426). Immunization with Ad26-EBOV or MVA-BN Filo (NCT02313077) did not cause any serious vaccine-related side effects in Up to 8 months after immunisation, long-lasting cellular and humoral immune responses were evaluated, and the observed safety profiles were satisfactory.

Additionally, a year later, the vaccine candidate consistently elicited immunological responses. Following the study, between 60% and 83% of subjects displayed vaccine-induced T cell responses and GP-specific antibody responses. In the United States, additional testing on the immunogenicity and longevity of the Ad26-EBOV vaccination regimens is ongoing or has already been completed (NCT02661464, NCT02543567, NCT02543268). A significant

phase 2/3 trial is also being conducted in Sierra Leone (NCT02509494, Pan African Clinical Trials Registry No. PACTR201506001147964). As of the time of writing, the trials' results had not been published. GamEvac-Combi, a vaccine that combines the VSV-EBOV and Ad5-EBOV strains, was developed in Russia. In Russia, one phase 1/2 open-label clinical trial with dose escalation involved 84 healthy persons of both sexes between the ages of 18 and 55. In Russia, one phase 1/2 open-label clinical trial with dose escalation involved 84 healthy persons of both sexes between the ages of 18 and 55. Additionally, 82.8% and 58.6%, respectively, of the subject Both CD4+ and CD8+ T lymphocytes were found.

In a more recent trial, a lyophilized vaccine's immunogenicity was assessed (NCT03333538). Russian licensing for the GamEvac-Combi vaccine approach was just granted. There is not much preclinical information

Available only in one phase 1/2 clinical data set has been made public for this vaccine strategy. Russia and Guinea are currently participating in a phase 4 clinical research to study the vaccine (NCT03072030).

Numerous human clinical trials using VSV-EBOV have been performed or are actively being planned in North America, Europe, and Africa since the EBOV pandemic. To assess the safety and immunogenicity of the vaccine as well as to determine the doses and regimens that may be further examined in phase 2/3 clinical trials, ten phase 1 clinical trials of VSV-EBOV were carried out. Five phase 2 trials using the VSV-EBOV vaccine candidate are now being conducted in the United States, Canada, Liberia, Sierra Leone, and Guinea as a result of this study or they have already been completed in these countries 2015 saw the completion of three clinical trials in phase 2/3 or phase 3. An open-label, cluster-randomized, ring vaccination phase 3 experiment in Guinea served as the initial phase 3 trial. To evaluate the effectiveness of the intramuscular (IM) administration of the VSVEBOV vaccine for the prevention of EVD during the pandemic and to break the transmission chains between humans. Eighty significant adverse events were discovered in the first clinical investigation, of which two (a febrile reaction and an allergic reaction) had been determined to be connected to vaccination, and one Personal randomization, phase 2/3 control, and the study were all conducted in Sierra Leone. The third research was possibly unconnected (influenza-like illness). All three of the patients experienced complete and trouble-free recoveries.

The second trial, which was open-label (NCT02503202) was a phase 3 clinical trial that was conducted across multiple centres in the US, Spain, and Canada.

The VSV-EBOV emergency vaccination is recommended for use in populations at risk for EVD, such as health care professionals, first responders, members of the immediate family of confirmed EVD patients, and contacts of those family members, according to these clinical trials. To find out more about the security and efficiency of one dosage of VSVEBOV against EVD, a phase 3b interventional, single-arm, open-label, nonrandomized trial was carried out in Uganda and the DRC. Between May and July a ring vaccination approach was used to administer the vaccine to contacts of confirmed EVD patients during the 2018 EBOV outbreak in the DRC. VSV-EBOV is the only vaccine being used during the ongoing, deadliest outbreak in North Kivu of the DRC, and has once again been given to around 93,000 people in a bid to combat.(9)

Conclusion

The 2014 EBOV outbreak, which has been described as the worst and largest viral hemorrhagic as sault, to date, has sparked a rapid uptick in research into creating efficient vaccines and treatments to combat it. Given the terrible and worrisome pandemic threat posed by the disease. In recent years, a number of medications have been developed to fight the devastating EBOV infections. In the case of Ebola, authorities may allow modifications from the standard drug/vaccine research methodologies to a reasonable amount.

High prices and high attrition rates can often make the protracted and challenging process of creating new medications more challenging, with only a small portion of the many substances tested in the preliminary stages of discovery ever reaching the clinic.

Initiatives to find new Ebola medications, like the ones discussed in this article, have largely centering on EBOV Zaire. However, a drug with broad-spectrum efficacy against additional filoviruses, including the Marburg and Sudan viruses, or other viral diseases is of great interest. GS-5734, which is effective against EBOV and MARV, and BCX4430, which is active against both of these viruses, are now being studied as two potential therapies' wide range of RNA viruses.

Importantly, these medications satisfy the essential tenets of PK/PD interactions and have shown sufficient triphosphate exposure at safe dosages. It should be thought about conducting additional research using clinical studies that are properly structured and statistically powered. However, additional measures, such as authorization under the Animal Rule, may be required in the absence of a current outbreak.

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Chapter: 6
Factors associated with incidence of cancer in India

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Abstract: Cancer has received considerable public attention worldwide as it becomes second leading cause of death after cardiovascular disease. This alarming increase in the cancer cases emphasizes the need for understanding varied factors that increase the risk of developing cancer. The risk factors responsible for this increasing rate of malignancy in both the developed and developing nations include advanced age, gender, and substance use, occupational and environmental exposure besides behavioral and genetic risk factors. A logical way to identify cancer control opportunities is to understand the causes and risk factors associated with cancers. Therefore, in this book chapter we present the comprehensive picture of causes and the known risk factors associated with the malignancy.

Keywords: Cancer, burden of disease, risk factors, lifestyle, additions, family history, genetics, oncogenes, tumour suppressor genes, immunogenomics.

1. Introduction:

Cancer is a major threat to human health in developing as well as developed countries. Cancer impacts people of all ethnicities, sexual identities and socio-economic backgrounds. Although cancer prevention and treatment strategies have improved over the years, the detection of malignant cases appears to be rising. It is defined as an abnormal growth of cells that results when the cells fail to undergo apoptosis and loss of contact inhibition, leading to uncontrolled growth and division of the cells with the potential to invade or spread to the other parts of the body. These uncontrolled multiplication of abnormal cells forms a mass anywhere in the body which is termed as tumor. During this process, the cancer cells can break away from its primary tumor mass and travel through blood and lymph systems to other parts of the body where they again grow and may develop into new tumors. This process is known as metastasis. [(1)] Cancer development is multistage process termed as carcinogenesis that includes three major steps viz initiation, promotion and progression. [(2)]

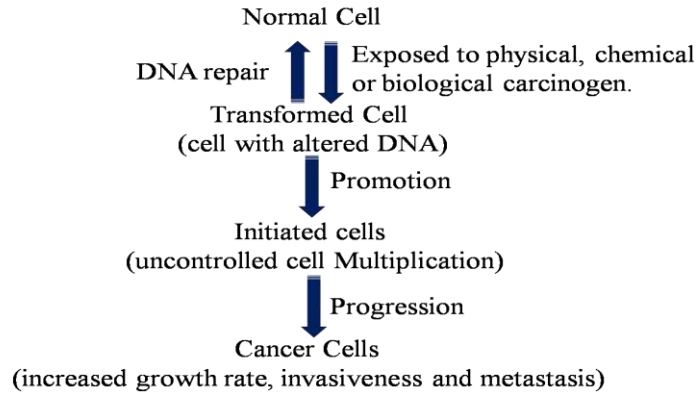

Figure 1: Representative summary showing stages of cancer development.

1.1 Types of Cancers:

Based on the types of cells affected, cancer can be classified into four major types viz; carcinomas, sarcomas, leukaemia's & lymphomas. Carcinomas include 90% of human cancers, such as the cancers of skin or tissues that line or cover internal organs. Sarcomas are the cancers of bone and soft tissues like cartilages, fat, connective tissue or muscles. While the leukaemia & lymphomas, which account 8% of human malignancies, arise hematopoietic cells and the cells of immune system respectively.

1.2 Prevalence of cancer:

Incidence and prevalence rate of cancer is rapidly increasing worldwide. In 2020, International Agency for Research on Cancer (IARC) global cancer observatory reported a total of 1,92,92,789 newly diagnosed cancer cases and 9,958,133 deaths worldwide including both the sexes and all age groups.[3] According to cancer statistics in India, the number of new cancer cases in 2020 was 13, 24,413 and 27,20,251 people were living with cancer. Cancer is responsible for 8, 51,678 deaths annually in India itself. [4] It is also observed that incidence rate is higher in males in comparison with females. It is estimated that cancer burden in India may increase up to 1.57 million by 2025 from 1.39 in 2020. [5] In fact these figures are just the numerical representation of the vast damage caused by cancer worldwide.

2. Causes and Risk factors of cancer:

The etiology of cancer is multifactorial. The exact cause for cancer is unknown; however, there are certain risk factors like change in life style, dietary habits and various addictions that are considered to be associated with the development and progression of different types of cancer. Besides these modulatory impacts of socio-cultural factors, environmental factors and host genetic factors also contribute to malignancy.

2.1 Age & Sex:

As aging is associated with a number of events at the molecular, cellular and physiologic levels that influence carcinogenesis, the incidence of cancer is known to increase with the age. The population group above the age of 50 years is at higher risk of developing cancer as compared to the younger population. [6] Cases in population younger than 30 years of age are less as compared to that of incidences occurring at 60-80 years of age. [7] Studies carried out by Nagini et.al. suggests that in India, the age of cancer occurrence ranges from 35-55 years in South and 45-55 years in North. [8] In a developing country like India, the cancers of esophagus and stomach show preponderance among males as compared to females. [5]

2.2 Diet and Lifestyle:

It has been curious to researchers to know how the foods, nutrients, and eating patterns are related to cancer. It is evident from the literature that diet plays a vital role in development of gastrointestinal cancer. The evidences suggests that diet with high fibre, plant based and low fat content can provide protection against gastrointestinal (GI) malignancies.[9] Micronutrients such as vitamin C, calcium and folate play an important role in lowering the risk of many cancers. Higher consumption of carbohydrates in the form of maize, cereals and refined grains and tubers are found to be responsible for increased risk of esophageal cancer.[10] The association between meat intake and GI cancer confers an increased risk. The studies from 66 counties in eastern Nebraska, examined dietary intake of meat in various forms like boiled, grilled or fried was associated with increased risk for gastric and pancreatic cancer due to the production of heterocyclic amines which act as animal carcinogen. [11] Consumption of excess of salt in diet can also directly damage to the gastric mucosa resulting into the increased cell proliferation thereby increasing the probability of stomach cancer. Both epidemiological and experimental studies have suggested that consumption of salted, smoked, pickled and preserved, spicy, high temperature foods, nitrite and preformed N-nitroso (soda) compounds are associated with an increased risk of GI cancer. [12-13]

Lifestyle-related factors are not cancer causing agents, but are risk factors associated with the occurrence and progression of cancer, through professional exposures, and behaviours that may lead to exposure to recognized or suspected carcinogens. Positive associations have been observed between increased risk of lung cancer and dusty occupations like mining, farming, refining, wood processing and lead processing. Workers associated with these work profiles are found to have increased risk of lung cancer. [14]

Many epidemiological studies have consistently shown association between obesity, as assessed by body mass index (BMI), and the risk of several cancer types. Obesity is on the rise in population worldwide due to lack of physical exercise and sedentary working

conditions, thereby increasing the evidence base for a link between body-fatness and cancers. [15] The risk of colon cancer has been related to sedentary work. [16] It has also been found that people who are obese, have an increased risk of stomach and colorectal cancer. Of the major concern, outdoor air pollution by carbons and hydrocarbons and indoor air pollution by food additives, pesticides and other organochlorines also contribute to cancer.[17] Lifestyle recommendations for reducing the risk of cancers include being lean and physically active, consumption of a plant-based diet, a limited consumption of energy-dense foods and drinks and a reduced intake of salt, red and processed meat.

2.3 Addictions:

Alcohol:

The excessive use of alcohol and tobacco can lead to many health problems including cancer. Alcohol intake is one of the leading risk factors for adverse health worldwide and is strongly linked to the development of several cancers. In 1988, International Agency for Research on Cancer (IARC) has declared alcohol as a type I carcinogen. Mechanisms of carcinogenesis is due to the conversion of consumed alcohol into acetaldehyde, that increases Reactive oxygen species (ROS) production within the cells, thus promoting an oxidative stress that contributes to genetic instability causing DNA damage. [18] Studies reveal that alcohol intake is associated with oropharyngeal and larynx cancer, oesophageal, gastric cancer, hepatocellular carcinoma, and most likely also with pancreatic cancer. [15] Zaridze *et al.* (2000) have reported that men and women who regularly consume alcoholic beverages have an increased risk of stomach cancer. [19] In a developing country like India alcohol consumption becomes a major health problem where the individual engages in excess drinking pattern that puts them greater risk of developing adverse health events. Studies across country have proved the association of alcohol with an increased risk of carcinomas of the esophagus, [20] colorectal, [21] liver, [22] pancreatic. [23] Consumption of alcoholic beverages in any form beer, wine, whiskey, rum, vodka, gin and brandy and locally brewed beverages like arrack and toddy contains 5-30% of alcohol and has also proven to give adverse effect on health thereby increasing the risk of cancer among the population. [24]

Tobacco-

Tobacco is used in different forms all around the world and the cigarette smoking is the most common form of tobacco used worldwide. World Health Organization (WHO) has estimated more than 7 million of deaths occur annually due to the direct use of tobacco while around 1.2 million deaths are the result of non-smokers being exposed to second-hand smoke. [25] Use of tobacco in any form (chewing or smoking) has been observed to increase the risk of cancer

in various epidemiological studies. National Cancer Registry Programme (NCRP) report estimates about 27% of all cancers in India are tobacco related cancers. In India use of smokeless tobacco in the form of Pan, slaked lime with some spicy ingredients and mishiri is the most common form of chewing habit in men and women and is common addiction responsible for all cancer sites. [26] Besides these other tobacco forms like ghutka, hukka, snuff, bidis, cigars, taibur, meiziol, and pipe have also been found to be more common among the teenagers. [27] Tobacco contains more than 60 carcinogens, including N-nitrosamines (TSNAs), nitrite, nitrate, PHAs, aromatic amines and heavy metals such as nickel, cadmium and chromium, that plays vital role in carcinogenesis by forming DNA adducts. [28] Some Indian studies also have implicated the role of tobacco in the development of stomach, oral, pharyngeal and esophageal cancer. [29-30] It is also noteworthy, that tobacco is risk factor independently and the combination of alcohol consumption and smoking together shows a strong interface with the gastric cancer risk. [31] The incidence of carcinogenesis in smokers that consume alcohol is high, as alcohol helps to dissolve chemicals in the cigarette, leaving them in high concentration; this releases toxins and thermal aggression consequently, providing the entry of carcinogenic agents present in tobacco into tissues. [32] The use of e-cigarettes has increased in recent times due to notion that it is a safer alternative to traditional smoking. It is a battery operated having a cartridge or tank, which when lighted up, releases nicotine in the form of vapour. A study conducted by Chidharla et.al stated that, the e-cigarette smokers had 2.2 times higher risk of having cancer as compared to the non-smokers. [33] In a developing country like India where the consumption of smoking and chewing tobacco in different forms is very high, it is demonstrated to be strongly associated with many types of cancers in both males and females.

