Smt. Taisaheb Kadam Sevabhavi Foundation & Research Center, Sonai's
YASH INSTITUTE OF PHARMACY
AURANGABAD (CHHATRAPATI SAMBHAJI NAGAR)
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Supporting Document

Metric No. 3.2.1

3.2.1 Number of papers published per teacher in the Journals notified on UGC website during the year

Sr. No.	Title of paper	Name of the author/s	Name of journal	Page No.
1	Phytochemical, pharmacological and nutritional values of Mangifera Indica: an overview	Dr.Sachidanand Angadi, Dr. V.P.Patil, Ms. Suwarna Kale	International Journal of Creative Research Thoughts (IJCRT)	3
2	A review article on effective patient counselling and role of pharmacist	Dr. R. B. Chavhan	Clinical pharmacology and biopharmaceutics	17
3	Comprehensive insights into breast cancer: from molecular pathways to personalized therapies	Dr. Sachidanand Angadi , Dr. Rohit chavhan, Raman Naiknaware , Pradnya Naykodi	International Journal of Creative Research Thoughts (IJCRT)	22
4	Maximizing patient outcomes: Assessing the implementation and impact of medication therapy management (MTM) services	Dr.Sachidanand Angadi, Dr. Gajanan Vaishnav, Abhay Joshi, Dr. R. B. Chavhan, Raman Naiknaware	International Journal of Creative Research Thoughts (IJCRT)	44
5	Enhancing patient safety through pharmacovigilance: effective monitoring and reporting of adverse drug reactions	Dr. Sachidanand Angadi , Dr. R. B. Chavhan , Raman Naiknaware	International Journal of Creative Research Thoughts (IJCRT)	62
6	Navigating precision healthcare: the intersection of pharmacogenomics and personalized medicine in unravelling the genetic tapestry	Dr. Sachidanand Angadi , Dr. R. B. Chavhan	International Journal of Creative Research Thoughts (IJCRT)	73
7	Review article on Butterfly pea: its Ethanopharmacologial and ethanomedicinal uses	Mrs. D.M.Kulkarni	International Journal of Creative Research Thoughts (IJCRT)	88
8	Ethno-medical values of Amla	Dr.Sachidanand Angadi, Dr. V.P.Patil, Ms. uwarna Kale	International Journal of Research And Analytical Reviews (IJRAR)	97
9	A mini review: Nutritional and Pharmacological Importance of Psidium guajava	Dr.Sachidanand Angadi, Dr. V.P.Patil, Ms. Suwarna Kale, Reshma Patil	International Journal of Research And Analytical Reviews (IJRAR)	107

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INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

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PHYTOCHEMICAL, PHARMACOLOGICAL AND NUTRITIONAL VALUES OF MANGIFERA INDICA: AN OVERVIEW

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ABSTRACT:

Naturally occurring products are an important source of new compounds that lead to drugs in all major diseases. *Mangifera indica* (M.I.) commonly known as mango belongs to the family *Anacardiaceae* & genus *Mangifera*, which consists of about 30 species of tropical fruiting trees. Mangifera indica consists of active substances with high therapeutic potential. The ethnomedicinal parts of the plant viz roots, stem, bark, leaves, flowers, and fruits are widely used to treat various diseases and disorders. It has a wide range of medicinal uses, including anti-inflammatory anti-hyperglycemic, hepatoprotective, antibacterial, anticancer, immunomodulatory, antiulcer, and antioxidant, properties. The objective of the overview is to highlight the information on the plant's botanical description, pharmacological actions, and its traditional uses. The authors collect research and review articles for findings of other additional potential and therapeutic effects. The current overview emphasizes the phytochemical investigation, pharmacological actions, and nutritional value of Mangifera indica. By using this overview, the researcher finds future scope related to phytoconstituents that are responsible for therapeutic activity the overview.