2.4 Family History:

In addition to the environmental factors, heredity also plays an important role in carcinogenesis. A family history of cancer can increase the risk for cancer progression and is recognized as one of the most important tools to determine the factors in personal cancer risk. As family members share the same environment, inherit genetic predisposition and have similar socioeconomic status, other risk factors act independently or in combination with genetic factors thereby increase the risk of cancer. [34] According to the Online Mendelien Inheritance in Man (OMIM) database, only 10% of the cancers have genetic factors attribute while rest 90% are not attributable to heredity. Studies from Iran, [35] USA, [36] Italy [37] Japan [38] and Europe [39] have shown significant association of family history with the development of gastrointestinal tract, stomach and lung cancers.

2.5 Genetics of Cancer:

Besides the other risk factors, host genetic factors also confer risk for different types of cancer. Cancer is genetic disease that is caused by changes in the genes that control the cell's functions. Genes are the coded messages located on the chromosomes, which carry the instructions to make proteins for normal functioning of the cells. A change in these genes may inhibit protein formation or produce an abnormal protein leading to violent functioning of the cell, where the cell loses its ability to undergo apoptosis or lose ability of contact inhibition causing cells to multiply uncontrollably and lead to the development of cancer. This change in the gene is called a mutation. In order to ensure genomic stability, cells utilize several regulatory mechanisms to correct these changes however the malfunctioning of these regulatory mechanisms can lead to tumor formation. [40] Cancer development is a multifaceted and multistage process comprising of several molecular genetic and epigenetic alterations in DNA repair genes, tumor suppressor genes, oxidative stress related genes, metabolic genes and carcinogen detoxifying genes. These alterations influence the initiation and development of the tumor through abnormal gene expression and protein alterations. Accumulation of such genetic alterations results in perturbations in normal cellular homeostasis, uninhibited cell growth, tumor development and in due course resulting in tumorigenic processes. Cancer is characterized by genomic instability caused either by chromosome instability (CIN), Microsatellite instability (MSI) & Single nucleotide polymorphism (SNPs).

2.5.1 DNA Repair Genes:

DNA repair genes are the major components in DNA repair system which help in restoration altered DNA structure by means of different mechanisms. Multiple DNA repair pathways including base excision repair (BER), nucleotide excision repair (NER), double strand break repair (DSBR) and DNA mismatch repair have been implicated in damaged DNA repair contributing to genetic stability. There are more than 70 genes involved in DNA repair pathways in humans. [41] Genetic variation due to mutations or polymorphisms in the genes encoding these DNA repair pathways can lead to genomic instability that in turn increases the risk of developing various types of cancer. [42] A number of X-ray repair cross complementing group (XRCC) genes are found to be involved in the DNA repair by repair of single strand breaks (SSBs) and are thereby associated with various cancer related pathways in humans. [43]

2.5.2 Oncogenes:

In the normal cells, genome contains a range of proto-oncogenes, responsible for cell differentiation and proliferation. The changes in these genes due to the gene amplification,

activating mutations and chromosomal rearrangements lead to activation of proto-oncogenes which causes them to change into tumour inducing gene, oncogene. Till date there are 50-60 oncogenes identified like RAS, WNT, MYC, ERR, TRK etc.[44] The classical example is gene amplification of N-myc that has been associated with progression of human neuroblastoma [45], and chromosomal translocation of oncogene in BCR-ABL gene found on Philadelphia chromosome observed in chronic mylegenous leukaemia.[46] The point mutations in GIP and GSP oncogene have also been associated with ovarian and thyroid cancer respectively. [47]

2.5.3 Viruses and cancer:

Viruses are the infectious agents that enter the living cell and replicate within the host cell by inserting their nucleic acid (DNA/RNA) into the host genome. The insertion of this DNA/RNA affects the host cells genes and tends them to become the cancerous cells.

Some common viruses linked to cancer are discussed in the table1.

Table 1: Viruses associated with human cancers

Virus	**Mechanism**	**Associated cancer**
Epstein-Barr	B cell immortalization	Nasopharengeal cancer, stomach cancer Burkitt's lymphoma
Human papilloma virus (HPV)	Interfering with tumour suppressor protein p53	Cervical cancer
Hepatities B virus (HBV), Hepatities C virus (HCV)	Alerting the expression of host related genes through protein-protein interaction.	Hepatocellular carcinoma
Human T- lymphotrophic virus	Inducing cellular proliferation, activating cell survival proteins,	Adult T-cell leukaemia

2.5.4 Tumor suppressor Genes:

Another group of genes that plays an important role in tumorigenesis are tumor suppressor genes also called as anti- oncogenes. They are the group of genes encoding the protein that regulate the cell division, repair DNA mistakes and act as brake for cell growth and cell cycling. As compared to the activation of oncogenes, the mutations in tumor suppressor genes may lead to the loss of function for these genes and promote the development of cancers in humans. As p53 and p21 play a crucial role in cell cycle regulation, the genetic alterations in these genes lead to formation and progression of cancer. In this regard the polymorphism of p53 and p21 gene is one of the major research focuses worldwide. The single nucleotide polymorphisms (SNPs) in the p53 and p21 gene are the most common genetic alterations that affect the expression and activity, thereby increasing the risk of

cancer. Several studies have been demonstrated and published regarding the SNPs in p53 and p21 gene and its association with different cancers in various populations. [48-51]

2.5.5 Immune check point and cancer:

In 1957, Burnet and Thomas proposed a cancer immunosurveillance hypothesis where the Immune checkpoint therapy is used to treat patients to fight cancer by reactivating a patient's own immune system. [52] Under the normal conditions body's immune check points allow the immune system to respond against infection and malignancy to protect the tissue from harm caused by this infection. However, the cancer cells can acquire somatic mutations that encode nonself immune antigens called as neoantigens which induces the expression of some of these immune checkpoint proteins by malignant cells dysregulates the antitumor immunity and favour the expansion of cancerous cells. [53-54] With a greater understanding of different cells and mediators of the immune system and their functioning, results in development of the cancer due to insufficient immunosurveillance. One of the approaches emerging out of understanding of immune function was immunotherapy. Immunotherapy approach involves targeting immune check point like cytotoxic T-lymphocyte associated molecule-4 (CTLA-4), programmed cell death receptor (PD-1) and programmed cell death ligand-1(PD-L1) for the enhancement of anti-tumour immune response. Studying these critical checkpoints in relation to genomic mutations and neo antigens may provide the development of immunotherapy in the patients with cancer.

3. Concluding Remark:

In conclusion, the identification of causes and risk factors for cancer is necessary to improve patient treatment. Moreover, for a developing country like India with huge population, varied culture and with geographical variations, a number of risk factors have been identified for many cancers. They include literacy, diet, age and family history and individual genetic makeup, occupational and environmental factors, substance abuse etc. Identification of main causes and risk factors for cancer provides some key strategies for addressing the prevention and treatment of the disease by setting forth a clear and realistic vision for the future. More in-depth research is required to understand the etiology of the disease and to develop suitable screening test to demarcate high risk population. This would help in development of primary prevention strategies and evaluate their effect.

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Chapter: 7
Anopheles: The Deadly Demon

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Abstract: *Anopheles mosquitoes* are the oldest foes of human and its live stock are vectors of *Plasmodium* species. *Anopheles stephensi and Anopheles gambaie* are predictable species as major vector for malaria having parasite *plasmodium falciparum.* Because of malaria 300 millian of people are falling ill and about one million people deaths are annually (WHO 2007). Interruption of malaria vector is priority to stop the transmission of series of malaria parasite vectors. Malaria diseases directly affects to human health, poverty, diseases problem so that malaria considered prevalent in 104 countries and territories around the world. Our government have made many programme to controlling malaria and provided mosquito repellents. That prepared many chemical insecticides and natural insecticide for management and prevention of malaria.

Keywords: *Anopheles stephensi, Anopheles gambiae*, malaria, mosquito management

Introduction:

Malaria is major life- threathing diseases related to health all over the world. Human being highly suffered because of activity of mosquito vectors since long time so that mosquitoes are called most significant human pest. Mosquito vectors belong to genus *Anopheles, Culex, Aedes* causes various diseaseses like malaria, dengue, filariasis, Japanese-encephalitis, yellow fever, chikunguniya (Jaswanth *et al.,* 2002). Mosquito vectors are a major problems for all over world 2 billion people suffered in the tropical regions (Odalo *et al.,* 2005). There are almost 3500 species of mosquitoes are found in tropical and sub- tropical areas (Ghosh *et al*., 2011). Malaria disease is transmitted by various species of *Anopheles* vectors depending upon different season and different areas (Burfield and Reekie, 2005). *Anopheles* is genus of mosquitoes belong to order Deptera. Approximate 484 species discovered beyond the tropical and sub- tropical region in which 100 species transmit malaria dieseases, but only 30-40 species generally conduct parasites of the genus plasmodium of Eukaryotic Protists that causes malaria dieseases. This severe malaria disease is mostly caused by some vectors *Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax and plasmodium* malaria by female *Anopheles* mosquitoes. Here some important species are mention.

• *A. albimanus*	*A. gambiae*	*A. latens*
• *A. stephensi*	*A. arabiensis*	*A. maculipennis*
• *A. culicifacies*	*A. funestus*	*A. moucheti*
• *A. crucians*	*A. darling*	*A. nili*
• *A. barberi*	*A. bellator*	*A. punctipennis*
• *A. introlatus*	*A. latens*	*A. quadrimaculatus*
• *A. cruzii*	*A. dirus*	*A. earlei*
A. freeborni	*A. subpictus*	*A. sundiacus*

Anopheles mosquitoes has four stages of life cycle egg, larvae, pupa and adult and life span is about 10-14 days on the basis of species and the ambient temperature first three stages are aquatic and last one is adult stage. Adult male mosquitoes live usually about one week and feed on source of sugar and Adult female *Anopheles* mosquito can live about two weeks in nature, female mosquito also feeds on nectors and source of sugar. Female *Anopheles* mosquito is needed to have blood source for development of their eggs. Female *Anopheles* lays eggs one at a time and directly on the water surface 50- 200 eggs per oviposition, but normaly takes two- three days in tropical region and eggs hatch within two- three days usually but takes two- three weeks in winter season (" *Anopheles* Mosquitoes"., 2016). Scientific classification is:

Kingdom: Animalia
Phylum: Arthropoda
Class: Insecta
Order: Deptera
Family: Culicidae
Sub family: Anophelinae
Genus: *Anopheles*

Anopheles stephensi:

Malaria is major life- threathing diseases related to health all over the world. *Anopheles stephensi* is a primary vector of malarial diseases in India and also in Africa and other west Asian countries (Burfield and Reekie, 2005). *Anopheles stephensi* is most important pathogen of malarial diseases throughout in the south Asian and Middle East, including Indo- Pakistan land mass (Krishnan *et al*., 1961). *Anopheles stephensi* species observed to be pre-dominent malaria vector in the Persian Gulf region (Davidson and Jackson, 1961). On the basis of morphological features of eggs, egg bredth, egg length and numbers of ridges present on egg

floats surface. There are three type of races have found: first one is type form second one is intermediate form and third is variety form and examples are, *Anopheles stephensi sensu stricto* species is type form which is considered as effective vector in urban areas while *Anpheles Mysorensis* is the variety form. A component of malarial vector found in rural region with of low vectoral capability and zoophilic behavior (Subbarao *et al.,* 1987). *Anopheles stephensi mysorensis* is dominant in the Jiroft district of southest of Iran with parasite of southest of Iran with parasite of *plasmodium vivax* (Ahmad *et al.,* 2011). Mostly is rural areas mosquito larvae of *Anopheles stephensi* were found in various habitat sources of collected water such as: swamps, ponds, steams, marshes, pools containers, small drinages craters and water tanks. Larvae of *Anopheles stephensi mysorensis* mostly found in stone made pots and clay made utensils and containers (Sinka *et al.,* 2011). *Anopheles stephensi* breed at the temperature 27± 2^0c, and humidity 75-85% RH. *Anopheles stephensi* mosquito species typically found sub- tropical and tropical climates areas where *plasmodium* parasite present. Malaria diseases is most prevalent epidemic in the tropical world. Species *Anopheles stephensi liston* is common prevalent vectors of malaria in India country and west Asian countries (WHO, 1994). There are four stages in life cycle of *Anopheles stephensi* mosquito species, egg, larvae, pupa and adult. Life span of *Anopheles stephensi* mosquito species have 10-15 days depending upon season. Female mosquito lived more days than male mosquito. In winter season *Anopheles stephensi* life time is longer than summer season.

Anopheles gambiae:

Anopheles gambiae is also belong family culicidae. *Anopheles gambiae* is important malaria vector found in sub-Saharan Africa and it includes most hazardous parasite of malaria diseases. *Anopheles gambiae complex* or *Anopheles gambie sensu lato* had known as only species complex and *Anopheles gambiae complex* involves some species are *Anopheles arabiensis*, *Anopheles bwambae, Anopheles merus, Aopheles melas, Anopheles gambiae sensu stricto ,Anopheles quadriannulatus, Anopheles amharicus* and *Anopheles amharicus.* These *Anopheles gambiae* complex specises are difficult to recognize individually each other, these species have various behavioural changes some species survive in salt water, mineral water and some in freshwater. Some *Anopheles gambiae complex* species feed from zoophilic animal and some feed human blood (C. Fanello *et al.,* 2002). *Anopheles gambaie* larvae are mostly found in puddles, pools and fresh water ground bodies e.g. rice fields, flooded areas whereas Bamako/ Savana and S forms had seen more generally rain dependent sites as ground ponds. Larvae swim horizontally on water surface and light green in colour. Egg of *Anopheles gambiae* is dark in colour having one pair of air floats on both sides. Anopheles

gambiae female lays eggs singly on water surface swim freely. Pupa of *Anopheles gambiae* having long respiratory siphon on cephlothorex and paddle bear a single long bristle on 9th segments. *Anopheles gambiae* are mostly anthropophilic and less discriminant. Female *Anopheles gambiae* mosquitoes feed blood at late night and endophagic and endophilic both in nature.

Life cycle of *Anopheles*:

Anopheles mosquito life cycle having four stages: **egg, larva, pupa** and **adult**. There 3 stages go to through aquatic but rest seven to fourteen days are depend on the temperature, humidity and rainfall. Life cycle of *Anopheles* mosquitoes may differ depending upon particular species.

Eggs:

Female *Anopheles* mosquitoes lay eggs (50-200) once. These eggs are unique than other because of having floats on both sides and quite small in size. Eggs are directly and lonely rested on the surface of water (CDCP, 2015).

Larva:

Anopheles mosquito larvae have wholly developed with mouth parts including big thorax and abdomen having 9 segments. Anopheles larvae have not respiratory siphon and no legs. Larve respire with the help of spiracles found 8th segment of abdomen. Anopheles larvae feed on bacteria, algae and micro aquatic organism of water surface and swim parallel on surface but go into the water after disturb.

Pupa:

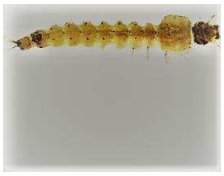
Pupa of *Anopheles* usually comma shaped and divided in head, thorax and abdomen curved shape but thorax merged in cephalothorax and it is main site where respiratory trumpets is present for respiration. After splitting of cephalothorax pupa becomes adult.

Adults:

Anopheles mosquito divided into 3 parts: head thorax and abdomen having slender body shape. Head is main and important section because of presence of mouth part which helps blood feeding and sensual activities. Second part is thorax having 3 pairs of legs and 1 pair of wings for movement and third part is abdomen which helps in digestion of food and egg formation. Adult male and female mosquitoes mate after few day of emergence of pupae, female mosquito feeds on vertribrates for nourishment of their eggs but male mosquito feeds on flowers and sugar sources. Male mosquitoes live only about one week. After feeding blood female adult rest for 2-3 days for development of their eggs then after lays eggs on the

water surface depending upon temperature and humidity of atmosphere. This cycle runs till when female adult was die.


1- Egg


2- Larva


3-Pupa


4-Adult

Life Cycle

Distribution:

Anopheles mosquito vector are found world-wide and all tropical and sub-tropical part of India mostly. In India where temperature is moderate, such regions *Anopheles* mosquito found through-out the year. Cold regions such as Himalayan are unfavorable for Anopheles development. *Anopheles* mosquito breeds in clean water bodies: cisterns, water tanks, tin cans artificial pond and tree holes etc.

Management of mosquitoes:

Malaria and other mosquito born- diseases are becoming major problem now a days, diseases burden for India so that mosquito control is very important (Prabhu *et al.,* 2011). Vectors-borne diseases diseases remains prevalent more than hundread developed countries and diseases control is big goal to reformed health of World people (Elangovan *et al.,* 2012). Mosquito vector borne diseases control has become more difficult because of high amount uses of chemical insecticide as like DDT(di cloro di fenyle tri cloro ethen), DEET(N N- di ethyl –methyl toluamide) and permethrin (Elangovan *et al.,* 2012) which causes so many skin problems and affect direct on the environment and ecological balanced. Richness of synthetic pesticides is harmful to human being and animal which are not degradable spread deadly effects. Some natural repellents are also used for mosquito control which obtained from the plants called essential oils which are volatile in nature (Sukumar *et al.,* 1991). Essential oil occurs in leaves, seeds, woods, flowers, fruits, roots, of various plants which have capacity of repellency of mosquito vector and insect (Uniyal *et al.,* 2015). Non chemical repellents are also used to control of mosquito vectors. 1- Medicated net are used to stop mosquito biting. WHO appropriate the medicated net for controlling of vectors which more effective than coil or liquidators (Atieli *et al.,* 2010). 2- non medicated net is available in markets which are made of different material as like polymide, cotton, polyester that protect from mosquito bite

(Gaddaguti *et al.,* 2016).3- mosquito traps are used to catch mosquitoes which opreted by propane and electricity so that safely used to manage of mosquito control (Raja *et al.,* 2015).

Conclusion:

Mosquito vectors may cause various types of diseases that enfluenced highly to human being and ecology. *Anopheles stephensi* is main malaria pathogen having parasite *Plasmodium* and found mainly in May month and then decreases regularly. Activity of *Anopheles stephensi* low during cold winters and hot summers (Ahmad *et al.,* 2011). Management of malaria diseases is big challenge to us and it is responsible for childhood and adult mortality. Our government has done so many practices for controlling of mosquito and management, provided various type of synthetic chemical pesticides, drugs, bug sprays that help to prevention of malaria. But that type of mosquito repellents are affect directly to human health and causes many skin problems so that we should use natural insecticides which are prepared from plant parts that are also easily biodegradable.

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Chapter: 8
An Introduction to neck pain and posture among Granthies

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Background

Pain is defined as an unpleasant emotional experience associated with actual or potential tissue damage. Neck pain is defined as pain in head and neck region caused by degenerative disease, trauma, inflammatory or mechanical disorders. Neck pain is the common source of Disability (Shah *et al.*, 2015). Neck pain is a second most common musculoskeletal problem after low back pain increasing in both the general population and in specific occupational Groups. As people are increasingly sedentary in nature, live a fast life, hectic occupational schedules; have more stress and strain on the upper back and neck regions of their Spine (Binder, 2007). The person suffering due to pain causes disability and impaired Quality of life and increases great socioeconomic burden on both patient andsociety (Borghouts *et al.*, 1999). The types of neck pain includes acute and chronic and occurs Suddenly which usually heals in several days to weeks .The source of pain is associated with muscles, ligaments, joints or discs .The chronic neck pain persists for more than 3 months and an individual all the time feels it which worsens with certain activities .It may occur due to nerve damage, tissue scarring, arthritis and emotional effects of pain .Neck pain may result from injury, poor posture, stress and disease. Injury or trauma like whiplash injury, sports injuries, herniated disc, pinched nerve, osteoarthritis and stenosis are the causes of neck pain. Neck pain is associated with a decrease in neck muscle strength. Neck strength training has been one of the means in seeking the cure for neck pain. In addition to gaining neck muscle strength, neck strength training has been shown to be effective in reducing neck pain and disability associated with it (Salo, 2010). University students seemed to have a higher risk for developing neck pain (Rose, 2000). Some of the perceived causes of neck pain among students are seats without back supports in lectures, long hours of reading, computer use, history of neck pain, posture assumed during lectures, long sitting hours, prolonged standing, ztype of pillow used when sleeping, prolonged writing, excessive physical activity, stress, prolonged driving and menstruation (Ayanniyi *et al.,* 2010)

The signs and symptoms of neck pain includes stiffness ,tightness, burning, aching, pressure and tingling .If nerves are involved pain ,tingling ,numbness or weakness may develop in shoulders, arms or hands (Ryan, 2013).

In obese individuals neck pain occurs because of systemic inflammation, deleterious structural changes, increased mechanical stress as well as psychological issues which lead to greater disability as compared with normal built people. The prognosis of acute neck pain isfound to be good as compared to the chronic neck pain (Cote *et al.*, 2016).

Functional disability is defined as an acquired difficulty in performing basic everyday tasks or more complex tasks needed for independent living. Performance in functional disability includes three dimensions: physical, emotional, and mental. Physical performance relates to the body's sensory and motor function, and is evaluated through activities of daily living which includes self-care tasks includes bathing, getting dressed, going to the bathroom, getting from bed to a chair and vice-versa. To reduce functional disability we should have adequate knowledge of the risk factors involved in the process of loss of autonomy and implement preventive strategies. In this context, it is necessary to determine the role of gender in the incidence of functional disability in the elderly, in order to establish preventive measures, and the healthcare supply needs to be adjusted for men and women (Rodriguez *et al.*, 2009).

1.1 Epidemiology of Neck Pain

According to the epidemiological study records the annual prevalence of neck pain is ranging between 15% and 50%, According to one systematic review neck pain is the fourth leading cause of disability, with an annual prevalence rate exceeding 30%. The prevalence of neck pain is higher in females and peaks in middle age. The few episodes of acute neck pain will resolve without any treatment, but nearly 50% of individuals will continue to experience its frequent occurrences (Cohen *et al.,* 2015).According to this view, most affected individuals recover and few develop chronic neck pain and disability (Cote *et al.*, 2004).

1.2 Biomechanics of Cervical Spine

There are seven cervical vertebrae in cervical spine. The cervical column consists of upper cervical spine which is also known as cranio vertebral region and the lower cervical spine. The cranio vertebral region includes the occipital condyles and C1 and C2 or respectively the atlas and axis. The lower cervical spine includes the vertebrae of C3 to C7.

The atlas is in between the occipital condyles and the axis. The function of the atlas is to

cradle the occiput and to transfer forces from the occiput to the lower cervical vertebrae. There are two lateral masses on the atlas which are connected by an anterior and a posterior arch which together forms a ring structure and also creates large transverse processes for muscle attachments. These transverse processes contain a foramen for the passage of vertebral artery. The axis transmits the combined load of the head and atlas to the cervical spine and to provide motion for axial rotation of the head and atlas (Winter and Hayden, 1988).

1.2.1 The Lower Cervical Region

The body of the cervical vertebrae is small, with a transverse diameter greater than its antero posterior diameter and height. From C1 to C7 there are upper and lower end plates having transverse diameters that are greater than the corresponding anteroposterior diameters. The posterolateral margins of the upper surfaces of the vertebral bodies support uncinate processes which are present prenatally and between 9 to 14 years of age, but they enlarge gradually. The pedicles project posterolaterally and are located half way between the superiorand inferior surfaces of the vertebral body. The laminae are slightly curved in shape and project posteriomedially.

The articular processes support paired and superior and inferior facets. The superior facets are flat and oval and face superiorly and posteriorly. They lie between transverse and frontal planes. The width and height of the superior zygopophyseal facets gradually increase from C3 to C7 (Norkin and Levangie, 2012).Bilaterally in the transverse processes a foramen is present for the vertebral artery, vein, and venous plexus and for the spinal nerves. The spinous processes of lower cervical spine are short extending horizontally and with a bifidtip. The length of spinous process decreases slightly from C2 to C3 remains constant from C3to C5 and undergoes a significant increase at C7.The vertebral foramen is large and triangularin shape to accommodate large spinal cord (Norkin and Levangie, 2012).

1.3 Functions of Cervical Spine

The cervical spine provides a large amount of mobility. The motions of flexion, extension, lateral flexion and rotations are permitted in the cervical region. In flexion, the occipital condyles roll forward and slide backward and in extension these condyles roll backward and slide forward. There is little degree of lateral flexion and rotation available at this segment which is coupled motions. Approximately 55% to 58% of the total rotation of the cervical region occurs at the atlantoaxial joints and the remaining 40% of total rotation available is distributed evenly in lower joints. The cervical region is subjected to various stresses like

compression tension, bending, torsion and shear stresses (Norkin and Levangie, 2012). Excessive physical strain may cause micro trauma in connective tissue and psychological stress may lead to increase muscle tension and pain (Misailidou *et al.*, 2012). The laxity and weakness of the extensor muscles occurs due to prolong flexion and bending of neck (George, 2010).

1.4 Posture

Posture is the position in which you hold your body upright against gravity while standing, sitting or lying down. Good posture involves training the mind and body to stand, sit, lie and perform everyday life activities such as walking, bending down and exercising in positions where the least amount of strain and stress is placed on supporting structures, muscles and ligaments. It is the orientation of a body segment relative to the gravitational vector. It is an angular measure from the vertical.