Keywords: Mangifera indica, Mangiferin, Mango, Pharmacological activity

1.0 INTRODUCTION:

India has various systems of health like Ayurveda, Unani, Homeopathy, and Naturopathy that are mentioned even in the Vedas and other scriptures. These systems existed together with allopathic, containing vast, safe, and ongoing usage of multiple herbal drugs.[1] It is one of the Ayurvedic remedies for relieving acidity and digestion caused by pitta (heat). Mangiferin has potent antioxidant, antilipid peroxidation, immune-modulating, cardiotonic, hypotension, wound-healing, antidegenerative, and anti-diabetic effects. Various parts of plants are used as a dentifrice, antiseptic, astringent, diaphortic, stomachic, vermifuge, tonic, laxative, and diuretic and to treat diarrhea, dysentery, anemia, asthma, bronchitis, cough, hypertension, insomnia, rheumatism, toothache, leucorrhoea, hemorrhage, and piles. All parts are used to treat abscesses, broken horn, rabid dog or jackel bites, tumors, snakebites, datura poisoning, heat stroke, miscarriage, anthrax, blisters, mouth wounds, tympanitis, colic, constipation, glossitis, indigestion, bacillosis, bloody dysentery, liver and kidney disorder, excessive urination, teantus, and respiratory disorder.[2] A wide range of phytochemicals have recently been observed in Mangifera indica such as mangiferin, catechins, gallic acid, protocatechuic acid, propyl and methyl gallate, anthocyanins, quercetin, rhamnetin, kaempferol and ellagic acids.[3] As a result, Mangifera indica (M.I.) exhibits various pharmacological potentials, such as

anti-cancer, anti-inflammatory, anti-diabetic, anti-oxidant, anti-bacterial, anti-fungal, anthelmintics, gastroprotective, hepatoprotective, anti-plasmodial, anti-hyperlipidemic[4], immune-stimulating activities.[5]

Table 1: Taxonomical Classification [6]

Kingdom	Plantae
Class	Mangoliopsida
Phylum	Mangoliophyta
Order	Sapindales
Family	Anacardiaceae
Genus	Mangifera
Species	Indica

1.1 Botanical Description:

The genus Mangifera indica originates in tropical Asia, with the greatest number of species found in Borneo, Java, Sumatra, and the Malay Peninsula. Mangifera indica is now cultivated all over the tropical and subtropical world for commercial fruit production, as a garden tree, and as a shade tree for stock.[7] M. indica is a large evergreen tree as shown in Figure 1. It is 10-45 m high, bark thick, rough, dark grey; leaves linear-oblong or elliptic-lanceolate, 10-30 cm long and 2-9 cm wide, resinous odor, flower tiny, reddish-white or yellowish green, pungently odorous and melliferous; fruit forms a large drupe exceedingly variable in form and size: flesh (mesocarp) whitish-yellow or orange, firm, soft, absent or very little in others; seed solitary, ovoid-oblique, encased in a hard compressed fibrous endocarp (stone).[8]

Figure 1: Mango tree with fruits.

1.2 Ethnomedicinal uses:

For centuries, diverse components of mango have been employed for an extensive range of ethnomedicinal purposes.[9]

Roots & Bark: Used as astringent, acrid, refrigerant, styptic, anti-inflammatory antisyphilitic, vulnerary, antiemetic, and diarrhea. They are useful in vitiated conditions of pitta, metorrhagia, calonorrhagia, pneumorrhagia, lecorrhoea, syphilis, uteritis, wounds, ulcers, and vomiting. The juice of fresh bark has a strong effect on mucous membranes, in menorrhea leucorrhoea, diarrhea and bleeding piles.

Leaves: Used as astringent, refrigerant styptic, healing of wounds and constipating. They are also helpful in vitiated conditions of cough, hiccup, hyperdipsia, burning sensation, hemoptysis, hemorrhages, wounds, ulcers, constipation dysentery, pharyngopathy, scorpion string, and stomachopathy. The ash of burnt leaves is useful in burns and scalds. For the treatment of throat diseases, the smoke from burning leaves is inhaled.

Flowers: Used as astringent, refrigerant, styptic, vulnerary, constipating and haematinic. The dried flowers are useful in vitiated conditions of pitta, haemorrhages, haemoptysis, wounds, ulcer, anorexia, dyspepsia, uroedema gleet, catarrh of bladder, diarrhoea, chronic dysentery and anemia.

Fruits: The unripe fruits are acidic, acrid, antiscorbutic, refrigerant, digestive, and carminative. They are helpful in dysentery ophthalmia, eruptions, urethrorrhoea, and vaginopathy. The ripe fruits are refrigerant, sweet, emollient, laxative, cardiotonic, hemostatic, aphrodisiac, and tonic. They are helpful in vitiated conditions such as vata and pitta, dyspepsia, cardiopathy, hemoptysis, hemorrhages from the uterus, lungs, and intestine, emaciation, anorexia and anemia.