1.5 Sustained Posture

The sustained loading in a single direction occur in soft tissues without interruption of the further movement is known as creep. It always occurs due to the rearrangement of collagen fibres and water being squeezed from the soft tissue. If there is no excessive sustained loading soft tissues can recover reasonably quickly. However excessive loading, with limited interruption and frequent repetition, can alter the mechanical properties of the soft tissues. Thus fatigue is found to be more susceptible by this loading which causes insidious development of musculoskeletal symptoms without any obvious trauma (McKenzie 2003). Once these symptoms occur due to the sustained posture the discomfort increases day by day and recovery gets slower (Corlett, 2005).

1.5.1 Sustained posture neck pain

Neck pain from poor posture can be explained as the head is in a flexed posture while using microscope, the neck muscles and the associated soft tissue structures work harder to hold up that position for prolong period of time. As prolong sitting progresses these muscles and other soft tissues tighten up due to the excessive load on them. The anterior neck muscles and the associated neural structures become weak. As a result of overloading and tightening of structures there occur decrease in blood flow and oxygen to the soft tissue which ultimately become the reason for pain. This frequently increases tension headaches and formation of trigger points in neck. A feeling of heaviness in the head occurs which

result in poor posture and pain in the neck (Falla *et al.*, 2007).

1.6 Granthies

Granthies also have a prolonged sitting posture and reading; this can cause significant mechanical imbalances on the neck structures and may lead to neck pain. The work of Granthi constitutes to conduct weekly Sunday divans. Gurmat Katha conducts sanskaras suchas birth ceremonies, conduct Gurbani classes and provide spiritual counselling. Granthi is a spiritual leader, also a religious minister. He performs all the Sikh ceremonies from birth, baptism, and death. A Granthi is spiritual counsellors provide spiritual counselling to individual and families. Granthi is a teacher and role model. He teaches various disciplines of gurmat sangeet such as chanting shabad kirtan or Gurbani, playing musical instruments, and Punjabi language (Dhillon).

Prevalence of neck pain among prolong reading is one of the most common medical problems. Improper body posture and long hours in front of these instruments can result in many health hazards such as neck pain (Jensen *et al*., 2002). In the general population, neck pain and dysfunction are common, affecting up to 67% of the general population at some time during their life (Cote *et al.,* 1998). Neck pain may arise from any of the innervated structure of the neck, such as intervertebral discs, muscles, ligaments, zygopophyseal joints, Dura or nerve roots (Bogduk, 1998).However in the majority of cases, the pathophysiological mechanisms underlying neck pain are unclear. The factor which leads to neck pain among Granthi population depends upon number of hours of studying and reading, workplaces setting and poor postural pattern adapted by them. It is suggested that prolonged sitting and neck in forward flexion are risk predictors of neck pain (Blair *et al*, 2015). Neck flexion posture can lead to an increase in gravitational load movement, which increase cervical extensor muscle activity andcause strain on neck extensors.

In a slump sitting position, greater cervical and thoracic extensor activities are required to support the head in forward position and the combination of neck flexion and cervical extensor activities may produce specific stress regions and cause postural neck pain. On the other hand, sitting postures that offer support to the lumbo-pelvic region in a neutral position significantly reduces the level of cervical extensor activities that are associated with prolonged neck flexion and forward neck posture

Many studies are having investigated the relationship between neck pain and working

conditions. Office workers are a specific population at high risk of developing neck pain, with one year prevalence rates much higher than in general population. (Chiu *et al*., 2002; kamwendo, 1991). It is generally stated that the aetiology of work-related neck disorder is one of the multidimensional which is associated with and influenced by a complex array of individual, physical, and psychological factor (Cagnie *et al*., 2007). It has been said that physical and psychological factors are the most common risk factor associated with neckpain.

Ergonomic factor also plays role as one of the leading and widespread cause of neck pain. Forward head posture which is observed in many Indian a long term habitual posturecan result in abnormal loading of ligaments and muscles that might ultimately contribute to a reduction in the cervical ROM and to the development of neck pain (Edmondston *et al.,* 2005). It has also been observed in a study that a decreased cervical ROM is associated with poor sitting postures, such as forward head posture (Fernandez-de-las-Penas *et al*., 2006). Increased forward neck flexion may result in increased tension in posture-stabilizing muscles as well as increased compressive forces in the articulations of the cervical spine, resulting in ahigher risk of work-related musculoskeletal disorders (Ariens *et al*., 2001).

1.7 Outcome Measures

1.7.1 Neck disability index

Frequent neck pain can lead to inability to carry out daily work with full efficiency and productivity. Thus, when these day to day activities are not performed with same efficiency compared to symptom free period it can be referred as neck disability. Reduced health-related quality of life is associated with subjective pain and clinical signs from theneck and shoulders (Anderson *et al*., 2002).

Published in 1991, the Neck Disability Index (NDI) was the first instrument designed to assess self-rated disability in patients with neck pain. The NDI is the oldest and most widely used instrument for self-reporting of disability due to neck pain. Its internal psychometric properties have been well established in numerous cultural groups with neck pain. It is highly reliable, strongly internally consistent and has a strong and well-documented convergent and divergent validity with other instruments used in the evaluation of patientsand subjects with neck pain. NDI is a region specific instrument that focuses on the construct of neck pain or disability in order to gather information about the impact of disease. Clinicians can confidently apply a “minimum clinically important change” value of

3 to 5 points in their practice settings, whereas researchers can make use, in future clinical trials, of the large number of reports of the responsiveness of the instrument to various therapies over various time frames and according to various indices of responsiveness. The Neck Disability Index (NDI) is designed to measure neck-specific disability. The questionnaire has 10 items concerning pain and activities of daily living including personal care, lifting, reading, headaches, concentration, work status, driving, sleeping and recreation. The measure is designed to be given to the patient to complete, and can provide useful information for management and prognosis of those with neck pain.

Each item is scored out of five (with the no disability response given a score of 0) giving a total score for the questionnaire out of 50. Higher scores represent greater disability. The result can be expressed as a percentage (score out of 100) by doubling the total score (Vernon *et al*., 1992). Test retest reliability (r) is 0.89 (Vernon *et al.*, 1992), ICC 0.68 (Joshua *et al*., 2006). Validity of NDI internal Cronback's alpha is 0.80 (Vernon *et al.*, 1992).

1.7.2 Visual Analogue Scale

A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured (Crichton N., 2001). The visual analogue scale (VAS) was developed to allow the measurement of individual's responses to physical stimuli such as heat. The VAS is a method that can be readily understood by most people to measure a characteristic or attitude that cannot be directly measured. It was originally used in field of psychometrics and nowadays widely used to assess changes in patient health status with treatment (Watada *et al*., 2011). Haung, Willkie and Berry (1996) have concluded that VAS is a simple, reliable, reproducible, valid and sensitive tool. It has been found particularly useful with patients who are experiencing discomfort for nausea, pain, fatigue and shortness of breath. (Neiswiadomy, 2008). Advantages are that it provides a continuous data, thus means and standard deviations can be calculated and tests based on Normal distribution are possible. Statistical power is greater than other categorical rating scales and so it is possible to detect equivalent differences with smaller sample. Disadvantages are that the VAS score data are not true measurements in that they represent a subjective assessment (Peacock and peacock 2011) Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. This scale has been validated

in acute pain and change in pain (Ohnhaus and Adler 1975). Reliability of the VAS for disability is moderate to good (Boonstra *et al*., 2008).

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Chapter: 9
The Clinical Effect of Music: Music Therapy

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Abstract: India is a diverse country with various existing customs and music is one of them. Music is a well-organized sequence of sound and it is as melodious as its name. Every rhythm and tone of music can be recognized by our human brain and its interventions are believed to affect our body by promoting relaxation and other physiological changes. Music alters the mood and behavior of a person by inducing emotional changes in humans and is used as a therapeutic agent in the medical field in the form of therapy. The preference for music defines a person's mental health as some people love to listen to fast-beat music and some are fond of slow and soothing music. As per the literature review, several recent studies on music have suggested that music could be used as a treatment in the medical field and serve as an effective stress management tool for certain diseases. Even along with medicine, music can be used as an adjuvant to reduce anxiety and stress in patients after surgery.

Keywords: *Music therapy, Rhythm, Anxiety, Stress.*

Introduction

India is known as the most diverse country in the world where various languages, religions, dance, music, architecture, food, and customs exist. Here the music is considered as the worship of God and plays an important role in the daily affairs of society. Music is a well-organized sequence of sounds that has been captured by the auditory cells in animals where they are transformed into electrical signals, themselves conveyed to higher nervous centers (Exbrayat and Brun, 2019). Our human brain is programmed in such a way that it can recognize music by its rhythm, repetition, and even its tone. This actually comes into action with the help of auditory nerves which send signals from the ear to the temporal lobe of the brain where the auditory cortex exists and recognizes the type of particular music (Radstaak *et al*., 2014). It has been proposed that musical neural impulses may influence the release of hormones from the hypothalamus and sympathetic nervous system which in turn may impact changes in blood pressure, heart rate, and anxiety level. Gerra *et al*., 1998 demonstrated that techno-music was associated with a significant increase in heart rate, systolic blood pressure,

and significant changes in a self-related emotional state. As per the literature review, it has been observed that after being exposed to music, the stress-related hormones increased significantly and the normal circadian pattern of the hypothalamic-pituitary-adrenal (HPA) axis is altered (Jameel and Joshi, 2015).

Music interventions are believed to affect people not simply by promoting relaxation or offering diversion in a particular circumstance, but also by bringing about particular physiological changes in the body. Music can influence the body and brain from various perspectives, which is why a developing field is known as music therapy (Tripathi *et al.,* 2022). Kar *et al*., 2015 mentioned that there is various documentary evidence that shows the real power of music which has the capability to unlock the creative spirit that heals the body and strengthens the mind of a person. Positron emission tomography (PET) scanning and functional magnetic resonance imaging (fMRI) of the human brain proved that chilling and pleasurable music can increase regional cerebral blood flow to the mesocorticolimbic system including ventral striatum and midbrain, as well as the thalamus, cerebellum, anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) which are critical to reward and reinforcement as well as strong deactivations in the amygdala, hippocampus, parahippocampal gyrus, and the temporal lobes (Koelsch *et al*., 2006). This music could be rock or classical which induced an improvement in an emotional state. Indian classical (ancient) music is categorized into other two components i.e., Hindustani and Carnatic. The notes (*swara*) in classical music are structured in various forms of Ragas (Nayak *et al.,* 2020).

Ancient Vedic literature of India has mentioned "*Raag Chikitsa*" which is known as music therapy nowadays and the name simply defined its meaning i.e., 'healing through the use of ragas in Indian classical music' (Deekshitulu, 2014). In the Sanskrit language "*Raag*" means color or mood and each raag invokes certain emotions according to the time. Indian Classical music is bizarre to the present generation who admires pop and rock music more. The slow tune and long notes are a sleeping mode for the youth of the 21st century. But in ancient times classical music was the most fascinating thing. There is various research-based evidence that reveals that listening to certain different ragas has therapeutic benefits (Bardekar and Gurjar 2016). Various ragas have since been recognized for their different impact on certain ailments, like for defusing mental tension and reducing the intensity of pain, the Darbari kanhada, kamaj, and pooriya are responsible for this. For hypertension Ahir bhairav, Pooriya and Todi are prescribed (Sairam, 2004abc). These all ragas should be sung and presented in a proper balance of notes for the right impact over various physiological aspects. We all must

know about *Mia Tansen,* the one gem from the nine gems of Mughal Emperor Akbar's court. He was a well-known magician of Hindustani Classical music. Since he was born in the northwest area of modern Madhya Pradesh, his specialty in singing and composing music was *North Indian classical music (also known as Hindustani Classical music).* The ancient Hindus depended on music's therapeutic properties: the chanting and tone associated with Vedic mantras in the worship of God have been utilized since the dawn of time as a remedy for various environmental and personal disharmonies (Sarkar and Biswas 2015). Music therapy involves two primary forms i.e., active and receptive music therapy. Playing instruments, dancing, and singing are some common forms of active music therapy while listening to recorded music comes under receptive music therapy. According to several studies, instrumental music has a larger effect on de-stressing instead of lyrical music which is more stimulating and provocative than calming (Good *et al*., 2000).

Mechanism of Music Therapy

Music is considered as a soothing influence at all stages of life and can draw out a wide range of feelings which can be negative or pleasant depending on the different genres of the music. It has been shown in numerous studies that music produces major changes in the neurological system of the brain (Siebert *et al*., 2003). With the help of Magnetic resonance imaging and Positron emission tomography scans it is clear that neural networks in various areas of the brain region are responsible for interpreting and decoding various aspects of music (Ramalingam *et al*., 2022). When auditory nerves send electrical signals from the music to the brain, the right temporal lobe of the brain recognizes multiple pitches of the music that sounds at the same time.

The human brain is highly advanced in decoding various tunes of music and also in differentiating between different instruments playing the same note. The frontal lobe of the brain perceives emotional content whereas the cerebellum processes the rhythm of the music. An early study revealed that musicians and non-musicians have different brain lateralization in the discrimination of the melody based on the delivery of music to the right or left ear (Spiegel and Watson 1984). Numerous studies based on neuroimaging revealed structural variation in different areas of a musician's brain. Listening to music increases cognitive function in dementia patients and other neurological disabilities like depression, anxiety, and maniacal states and also helps in cognitive recovery, mood elevation, and muscle function. Relaxing and stimulating, both types of music lowered cortisol hormone levels i.e.,

responsible for stress but some studies depict lowering of cortisol happens only due to relaxing music (Ramalingam *et al*., 2022). Fancourt *et al*., 2014 found that stimulating music has a positive impact on other hormones like growth hormone (somatotropin) and adrenocorticotropic hormone, while during relaxing music these hormones remain unaltered. It can be concluded that physiological changes in the body occur due to music therapy.