Stone: The seed kernel of the mango has a high-protein content (8.5%) and is rich in gallic acid. Possessing sweet, acrid, astringent, refrigerant, anthelmintic, constipating, hemostatic, vulnerary, and uterine tonic. This kernel is beneficial in conditions associated with pitta and cough imbalances, as well as in treating helminthiasis, chronic diarrhea, dysentery, haemorrhages, hemoptysis, haemorrhoids, ulcer, bruises, leucorrhoea, menorrhagia, diabetes, heat burn, and vomiting.

1.3 Nutritional Importance:

Nutrients from various food components have played a vital role in maintaining the normal function of the human body. These functional or medicinal foods, phytonutrients, and phytomedicines play significant roles in maintaining and enhancing health and modulating the immune system to prevent specific diseases.[10] Mangifera indica is the most popular fruit due to its unique flavor and good nutritional value. It is one of the best sources of vitamins like vitamins A, B, and C and also has different materials such as calcium, magnesium, potassium, sodium, phosphorous, and iron. Citric, Tartaric, and Malice acids are also present in Magifera indica in small quantities.[11] The detailed nutritional content and phytochemical composition of Mango is shown in Table 2 and Table 3 respectively. Figure 2 and Figure 3 represent Phytoconstituents and Ethnomedicinal uses of various parts of Mango.

Table 2: Nutritional content of Mango

Vitamin A	Vitamin A is an essential content of Mangifera indica. It is essential for vision and protection against aged relaxed muscular degeneration. It helps to stimulate the circulation of blood in the mucous membrane and skin thus beneficial for various skin disease treatments.[12]
Vitamin C	The unripe mangoes and mature mangoes exhibit elevated levels of vitamin C, a component known to reduce LDL cholesterol levels in the body. Incorporating Mangifera indica into one's diet building resistance against infections and effectively neutralizes detrimental oxygen-free radicals.[13]
Prebiotic fiber	Present in Magnifera Indica helps in the growth of beneficial bacteria in the gut and prevent gastrointestinal disorders like ulcer, and irritable bowel syndrome.[14]
Copper	Mango peels are rich in copper which is essential for the formation of blood cells and acts as a cofactor for many enzymes.[15]
Potassium	It is a component of cell and body fluids that contributes to heart rate and blood pressure. Fresh mango is a very rich source of potassium.[16]

Table 3: Phytochemical Composition of Mango

Plant parts	Chemical constituents	Ethno-medicinal uses
Stem bark	Terpenoidal saponn indicoside A & B, Manghopana, Mangifera indicleanone[17] Mangifera indicasterol, manglupenone Mangifera indica coumarin, triacontane.[18]	Aqueous extracts of mango are used for the treatment of various diseases such as syphilis, anemia, scabies, diabetes, cutaneous infections, menorrhagia, and diarrhea[25]
leaves	Protocatechuic acid, catechin, mangiferin, alanine, glycine, kainic acid, shikimic acid, tetracyclic, terpenoids.[19]	Juices of leaves used for dysentery and ashes of burnt leaves used for scalds.[26]
Fruits	Mangiferin, Xanthophyll esters, cartenes, and tocopherols.[20]	Facilitates to prevent colon cancer by calming inflammation and juice made from the fruit acts as a restorative tonic used in heat stroke.[27]
Seed	Polyphenols such quercetin, Kaempferol, gallic acid, tannin, xanthone.[21]	Seed kernel in hemorrhages and bleeding hemorrhoids, seed can also be applied on the burn, to treat Asthma.[28]
Flower	Alkyl gallates such as gallic acid, methyl gallate ethyl gallate.[22-23]	Dried mango flowers serve as astringent in cases of diarrhea and chronic dysentery. Powder helps in the treatment of allergy dermatitis.[29]
Root	3-hydroxy-2-(4–methylbenzoyl)-chromone and 3-methoxy-2-(4-methyl benzoyl)-chromone, chromones.[24]	The paste of Mangifera indica roots applied on palms and soles to cure fever. The paste of root helpful in the healing of mouth wound.[30]