Music Therapy in Stress

Stress is encountered with a belief of insufficient energy, assets, or information to deal with the situation. Stress is a physiological response to an outside jolt that triggers a "fight-or-flight" reaction in a body (Tripathi *et al.,* 2022). The response to individual stress is depending upon the capacity of that particular individual to handle unexpected situations decently or abruptly. Stress impacts the physiological conditions of the body like stroke, depression, cardiovascular diseases, hypertension, and debilitated invulnerable framework. In response to stress, levels of catecholamines, adrenocorticotropic hormone, and glucocorticoids are increased (Matteri *et al*., 2000). According to the report of "*The American Institute of Stress*" named organization, in daily life almost each individual experiences a different kind of stress from time to time and shortly this stress can lead to reduced concentration and can cause hindrance in learning new information. It is commonly recognized that music affects mood and listening to a certain song can make one feel happy, sad, lively, or relaxed (Biasutti, 2015a).

Millions of people around the world use tranquilizer medication along with various negative side effects to cope up with stress (Bandelow *et al*., 2015). The medicine acts primarily on sharirik doshas (vata, pitta & kapha) and then Mansik doshas (raja & tama) are pacified but music act primarily on mansik doshas and then sharirik doshas are pacified (Malik *et al.,* 2019). Moreover, various types of research have suggested that when people are involved in fun and music activities then their important body functions like blood pressure, respiration, and heart rate which are considered stress markers, start normalizing or decreasing (Polychoronopoulou & Divaris, 2005). Yang et al., 2012 conducted research on the effect of music therapy on hospitalized psychiatric patients' anxiety, finger temperature, and electroencephalography: a randomized clinical trial and they took a total 24 patients for the study. The Beck Anxiety Inventory (BAI) was used for the measurement of stress levels. The experimental group in the study was exposed to music therapy and the results of the study suggested that Experimental group participants had lower scores on BAI in comparison to the

control group. Hence, research provides insight that music therapy intervention can help with mental health issues.

Music Therapy in Somatic Diseases

Somatic symptom disorder is diagnosed when a person has a significant focus on physical symptoms, such as pain, weakness, or shortness of breath. Patients at all levels of health care suffer from bodily complaints in frequent manner such as pain in different parts of the body due to the cause of fatigue, and disturbances of the cardiovascular, gastrointestinal, and other body organ problems (Henningsen, 2018). Research has shown a positive effect on various somatic symptom disorders. As per the literature review, music therapy should not be considered a first-line treatment for pain relief because the magnitude of the benefit of music therapy is small. Music listening for the treatment of pain offers potential advantages of lower cost, ease of provision, and safety.

Music Therapy in Psychological disorders

Psychological disorders are characterized by a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior. These are usually associated with distress or impairment in important areas of functioning. Behavioral and psychological symptoms are often associated with several neurological diseases and are usually overlooked due to the requirement of various diagnostic methods for depression, anxiety, maniacal states (violent behavior), and thought and perception disorders (Raglio *et al*.,2015). There is compelling scientific evidence that music has positive impacts on controlling psychological problems like stress and anxiety. Expressive therapies and non-verbal strategies for supporting, extending, and reshaping patients' modalities of expression and communication are what music therapy treatments fall under (Manarolo, 2005).

Conclusion

Music is a strong medium which we can include in our daily routine to improve our quality of life. Since western music is said to be based on precise mathematical calculations, its effects on the human body might be precisely assessed. Although it adheres to the idea of perfect harmonics, the impact of Indian music is mostly determined by the performer's personality, techniques, interpretations, and elaborations. While this elevates Indian music to a higher plane, it also lessens the likelihood that it will treat all known disorders universally. For a wide range of diseases, music therapy exists as a viable and effective treatment possible when

paired with the standard of care. There are many possibilities for the research of music therapy on endocrinology, post-operative symptoms effect, and stress markers. The selective effect of multiple ragas of Indian classical music can also be seen on different organ systems and other markers of inflammation during cardiopulmonary bypass. According to Kar *et al*., 2015 there are some limitations of music therapy that should also be overcome like failure to assess the catecholamine level as a stress response marker and extension of different ragas of Indian classical music into the postoperative period.

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Chapter:10

EARTH'S SIXTH MASS EXTINCTION EVENT UNDER WAY

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More than 99 percent of all organisms that have ever lived on earth are now extinct. As new species evolve to fit ever changing ecological niches, older species fade away. But the rate of extinction is far from constant. At least a handful of times in the last 500 million years, 75 to more than 90 percent of all species on earth have disappeared in a geological blink of an eye in catastrophes we call it as mass extinctions.

Though mass extinctions are deadly events, they open up the planet for new forms of life to emerge. The most studied mass extinction, which marked the boundary between the Cretaceous and Paleogene periods about 66 million years ago, killed off the non-avian dinosaurs and made room for mammals and birds to rapidly diversify and evolve.

I. What is a mass extinction?

Extinctions are a normal part of evolution: they occur naturally and periodically over time. There's a natural background rate to the timing and frequency of extinctions: 10% of species are lost every million years; 30% every 10 million years; and 65% every 100 million years. It would be wrong to assume that species going extinct is out of line with what we would expect. Evolution occurs through the balance of extinction the end of species and speciation the creation of new ones.

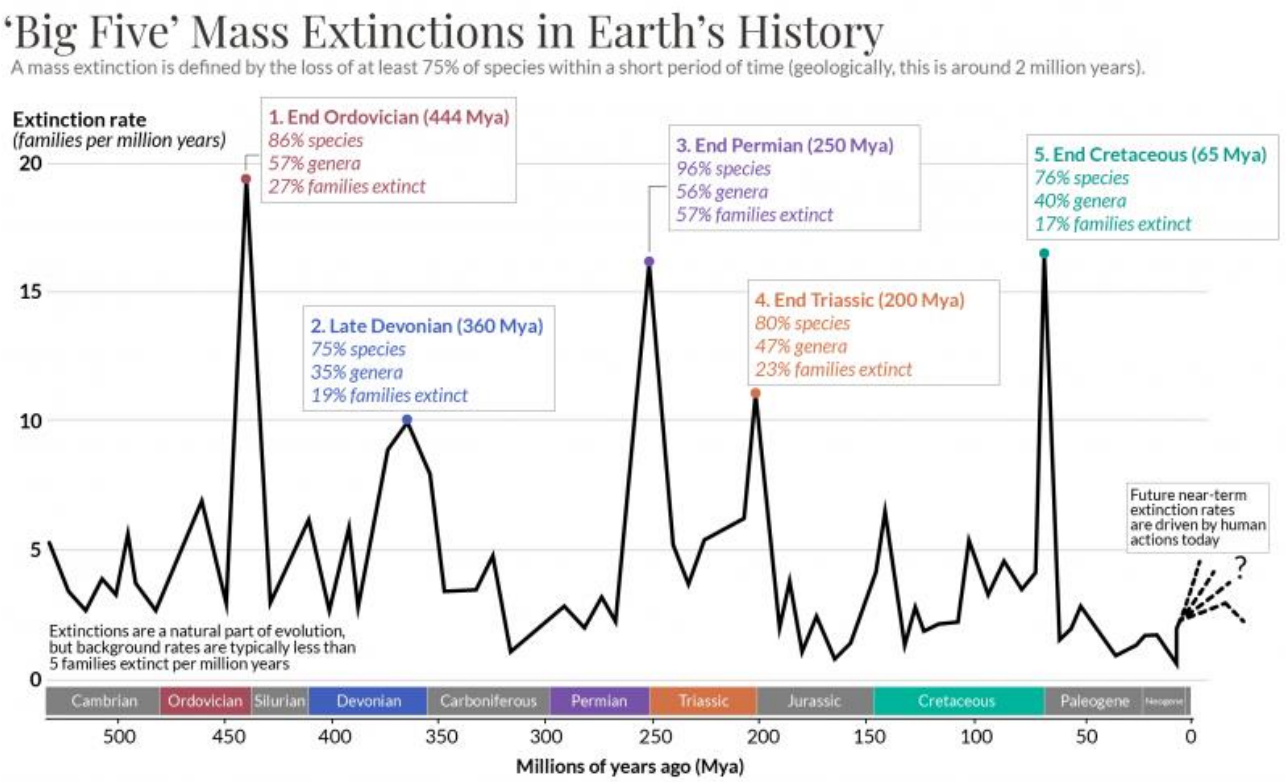
Extinctions occur periodically at what we would call the 'background rate'. We can therefore identify periods of history when extinctions were happening much faster than this background rate this would tell us that there was an additional environmental or ecological pressure creating more extinctions than we would expect.

But mass extinctions are defined as "periods with much higher extinction rates than normal". They are defined by both magnitude and rate. Magnitude is the percentage of species that are lost. Rate is how quickly this happens. These metrics are inevitably linked, but we need both to qualify as a mass extinction.

In a mass extinction at least 75% of species go extinct within a relatively (by geological standard) short period of time. Typically less than two million years.

II. The 'Big Five' mass extinctions

There have been five mass extinction events in earth's history. At least, since 500 million years ago; we know very little about extinction events in the Precambrian and early Cambrian earlier which predates this. These are called the 'Big Five', for obvious reasons.



In the chart we see the timing of events in earth's history. It shows the changing extinction rate (measured as the number of families that went extinct per million years). Again, note that this number was never zero: background rates of extinction were low – typically less than 5 families per million years but ever-present through time.

We see the spikes in extinction rates marked as the five events:

i. End Ordovician (444 million years ago; mya)
ii. Late Devonian (360 mya)
iii. End Permian (250 mya)
iv. End Triassic (200 mya) – many people mistake this as the event that killed off the dinosaurs. But in fact, they were killed off at the end of the Cretaceous period – the fifth of the 'Big Five'.
v. End Cretaceous (65 mya) – the event that killed off the dinosaurs.

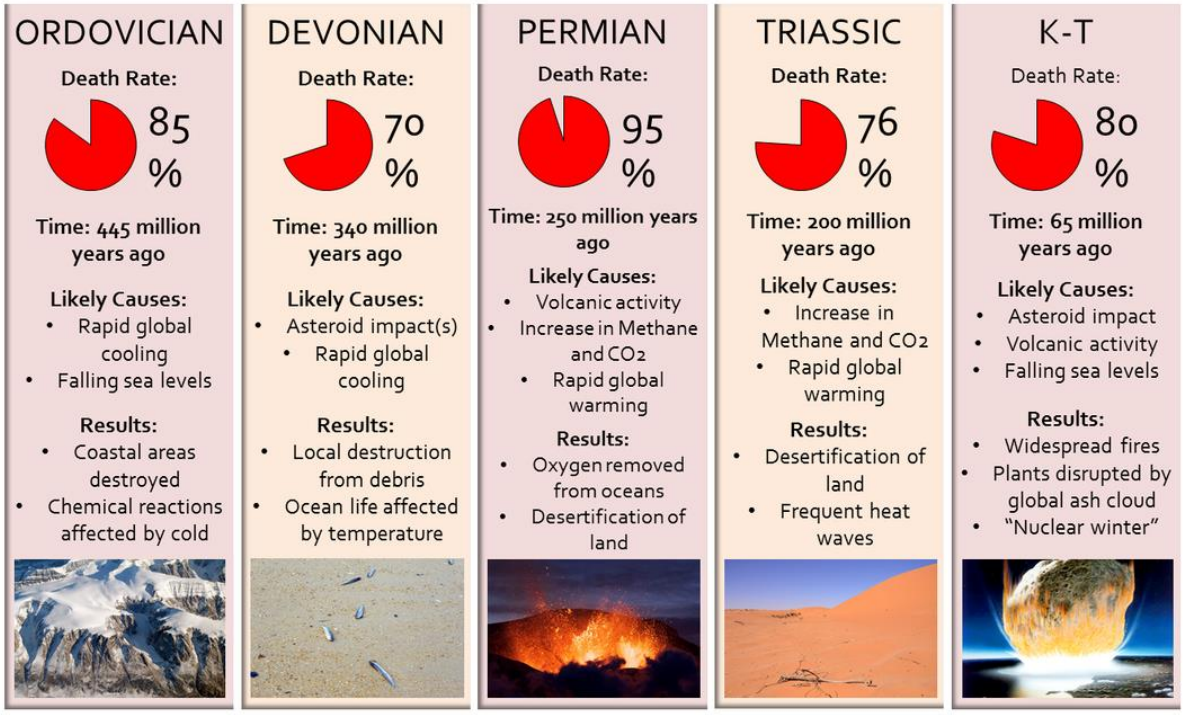
In the table here detail the proposed causes for each of the five extinction events.

Extinction Event	Age(mya)	Percentage of species lost	Cause of extinctions
End Ordovician	444	86%	Intense glacial and interglacial periods created large swings in sea levels and moved shorelines dramatically. Tectonic uplift of the Appalachian mountains created lots of weathering, sequestration of CO_2 and with it, changes in climate and ocean chemistry.
Late Devonian	360	75%	Rapid growth and diversification of land plants generated rapid and severe global cooling. When most species still lived in the sea, oceanic "dead zones" likely caused by deoxygenation killed three-quarters of species.
End Permian	250	96%	Intense volcanic activity in Siberia. This caused global warming. Elevated CO_2 and sulphur (H_2S) levels from volcanoes caused ocean acidification, acid rain, and other changes in ocean and land chemistry. The so called "great drying" destroyed 96% of species.
End Triassic	200	80%	Underwater volcanic activity in the Central Atlantic Magmatic Province (CAMP) caused global warming, and a dramatic change in chemistry composition in the oceans. About thee fourth species were destroyed that cleared the way for dinosaurs to dominate earth.
End Cretaceous	65	76%	Asteroid impact in Yucatán, Mexico. This caused global cataclysm and rapid cooling. Some changes may have already pre-dated this asteroid, with intense volcanic activity and tectonic uplift. This caused destruction of dinosaurs whereas smaller mammals survived and the got comploexed and dominated the earth.