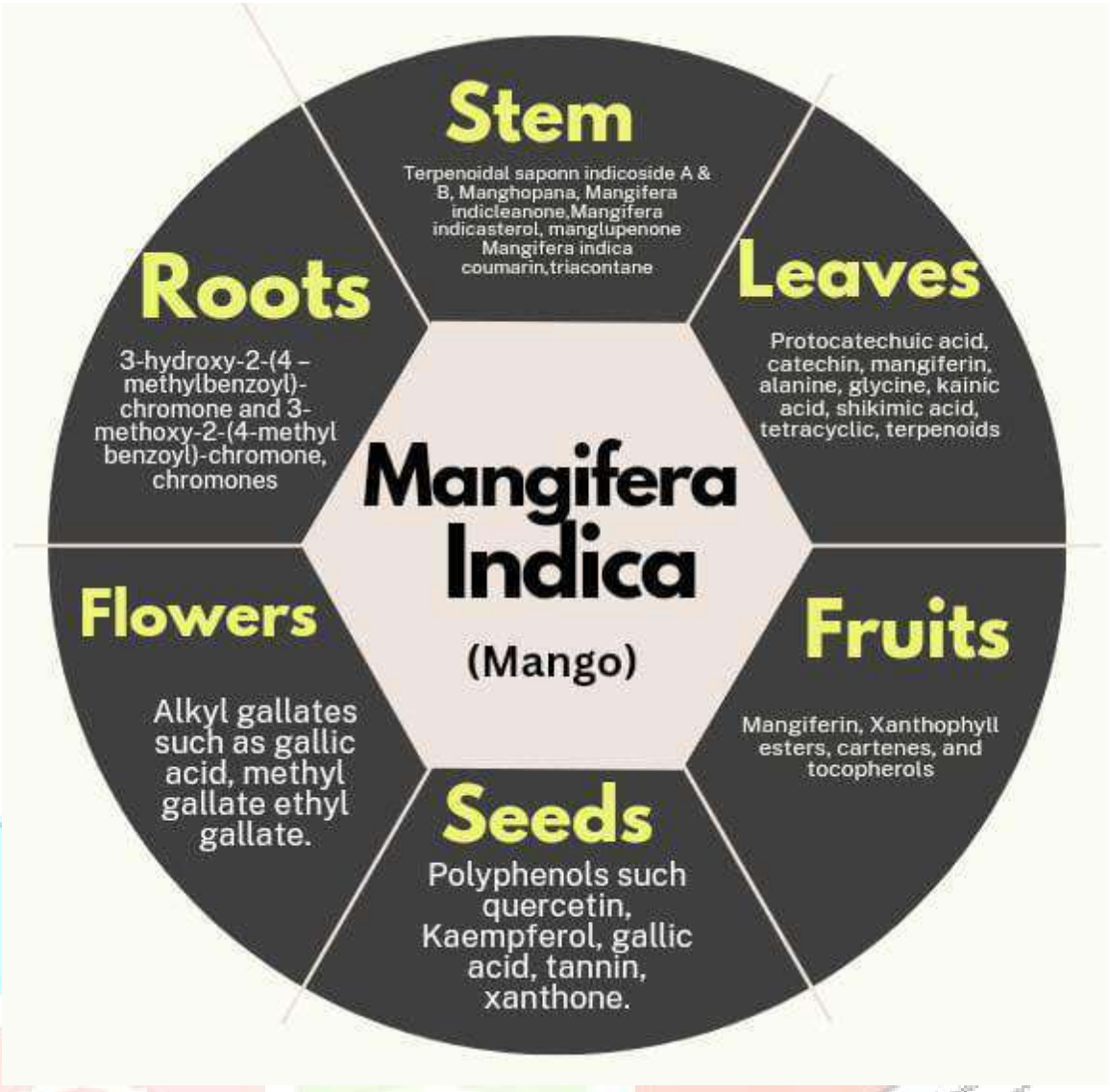

Figure 2: Phytoconstituents present in various parts of Mango.[17-24]