Finally, at the end of the timeline we have the question of what is to come. Perhaps we are headed for a sixth mass extinction. But we are currently far from that point.

1. Ordovician-Silurian extinction (about 443.8 million years ago), which eliminated about 25 percent of marine families and 85 percent of marine species.

2. Devonian extinctions (407.6 million to about 358.9 million years ago), which eliminated 15–20 percent of marine families and 70–80 percent of all animal species. Roughly 86 percent of marine brachiopod species perished, along with many corals, conodonts, and trilobites.
3. Permian extinction (about 265.1 million to about 251.9 million years ago), the most dramatic die-off, eliminating about half of all taxonomic families and about 90 percent of all species, which included some 95 percent of marine species (including all of the trilobites and nearly wiping out brachiopods and corals) and about 70 percent of land species (including plants, insects, and vertebrates).
4. End-Triassic extinction (about 201.3 million years ago), possibly caused by rapid climate change or by an asteroid striking Earth. This mass extinction event caused about 20 percent of marine families and some 76 percent of all extant species to die out, possibly within a span of about 10,000 years, thus opening up numerous ecological niches into which the dinosaurs evolved.
5. Cretaceous-Tertiary (K-T), or Cretaceous-Paleogene (K-Pg), extinction (about 66 million years ago), involving about 80 percent of all animal species, including the dinosaurs and many species of plants. Although many scientists contend that this event was caused by one or more large comets or asteroids striking Earth, others maintain that it was caused by climatic changes associated with the substantial volcanic activity of the time.



There are a range of trajectories that the extinction rate could take in the decades and centuries to follow; which one we follow is determined by us.

III. What caused the 'Big Five' mass extinctions?

All of the 'Big Five' were caused by some combination of rapid and dramatic changes in climate, combined with significant changes in the composition of environments on land or in the ocean (such as ocean acidification or acid rain from intense volcanic activity).

a. Causes of Mass Extinctions

Mass extinctions are associated in time with major environmental changes. The problem, of course, is that other times of no mass extinction also mark the times of environmental change, and it is fair to say that we could not easily predict all mass extinctions with non-fossil data alone. If environmental forcing, which transcends the abilities of species to survive or adapt, is a major cause of mass extinction, what are the factors? We can list them as.

1. Impact or a series of impacts of extra-terrestrially derived objects.
2. Volcanism.
3. Climate change.
4. Lowering of sea level, which reduces available habitats for marine species.
5. Anoxia, especially trans-aggressive spread of deep-anoxic waters onto the continental shelves.
6. Methane hydrates release, resulting in extreme global warming.

These causes stem more from associations in time between inferred geological events and extinctions, and not from a solid model linking environmental change to extinction. The best example of the latter is the Permian mass extinction. The vast marine regression may have been the driving force behind a variety of environmental changes, including a rise in carbon dioxide, which led to increased temperature and oceanic anoxia. At the end of the Permian, sea level dropped, perhaps about 200 m, which was followed by a trans-aggressive rise of sea level in the Lower Triassic. Seasonality and reduction of habitat complexity during the regression may also have begotten environmental instability, beyond the adaptive ranges of a number of specialized groups.

The drop may have been stimulated by a period of extensive volcanism, which in turn caused dry climates and the wide-spread drying of the planet, which reduced burial of carbon in swamps and released carbon dioxide to the atmosphere. This might have caused extensive warming and temperature stress. The reduction of oxygen might have been the trigger for

extinction both on land and sea. If oxygen in the ocean declined, hydrogen sulfide might have appeared, which would be poisonous to most marine life.

Volcanism might be a minor contribution to climate change at the end of the Permian, because calculations preclude much of a change in the large ^{13}C deviations at this time, due to outgassing. However, the extensive volcanism in Siberia might have risen to the surface and heated up carbonates and coal deposits, liberating lethal methane, which might have triggered extinctions and caused larger ^{13}C deviations.

The Siberian traps cover an enormous area of about two million square kilometers. Paleontologists Norman Newell and Anthony Hallam have implicated sea-level change in a number of extinctions throughout the Mesozoic, but they are also often combined with other events, such as bolide impacts, anoxia, and temperature change.

IV. The Planet Is Facing Its 6th Mass Extinction

Ice ages, volcanic eruptions, and asteroids have a new companion: human beings. Scientists are warning that the world has entered its sixth mass extinction an event when a majority of species on earth die off; and unlike past episodes, the cause is not some suddenly overwhelming natural phenomenon. Instead, it's the cumulative activity of humans.

The Holocene extinction, or Anthropocene extinction, is the ongoing extinction event during the Holocene epoch. The extinctions span numerous families of plants and animals, including mammals, birds, reptiles, amphibians, fish, invertebrates, and affecting not just terrestrial species but also large sectors of marine life. With widespread degradation of biodiversity hotspots, such as coral reefs and rainforests, as well as other areas, the vast majority of these extinctions are thought to be undocumented, as the species are undiscovered at the time of their extinction, which goes unrecorded. The current rate of extinction of species is estimated at 100 to 1,000 times higher than natural background extinction rates, and is increasing.

During the past 100–200 years, biodiversity loss and species extinction have accelerated, to the point that most conservation biologists now believe that human activity has either produced a period of mass extinction, or is on the cusp of doing so. As such, the event has also been referred to as the sixth mass extinction or sixth extinction; given the recent recognition of the previously unrecognised Capitanian mass extinction, the term seventh mass extinction has also been proposed for the Holocene extinction event.

The Holocene extinction includes the disappearance of large land animals known as mega fauna, starting at the end of the last glacial period. Mega fauna outside of the African

mainland, which did not evolve alongside humans, proved highly sensitive to the introduction of human predation, and many died out shortly after early humans began spreading and hunting across the Earth. Many African species have also gone extinct in the Holocene, along with species in North America, South America, and Australia, but – with some exceptions – the mega fauna of the Eurasian mainland was largely unaffected until a few hundred years ago. These extinctions, occurring near the Pleistocene–Holocene boundary, are sometimes referred to as the Quaternary extinction event.

The most popular theory is that human overhunting of species added to existing stress conditions as the Holocene extinction coincides with human colonization of many new areas around the world. Although there is debate regarding how much human predation and habitat loss affected their decline, certain population declines have been directly correlated with the onset of human activity, such as the extinction events of New Zealand and Hawaii. Aside from humans, climate change may have been a driving factor in the mega-faunal extinctions, especially at the end of the Pleistocene.

In the twentieth century, human numbers quadrupled, and the size of the global economy increased twenty-five-fold. This Great Acceleration or Anthropocene epoch has also accelerated species extinction. Ecologically, humanity is now an unprecedented "global super-predator", which consistently preys on the adults of other apex predators, takes over other species' essential habitats and displaces them, and has worldwide effects on food webs. There have been extinctions of species on every land mass and in every ocean: there are many famous examples within Africa, Asia, Europe, Australia, North and South America, and on smaller islands.

Overall, the Holocene extinction can be linked to the human impact on the environment. The Holocene extinction continues into the 21st century, with human population growth, increasing per capita consumption (especially by the super-affluent), and meat production, among others, being the primary drivers of mass extinction. Deforestation, overfishing, ocean acidification, the destruction of wetlands, and the decline in amphibian populations, among others, are a few broader examples of global biodiversity loss.

a. Extinction rate

The contemporary rate of extinction of species is estimated at 100 to 1,000 times higher than the background extinction rate, the historically typical rate of extinction (in terms of the natural evolution of the planet); also, the current rate of extinction is 10 to 100 times higher than in any of the previous mass extinctions in the history of earth. One scientist estimates the current extinction rate may be 10,000 times the background extinction rate, although most

scientists predict a much lower extinction rate than this outlying estimate. Theoretical ecologist Stuart Pimm stated that the extinction rate for plants is 100 times higher than normal.

Some contend that contemporary extinction has yet to reach the level of the previous five mass extinctions, and that this comparison downplays how severe the first five mass extinctions were. John Briggs argues that there is inadequate data to determine the real rate of extinctions, and shows that estimates of current species extinctions varies enormously, ranging from 1.5 species to 40,000 species going extinct due to human activities each year. Both papers from Barnosky et al. (2011) and Hull et al. (2015) point out that the real rate of extinction during previous mass extinctions is unknown, both as only some organisms leave fossil remains, and as the temporal resolution of the fossil layer is larger than the time frame of the extinction events. However, all these authors agree that there is a modern biodiversity crisis with population declines affecting numerous species, and that a future anthropogenic mass extinction event is a big risk. The 2011 study by Barnosky et al. confirms that "current extinction rates are higher than would be expected from the fossil record" and adds that anthropogenic ecological stressors, including climate change, habitat fragmentation, pollution, overfishing, overhunting, invasive species and expanding human biomass will intensify and accelerate extinction rates in the future without significant mitigation efforts.

In The Future of Life (2002), Edward Osborne Wilson of Harvard calculated that, if the current rate of human disruption of the biosphere continues, one-half of Earth's higher life forms will be extinct by 2100. A 1998 poll conducted by the American Museum of Natural History found that 70% of biologists acknowledge an ongoing anthropogenic extinction event.

In a pair of studies published in 2015, extrapolation from observed extinction of Hawaiian snails led to the conclusion that 7% of all species on earth may have been lost already. A 2021 study published in the journal Frontiers in Forests and Global Change found that only around 3% of the planet's terrestrial surface is ecologically and faunally intact, meaning areas with healthy populations of native animal species and little to no human footprint.

The 2019 Global Assessment Report on Biodiversity and Ecosystem Services, published by the United Nations' Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES), posits that roughly one million species of plants and animals face extinction within decades as the result of human actions. Organized human existence is jeopardized by increasingly rapid destruction of the systems that support life on

earth, according to the report, the result of one of the most comprehensive studies of the health of the planet ever conducted. Moreover, the 2021 Economics of Biodiversity review, published by the UK government, asserts that "biodiversity is declining faster than at any time in human history." According to a 2022 study published in Frontiers in Ecology and the Environment, a survey of more than 3,000 experts says that the extent of the mass extinction might be greater than previously thought, and estimates that roughly 30% of species "have been globally threatened or driven extinct since the year 1500." In a 2022 report, IPBES listed unsustainable fishing, hunting and logging as being some of the primary drivers of the global extinction crisis. A 2022 study published in Science Advances suggests that between 13% and 27% of terrestrial vertebrate species will go extinct by 2100, much of this through anthropogenic land conversion, climate change and co-extinctions.

b. Attribution

We are currently, in a systematic manner, exterminating all non-human living beings. There is widespread consensus among scientists that human activity is accelerating the extinction of many animal species through the destruction of habitats, the consumption of animals as resources, and the elimination of species that humans view as threats or competitors. Rising extinction trends impacting numerous animal groups including mammals, birds, reptiles, and amphibians have prompted some scientists to declare a biodiversity crisis.

c. Recent extinction

Recent extinctions are more directly attributable to human influences, whereas prehistoric extinctions can be attributed to other factors, such as global climate change. The International Union for Conservation of Nature (IUCN) characterises 'recent' extinction as those that have occurred past the cut-off point of 1500, and at least 875 plant and animal species have gone extinct since that time and 2009. Some species, such as the Père David's deer and the Hawaiian crow, are extinct in the wild, and survive solely in captive populations. Other populations are only locally extinct (extirpated), still existent elsewhere, but reduced in distribution,as with the extinction of gray whales in the Atlantic, and of the leatherback sea turtle in Malaysia.

Humans are rapidly driving the largest vertebrate animals towards extinction, and in the process interrupting a 66-million-year-old feature of ecosystems, the relationship between diet and body mass, which researchers suggest could have unpredictable consequences. A 2019 study published in Nature Communications found that rapid biodiversity loss is impacting larger mammals and birds to a much greater extent than smaller ones, with the body mass of such animals expected to shrink by 25% over the next century. Another 2019

study published in Biology Letters found that extinction rates are perhaps much higher than previously estimated, in particular for bird species.

The 2019 Global Assessment Report on Biodiversity and Ecosystem Services lists the primary causes of contemporary extinctions in descending order:

(1) changes in land and sea use (primarily agriculture and overfishing respectively);

(2) direct exploitation of organisms such as hunting;

(3) anthropogenic climate change;

(4) pollution and

(5) invasive alien species spread by human trade.

This report, along with the 2020 Living Planet Report by the WWF, both project that climate change will be the leading cause in the next several decades.

A 2020 study published in PNAS posits that the contemporary extinction crisis "may be the most serious environmental threat to the persistence of civilization, because it is irreversible" and that its acceleration" is certain because of the still fast growth in human numbers and consumption rates." The study found that more than 500 vertebrate species are poised to be lost in the next two decades.

V. Why should we care about mass extinction?

Species do not exist in isolation; they are interconnected. A single species interacts with many other species in specific ways that produce benefits to people, like clean air, clean water, and healthy soils for efficient food production. When one species goes extinct in an ecosystem or its population numbers decline so significantly that it cannot sustain its important function, other species are affected, impacting the way the ecosystem functions and the benefits it provides. And the potential for species extinction rises. Monitoring these trends is vital because they are a measure of overall ecosystem health. Serious declines in populations of species are an indicator that the ecosystem is breaking down, warning of a larger systems failure.

Currently, the species extinction rate is estimated between 1,000 and 10,000 times higher than natural extinction rates the rate of species extinctions that would occur if we humans were not around. While extinctions are a normal and expected part of the evolutionary process, the current rates of species population decline and species extinction are high enough to threaten important ecological functions that support human life on earth, such as a stable climate, predictable regional precipitation patterns, and productive farmland and fisheries.

If we do not course correct, we will continue to lose life-sustaining biodiversity at an alarming rate. These losses will, at best, take decades to reverse, resulting in a planet less able to support current and future generations.