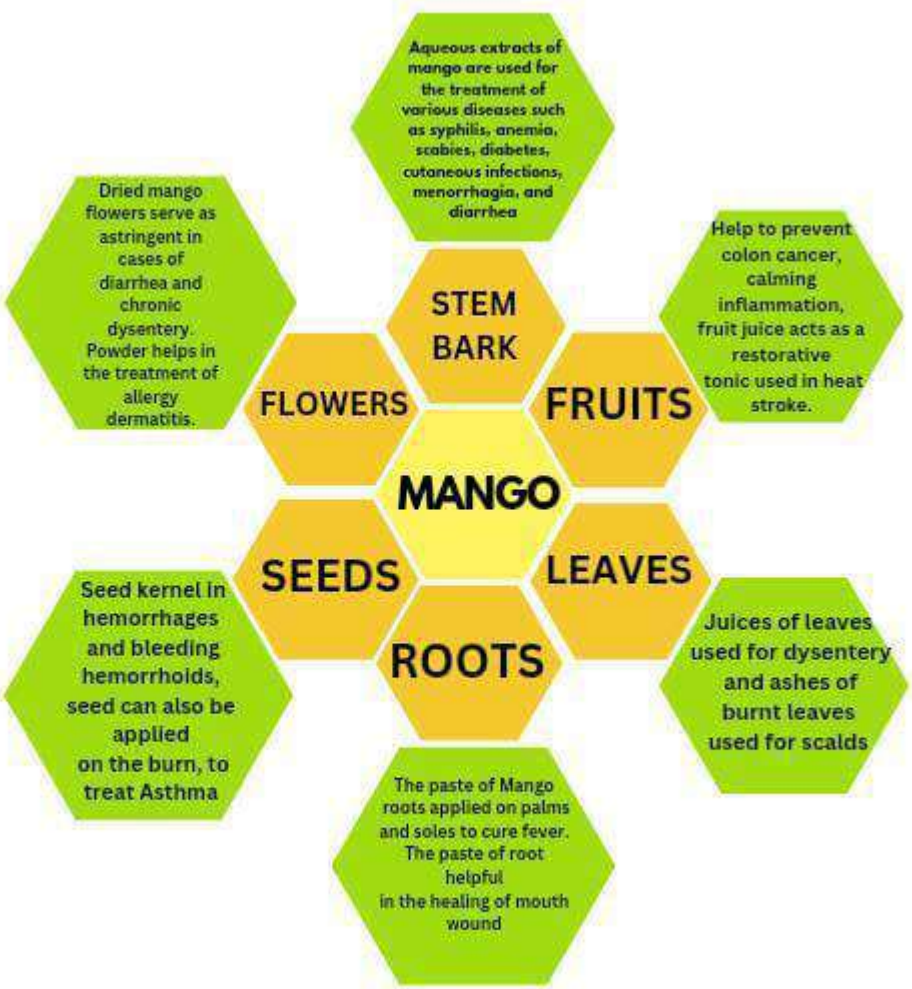

Figure 3: Ethnomedicinal uses of various parts of Mango.[25-30]

1.4 Pharmacological Action:

Every component of these plants possesses medicinal significance and has been traditionally employed to address a variety of ailments. Numerous in vitro and in vivo investigations have been conducted to unveil the diverse pharmacological capabilities of M. indica. Various segments of M. indica tress have been demonstrated potential in offering anti-fungal, anti-cancer, anti-plasmodial, hepatoprotective, immune-modulating, anthelmintic, and anti-hypertensive effects.[31] The following pages will focus on the pharmacological activities excreted by the Mangifera indica.

1.4.1 Anti-inflammatory activity

The anti-inflammatory activity of the aqueous extract of leaves of the Mangifera indica variety (Thotapuri) shows the best action. The activity was carried out by the carrageenan-induced rat paw edema used to assess acute inflammation and the cotton pellet granuloma was used to examine chronic inflammation. Diclofenac sodium a standard drug (10 mg/kg) used for both models. In these techniques, ethanol extracts and ethyl-acetate at a dose of 300mg/kg have shown significant activity which is comparable to that of the standard.[32] Numerous studies indicate that extracts derived from mangoes possess anti-inflammatory properties in experimental models of ulcerative colitis. In a recent investigation, the administration of mango beverages from the fruits of the Mexican variety and containing vitamins and polyphenols resulted in the alleviation of colitis symptoms. The effect was attributed to the modulation of the PI3K/ AKT/ mTOR pathway.[33] Additionally, in another study, aqueous extract obtained from the stem-bark extract from M. indica which is rich in flavonoids and polyphenols demonstrated the ability to attenuate colitis symptoms in a model of colitis.[34]

1.4.2 Anti-Hyperglycaemic activity

The study showed that a significant (P<0.05) increase in the fasting blood glucose concentrations was obtained in the alloxan-induced diabetic rats. When the diabetic rats were induced with the ethanol leaf extract of Mangifera indica showed significant (P<0.05) decreases in the fasting blood glucose levels compared with the untreated diabetic rats.[35]