VI. What can we do to stop mass extinction?

Urgent action is needed if we are to curb human impacts on biodiversity.

a. Paris Agreement. We can ramp up our commitments to cutting carbon emissions under the Paris Agreement and limit global warming to 1.5 degrees Celsius. Our leaders can support the America the Beautiful initiative to conserve lands and waters by 2030.

b. Kunming-Montreal Agreement. US leadership can play a critical role alongside 195 other countries in conserving at least 30% of lands, inland waters, and oceans worldwide.

c. Grassroots action. While the federal government can set high-level policies to conserve nature, businesses, communities, and individuals have a powerful role to play in shifting corporate behavior with their consumer choices and demanding accountability from political leaders.

VII. Evolutionary importance

Mass extinctions have sometimes accelerated the evolution of life on earth. When dominance of particular ecological niches passes from one group of organisms to another, it is rarely because the newly dominant group is "superior" to the old but usually because an extinction event eliminates the old, dominant group and makes way for the new one, a process known as adaptive radiation.

For example, mammaliaformes ("almost mammals") and then mammals existed throughout the reign of the dinosaurs, but could not compete in the large terrestrial vertebrate niches that dinosaurs monopolized. The end-Cretaceous mass extinction removed the non-avian dinosaurs and made it possible for mammals to expand into the large terrestrial vertebrate niches. The dinosaurs themselves had been beneficiaries of a previous mass extinction, the end-Triassic, which eliminated most of their chief rivals, the crurotarsans.

Another point of view put forward in the Escalation hypothesis predicts that species in ecological niches with more organism-to-organism conflict will be less likely to survive extinctions. This is because the very traits that keep a species numerous and viable under fairly static conditions become a burden once population levels fall among competing organisms during the dynamics of an extinction event.

Furthermore, many groups that survive mass extinctions do not recover in numbers or diversity, and many of these go into long-term decline, and these are often referred to as "Dead Clades Walking". However, clades that survive for a considerable period of time after

a mass extinction, and which were reduced to only a few species, are likely to have experienced a rebound effect called the "push of the past".

Darwin was firmly of the opinion that biotic interactions, such as competition for food and space the ‘struggle for existence’ were of considerably greater importance in promoting evolution and extinction than changes in the physical environment. He expressed this in The **Origin of Species:**

"Species are produced and exterminated by slowly acting causes ... and the most import of all causes of organic change is one which is almost independent of altered ... physical conditions, namely the mutual relation of organism to organism the improvement of one organism entailing the improvement or extermination of others".

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Available on
Book available at amazon
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ISBN:978-93-91248-56-7

PRICE
INR (₹): 299/-
USD ($): 10/

Lecture Notes in Networks and Systems 558

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Smart Technologies in Data Science and Communication

Proceedings of SMART-DSC 2022

Springer

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ISSN 2367-3370 ISSN 2367-3389 (electronic)
Lecture Notes in Networks and Systems
ISBN 978-981-19-6879-2 ISBN 978-981-19-6880-8 (eBook)
https://doi.org/10.1007/978-981-19-6880-8

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Contents

Cancer Cell Detection and Classification from Digital Whole Slide Image

Anil B. Gavade, Rajendra B. Nerli, Shridhar Ghagane, Priyanka A. Gavade, and Venkata Siva Prasad Bhagavatula

Abstract The World Health Organisation has identified cancer as one of the foremost causes of death globally which reports that nearly one in six deaths is due to cancer. Hence, an early and correct diagnosis is required to assist doctors in selecting the accurate and best treatment option for the patient. Pathological data have huge tumour information that can be used to diagnose cancer. Digitizing pathological data into images and its analysis using Deep learning applications will be a significant contribution to clinical testing. Due to advancements in technology, artificial intelligence (AI) and digital pathology can now be combined allowing for image-based diagnosis. This study uses residual networks (ResNet-50) and convolutional neural network (CNN), which is pre-trained on ImageNet dataset to train and categories lung biopathology images into non-cancerous, lung adenocarcinoma, and lung squamous cell carcinoma delivering an accuracy of 98.9%. Experimentation results show that the ResNet-50 model delivers finer classification results when compared to state-of-the-art methods.

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R. A. Ogunfu et al. (eds.), *Smart Technologies in Data Science and Communication*,
Lecture Notes in Networks and Systems 558,
https://doi.org/10.1007/978-981-19-6880-8_31

Keywords Histopathological image · Deep learning · Convolutional neural network · Classification · Artificial intelligence · Residual networks · Graphic processing unit

1 Introduction

Cancer is a disease that has a very low survival rate, accounting for nearly 10 million deaths in 2020. The most common in them were breast and lung. Due to the high recurrence and death rates, the treatment is lengthy and costly. Cancer early stage prognosis is not easy, due to lack of availability of diagnostic tools that are critical in clinical cancer research. Accurate early cancer identification and prognosis are crucial for improving the patient's survival rate.

Pathology is a branch of medical science that studies and diagnoses disease by analysing surgically removed tissues, organs, fluids and in some instances, even the entire body. Pathology also encompasses the closely related scientific study of disease processes, which examines the causes, mechanisms, and consequences of illness. Under a microscope, the pattern of tissue samples is examined to help determine whether a sample is malignant or not. This requires a lot of time investment and labour work, resulting in reduced efficiency of workflow. Thus, digitising this process will help in increased work efficiency and faster diagnosis. This can be achieved by digital pathology, which is a dynamic and image-based platform that allows pathology data generated from a digitised glass slide to be acquired, managed, and interpreted.

With the practice of whole slide imaging, glass slides can be converted into digital slides that may be viewed, managed, and analysed on a computer. Development of AI and machine learning leads to efficient and less expensive disease diagnosis, prognosis, and prediction systems.

Deep learning extracts biomarkers from histology images directly and summarises the research of cancer histology image analysis. They are designed to automate workflows. These algorithms can be used for the purpose of segmentation and classification of whole slide images.

In digital pathology, first, we classify whole slide images as cancerous or non-cancerous, further, we use segmentation to identify the size and location of the cancer, all this is achieved through training the model on convolutional neural networks (CNNs). CNN is a type of deep neural network that is commonly used to analyse visual data and has a pre-trained learning model for image classification. The model also contains nearly 23 million trainable parameters, indicating a deep architecture.

ResNet is one such CNN that can be used for classification of image-based dataset. ResNet-50 is a 50 layers deep CNN that can load a pre-trained network model from the ImageNet database that has been trained on over 1 lakh images. There are 48 convolution layers, one Maxpool layer, and one average pool layer in the model. The ResNet-50 model has 5 stages. Each stage has a residual block. These residual blocks have 3 layers, each with 1×1 and 3×3 convolutions. Each convolutional layer is followed by a batch normalisation layer and a ReLU activation algorithm. In

traditional neural networks, each layer feeds into the next, but in ResNet, each layer feeds directly into the next layer and into layers 2/3 hops away. These are known as identity connections.

2 Contributions

The paper is implement for cancer detection and classification using digital whole slide and deep neural network architecture, i.e. CNN models. From literature, it is observed CNN which is considered as one of the best pre-trained model for large data image classification applications, and we find ResNet-50 widely used in medical image classification applications. The paper mainly divided into literature review, implementation, performance comparison analysis, results, and conclusion.

3 Related Works

Image segmentation is one of the important and challenging task in the area of medical image processing. For nuclei segmentation,

Shyam Lal et al. [1] proposed an encoder–decoder style U-net model with an attention-gating mechanism and a dimension wise pyramid pooling approach. The model was evaluated on kidney and breast histopathology images that resulted in a $F1$-score of 0.9294 and an average Jaccard index (AJI) of 0.8688 for publicly available kidney dataset, and a F1-score of 0.8243 and an AJI of 0.7039 for breast dataset.

Zilan Zengin et al. [2] presented a model which uses a multi-task learning technique to segment nuclei and cell content simultaneously. This model delivered the $F1$-score as 0.8278 and the dice score as 0.7844.

Amit Kumar et al. [3] proposed separable convolution pyramid pooling network with an encoder–decoder. Evaluation was done on kidney and breast datasets which resulted to give $F1$-scores as 0.9203 and 0.8168 and AJI as 0.8592 and 0.6998 for kidney and breast datasets, respectively.

Shyam Lal et al. [4] presented an architecture having three blocks. A robust residual block, bottleneck block and an attention decoder block. To extract high level semantic maps robust residual block is proposed, along with attention block for effective object localization this improved the architecture. During segmentation, the model claims to be more precise in tackling shape variability and nuclei connecting challenges.

Qasim et al. [5] used the ResNet-50 CNN pre-trained model on ImageNet to categorise the dataset into benign and malignant category. This model was compared with various CNN models, and it was found that the proposed method has the accuracy of 99.10% outperforming the state-of-the art methods.

Pin Wang et al. [6] gave an architecture for automatic segmentation and classification of breast histology images. The method uses wavelet transformation and multi-scale region growing to detect the regions of interest and morphological operation along with a CSS detection algorithm to separate the overlapped cells.

Anmol Verma et al. [7] proposed a model production and classification of breast cancer histopathology images. For detection, the model was influenced by the IRRCNN algorithm, and for classification, it was influenced by WSI-Net. The accuracies for detecting the cancer and classifying them were 95.25% and 80.43%, respectively, which outperformed WSI-Net.

Muhammad Talo [8], presented deep learning ResNet-50 and DenseNet -161 models to classify histopathology images automatically, with accuracy of 97.89% (Gray image and colour) and with dataset Kima Path 24 datasets as 24 classes with classification accuracy of 98.87%.

Yingqin Feng et al. [9] implemented cell nuclei classification using Breast Cancer histopathology images using stacked denoising autoencoder and compared with 8 different techniques and their classification accuracy of 89.25% result outperformed with others.

Yan Jiang et al. [10] presented a small SE-ResNet module that combines a residual module with a squeeze-and-excitation block. The model classifies histopathological images of breast cancer into benign, malignant, and eight subgroups. For binary classification, the achieved accuracy ranges between 98.87 and 99.34% and 90.66 and 93.81% for multi-class classification.

Krithiga and Geetha [11] published a review on detection, segmentation, and classification of breast histopathology images. The study provides an overview of tissue preparation, stained image analysis, preprocessing techniques, methods of segmentation, methods of feature extraction, feature selection, and classification. This work drew attention to several algorithms and methodologies, as well as listing the performance of various models with various characteristics such as accuracy, specificity, sensitivity, and F1-score.

Kourou et al. [12] present a review overview of cancer prognosis and prediction using machine learning in this literature they have considered papers related to different cancers like oral cancer, Brain Cancer, Colon cancer, Cervical cancer addressed cancer detection and classification using ANN, SVM, Graph based SSL algorithm.

Mesut et al. [13] proposed a model that includes an attention module, hypercolumn technique and a residual block for improved cancer detection. When evaluated on BreakHis dataset, this model achieved an accuracy of 98.80%.

Soulami et al. [14] used DDSM and INbreast mammographic database for breast cancer automatic segmentation and classification of breast cancer, proposed an end-to-end U net model, results are assessed with evaluation matrices such as IOC, AUC, F1 and dice coefficient.

Ting- Wei Chiu et al. [15], addressed the position of lung nodule lung cancer and carcinoma with U-Net and 2DU-Net segmentation architecture. Evaluation matrixes used were Dice coefficient, accuracy, sensitivity and specificity comparisons carried

with data without preprocessing (mono input positive) and with processing (mono input negative).

Devvi Sarwinda et al. [16], implemented CNN ResNet model architecture ranging from 18 layers to 152 layers. Colorectal gland image dataset tested on ResNet-18 and 50, different set of training and testing ratios are considered for results verifications, classification results assessed with accuracy, sensitivity and specificity, it is observed that, the higher number of layers too more time for computation, final inference was with less number in ResNet architecture, it is possible to achieve good classification accuracy with less time.

Brij Rokad and Nagarajan [17] demonstrated skin cancer detection and classification using Deep Residual Network (ResNet) for International Skin Imaging Collaboration (ISIC)-2017 challenge skin dataset (dermoscopic lesion images) around 2000 images (374 melanoma 254 Sebohemic Keratosis and 1372 Nevus (Begnin)) achieved classification accuracy of 77%.

Jiazhi Liang [18] implemented CNN ResNet-110 V1 for classification of CIFAR-10 datasets, different training and testing combination used for experimentation and it is observed to have the highest accuracy at 110 layers.

Yasin Yari et al. [19], developed an effective training-learning architecture that consists of fully connected classifier and input layers combined with the ResNet-50 and DenseNet-121 model. Different magnifying images are employed to test the proposed techniques with 8 other techniques, binary and multi labeled classification algorithms tested on histology datasets.

Varsha Prakash and Senthil Vaa [20], reviewed lung cancer using modalities like X-ray and CT-Image, this paper overview with segmentation and nodule extraction, nodule classification and emphasis on CNN data augmentation and nodule detection.

Sham lal et al. [21], demonstrated segmentation of nuclear cell from stained histological slide, implemented algorithm is compared with four different methods for results performance assessment. Algorithm experimented with two different datasets such as Stephan Wienert and liver tissues datasets from KMC Mangalore. Results are compared with parameters such as precision, recall and F1 as quality metrics and implementation is outstanding with other 4 algorithms.

Hao Dong et al. [22], used BRAT-2015 dataset to develop the U-net CNN algorithm, which segments patient specific brain tumors without manual intervention and this potentially enables objective lesion assessment for clinical tasks such as diagnosis, treatment planning and monitoring.

Anmotdeep et al. [23], reviewed and addressed several diseases with different modalities and classification of interested areas from radiological modalities. The application of modalities includes brain MRI, X-ray, Cardic MRI, CT, mammography and lung CT. Focus of review is on classification and segmentation architectures with CNN and it derivatives models, SVM and Hybrid CNN.

Vesal et al. [24] provide a performance comparison between ResNet-50 and Inception-V3 which have been pre-trained on ImageNet dataset and then trained on BACH dataset. A transfer learning-based approach is been proposed, in which ResNet-50 achieves 97.50% accuracy outperforming Inception-V3 with 91.25% accuracy.

Nur Syahmi Ismail and Chuah Soo Sothy [25], addressed breast cancer with dataset IRMA, implementation comparisons done with three different techniques. VGG-16, ResNet-50 and implementation carried out by Q. Zhang, aim is to classify as normal or abnormal tumor, the results are assessed with precision, accuracy and recall as quality matrices, it is observed VGG-16 outperformed other two algorithms.

Asmaa Hekal et al. [26], developed deep learning model for breast cancer detection and classification using dataset CBIS-DDSM ROI dataset. The CNN model is refined at last fully connected layer of the pre-trained model is substituted with a SVM shallow classifier, this lead with improved classification of tumors.

Hao Zhang et al. [27] propose a ResNet model for detection of metastatic cancer, and test time augmentation is employed in the model to make it more robust and to improve detection accuracy.

Saber et al. [28] proposed a DL model for enhancing the classification results using transfer learning on the Mias dataset. The VGG-16 model achieved the best accuracy of 98.96% compared to ResNet-50 Inception_V3, VGG-19, and Inception_V2 ResNet.

Ahmad et al. [29] present the use of transfer learning for classification of breast cancer. The ResNet-50 model has achieved an 85% accuracy on image-wise classification and 83.60% on patch-wise classification on BreakHis dataset.

Shallu Sharma and Rajesh [30], proposed comparison of hand crafted features to conventional classifiers and transfer learning baseline CNN pre-trained model for feature extraction with classification with CNN classifier. Breast cancer histopathology datasets used for experimentation, the datasets used are in different magnification (40X, 100X, 200X and 400X). It is observed that the pre-trained model as feature extractor outperformed the hand crafted features to conventional classifiers for different magnification images.

4 Dataset and Computing Machine Details

In the implementation, only the lung organ dataset [31] is used with a total of 3 classes and 15,000 images, patch dimension of 768 × 768 in colour JPEG format.

(1) **Lung**: Benign tissue (5000 samples), adenocarcinoma (5000 samples), and squamous cell carcinoma (5000 samples)
(2) **Colon**: Benign tissue (5000 samples) and adenocarcinoma (5000 samples).

The dataset has 25,000 histopathological images which divided into five classes. All the images are 768 × 768 pixels in size and saved as jpegs. The images were augmented to 25,000 that included a total of 750 images of lung tissue and 500 images of colon tissue. Algorithm implemented on **Dell Precision Tower 5810 work station** with specification Xeon CPU, 512 GB SSD, 32 GB RAM, and 8 GB Quadro P4000 Nvidia GPU.

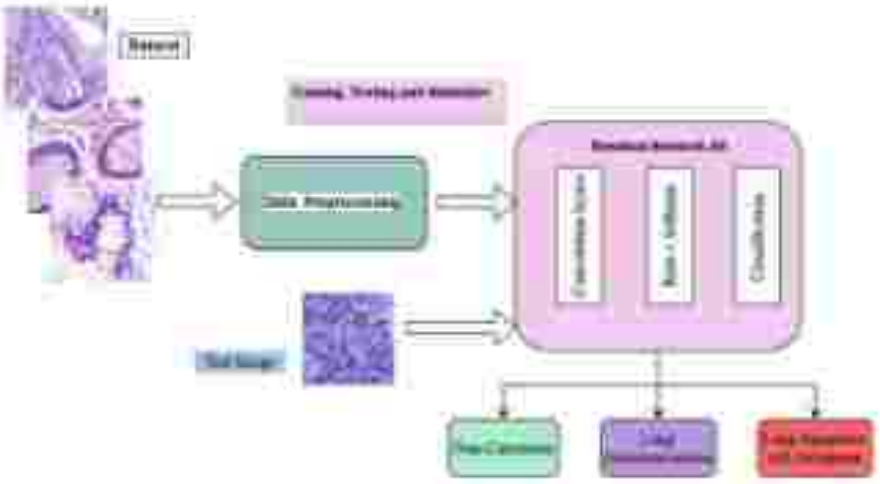


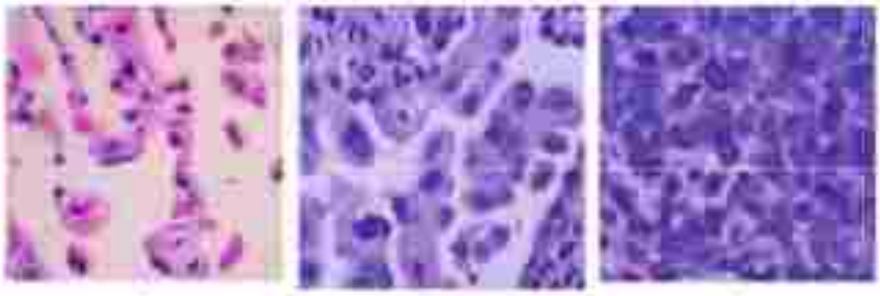
Fig. 1 Whole slide image cancer classification

5 Implementation Details

The implementation block diagram is represented in Fig. 1, which involves dataset, ResNet-50 CNN model and test image. The model is trained, tested, and validated with different percentage combination of dataset, and it is observed the model performed efficiently with **70:15:15** ratio combination. Algorithm 1 explains the procedure for cancer classification. Samples of digital histology images are shown in Fig. 2, which consist non-cancerous tissue, malignant tissue of type lung adenocarcinoma and malignant tissue of type lung squamous cell carcinoma.

Algorithm 1 | Cancer cell detection and classification

(continued)



(a) (b) (c)

Fig. 2 Bilipse sample data **a** non-cancerous tissue, **b** malignant tissue of type lung adenocarcinoma, **c** malignant tissue of type lung squamous cell carcinoma

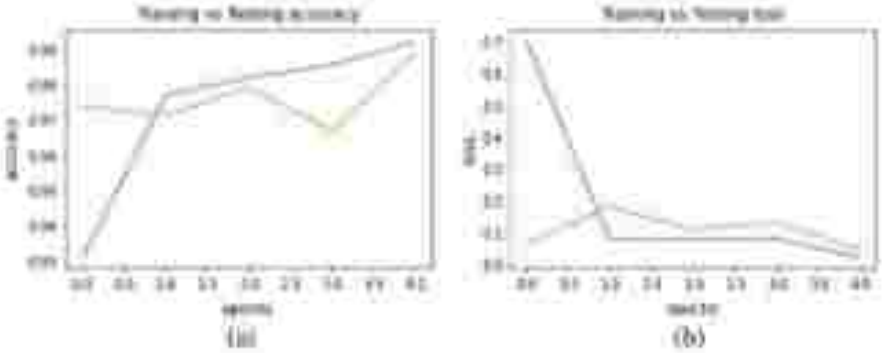
(continued)

	Input: Digital whole slide image Output: Non-cancerous tissue/a malignant tissue of type lung adenocarcinoma/malignant tissue of type lung squamous cell carcinoma
Step 1:	Importing required libraries and loading lung cancer dataset
Step 2:	Data pre-processing and data splitting with balanced test, train split
Step 3:	Loading ResNet-50 model
Step 4:	Defining final output layers as 3 same as number of classification folders
Step 5:	Compiling the model with loss and optimizing functions as categorical cross entropy and Adam, respectively
Step 6:	Executing the model
Step 7:	Plotting confusion matrix
Step 8:	Evaluating the model
Step 9:	Prediction and classification of lung cancer into its subtypes

6 Experimental Results

The dataset has 25,000 histopathological images which divided into five classes. All the images are 768 × 768 pixels in size and saved. The ResNet-50 is trained, tested, and validated with **70:15:15** ratio combination performance analysis of accuracy and loss which is shown in Fig. 3.

The data tested for five different pre-trained CNN models like VGG-16, EfficientNetB0, EfficientNetB7, AlexNet and ResNet-50. The accuracy parameter is considered as performance concluding parameter shown in Table 1, amongst these tested model ResNet-50 outperformed, Table 1 shows the classification accuracy of 0.989, and this is the highest achieved classification accuracy.



(a) (b)

Fig. 3 Performance analysis a accuracy, b loss

Table 1 Comparative discussion accuracy matrix

Model	VGG-16	EfficientNetB0	EfficientNetB7	AlexNet	ResNet-50
Accuracy	0.9363	0.870	0.9656	0.948	0.989

Table 2 Comparative discussion ResNet-50

Class	Precision	Recall	Support	F1-score
Lung adenocarcinoma	0.926	0.955	0.948	0.937
Lung benign	0.909	0.923	0.933	0.941
Lung squamous cell carcinoma	0.951	0.950	0.942	0.938

The data tested for five different pre-trained CNN models like VGG-16, EfficientNetB0, EfficientNetB7, AlexNet, and ResNet-50.

The implementation is assessed with three different datasets, and classification performance comparisons are made with reference to precision, recall, support and F1-score parameters shown in the Table 2.

7 Results Overview

The implementation performance analysis presented in above tables, different deep neural network—CNN model comparisons is shown in Table 1, and classification accuracy is considered. From Table 2, it is clear that ResNet-50 outperforms other models, trained on the same parameters achieving an accuracy of 98.9% and also properly classifying the tissue into its cancer subtypes classified as non-cancerous or cancerous tissue. From the plots Fig. 3, we can infer that there is a drastic accuracy increase and proportional loss decrease till the first epoch, then a gradual increase in accuracy and decrease in loss after the **first epoch till fifth epoch**.

8 Conclusion

This paper presents implementation of digital whole slide image cancer detection and classification using deep neural network CNN pre-trained model ResNet-50. The performance of CNN is much superior with high classification accuracy. In conclusion from the results obtained, ResNet-50 outperforms compare to other models. As a future scope, the algorithm could be implemented with U-net for segmentation and classification accuracy still further improved. Also we can extract large number of features using CNN, dimension reduction could be done using principal component analysis (PCA) and optimised the code for higher processing, improved accuracy with the help of graphic processing unit computing architecture.

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Honey: Composition and Health Benefits, First

Chapter 24

Economic Benefits of Honey and Honey Products

Sridevi I. Puranik,, Aimen A. Akbar, and, Shridhar C. Ghagane

Book Editor(s):Md. Ibrahim Khalil, Siew Hua Gan, Bey Hing Goh

First published: 24 March 2023
https://doi.org/10.1002/9781119113324.ch24

Abstract

Honey production has significant social influences and a substantial impact on biodiversity. Economically and ecologically, it produces important profits to society. This chapter focuses on the international trade of honey, products of honeybees, segment analysis, regional industries, and their applications in the pharmaceutical industry and food market. Worldwide production of honey was estimated as 1.72 million metric tons with China being the largest contributor to total honey production followed by other major producers such as Turkey and Canada. The global market is highly competitive because it depends on environmental conditions, and even the slightest change in the climate can drastically hamper production. Global demand for honey depends on the nature, application, packaging, and location of production. Honey is used in the personal care and cosmetic industry in the form of face washes, moisturizers, soaps, lip balms, and other products.

Honey: Composition and Health Benefits

Editor(s): Md. Ibrahim Khalil, Siew Hua Gan, Bey Hing Goh
First published: 24 March 2023
Print ISBN: 9781119113294 | Online ISBN: 9781119113324 | DOI: 10.1002/9781119113324

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Chapter 14

Use of Honey in Cardiovascular Diseases

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Book Editor(s):Md. Ibrahim Khalil, Siew Hua Gan, Bey Hing Goh

First published: 24 March 2023
https://doi.org/10.1002/9781119113324.ch14

Abstract

Globally, one of the major causes of death is cardiovascular disease (CVD), with an estimated of about 17.9 million deaths per year. Honey in modern medicine is used in management of wound and burn healing. This chapter focuses on the antioxidant properties of honey and its ability to protect against CVDs. The risk factors leading to the onset of CVDs are well recognized and can be categorized into modifiable and nonmodifiable risk factors. Nonmodifiable risk factors are those that cannot be altered. These include ethnicity, age, and genetics. Modifiable risk factors include adiposity, raised blood sugar levels, alcohol consumption, smoking, high blood pressure, high body mass index, high cholesterol, dietary habits, and physical inactivity. Primarily, the composition of honey depends on several factors such as the floral source, seasonal and environmental factors, and processing. Phenolic compounds of honey are divided into phenolic acids and flavonoids such as quercetin, caffeic acid phenethyl ester, and galangin.

Honey: Composition and Health Benefits, First

Chapter 16

Use of Honey in Kidney Disease

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Book Editor(s):Md. Ibrahim Khalil, Siew Hua Gan, Bey Hing Goh

First published: 24 March 2023
https://doi.org/10.1002/9781119113324.ch16

Abstract

The kidneys' functions are to filter excess water and wastes from the blood and make urine. A number of studies have been assessing the safety and efficacy of honey in the remedy of skin and wound infections in patients vulnerable to chronic kidney ailments. In a study by Ajibola et al., stingless bee honey was shown to be defensive against oxidative stress and lipopolysaccharide-induced chronic subclinical systemic inflammation (CSSI) in rats. CSSI plays an imperative part in homeostasis and is triggered by oxidative stress and metabolic malfunction, which is known to have a positive feedback mechanism at the systematic or local level. Inflammation and oxidative stress are the major contributors of drug-induced nephrotoxicity such as cisplatin-induced acute kidney injury. In summary, oral administration of honey is effective in preventing cisplatin nephrotoxicity through the suppression of inflammation. Suppression of inflammation may be related to the reduction of oxidative stress.