Further exploration of the anti-diabetic and hypolipidemic effects of Mangifera was conducted using rat models for both type 1 and type 2 diabetes. Type 1 and type 2 diabetic rats were induced by administering streptozotocin. The stem bark of m. indica was used in the study at a dose of 10 and 20mg/kg was administrated intra-peritoneally in both type 1 and type 2 diabetic rats. Mangifera exhibited notable inhibitory effects on alpha amylase and alpha-glucosidase activities, surpassing the effects observed with the standard drug, acarbose. Additionally in the type 2 diabetic rat models, Mangifera demonstrated anti-diabetic effects by significantly reducing total cholesterol, LDL, triglyceride, and VLDL levels, which concurrently elevated HDL levels. These findings underscore the potential therapeutic benefits of Mangifera in managing diabetes and associated lipid abnormalities.[36]

1.4.3 Anti-ulcer activity

Histopathological findings also confirmed the antiulcer activity of M. indica leaf extracts in albino rats. The antiulcer potential of the petroleum ether and ethanol extracts of leaves of mango was evaluated against in vivo aspirin-induced gastric ulcer. The ulcer index was substantially decreased by petroleum ether 250mg/kg and ethanol extract 250mg/kg of leaves of mango trees.[37],[38] Other findings show that mangiferin affords gastroprotection against gastric injury through the antisecretory and antioxidant mechanisms of action.[39]

1.4.4 Analgesic and Antipyretic activity

The anti-pyretic activity of Mangiferai indica was assessed using extracts from its stem and bark in the mouse model. The results indicated a significant reduction in yeast induced hyperpyrexia following the administration of the extract.[40]

1.4.5 Hepatoprotective activity

Three poylphenolic principles, 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose (PGG), methyl gallate (MG), and gallic acid (GA), were isolated from the ethanolic extract of seed kernels of Thai mango. Evaluating their hepatoprotective potentials against liver injury in rats induced by carbon tetrachloride. The result shows that the extract has significant anti-oxidant activity.[41] Hepatoprotective activities in mango seed kernels demonstrate the various chemopreventive properties of mango pulp extract (MPE) was evaluated in alteration in liver of Swiss albino mice. Modulating of cell groeth regulators, MPE was found to be effective in combating oxidative stress induced cellular injury in mouse liver.[42]

1.4.6 Antioxidant activity

Recent studies have shown that these free radicals developed during the metabolic process contribute to various wide range of diseases such as acquired immunodeficiency syndrome, ischaemic diseases, neurological disorders, and many others.[43] Phytochemicals like ascorbic acid methyl gallate and tannic acid show significant anti-oxidant activity and their leaf extracts inhibit lipid peroxidation which is against lipofundin-induced oxidative stress.[44]

1.4.7 Anticancer activity

Cancer ranks among the foremost global challenges, following cardiovascular disease. Therefore, it is crucial to explore innovative treatment approaches to address these worldwide concerns. Polyphenols found in Mangifera indica, such as gallotannin, phenolic acids, mangiferin, and quercetin demonstrate chemo-preventive effects against diverse cancer types owing to their anti-inflammatory and antioxidant properties.[45] Mangiferin was found to mitigate oxidative stress and inhibit methylmercury-induced DNA damage in human neuroblastoma cell line IMR-32.[46] Further study was conducted for the antitumoral effects of ML extracts on MDA-MB-231 highly and MCF7 minimally invasive breast cancer cells and MCF10 non-tumorigenic cells at IC50 >200 µg/ml.[47] The anti-proliferative effect is shown by the accumulation of cells in the G2/M phase of cell cycles with 90% methanolic extract of Mangifera indica leaves. The leaf extract of Mangifera indica in different concentration ranges (62.5-500µg/ml) showed

anticancer activity. The leaf extract inhibits cancer cell proliferation in vitro mainly by accumulating cells in the G2/M phase.[48]

1.4.8 Immunoregulation

Mangiferin has been considered as a candidate for immune regulators. As an immune-stimulant, it rescued the cyclophosphamide-induced immune depression, such as the lymphoid organ atrophy, less cellular response, low antigen-specific IgM, more lipid peroxidation, and decreased superoxide dismutase activities. It also increased remarkably the levels of serum hemolysis IgG and IgM in mice.[49]

1.4.9 Antiallergic and Antihelmintic activity

The stem bark of the mango tree contains an aqueous extract with chemical constituents known as vimang and mangiferin. These compounds exhibit anti-allergic and anti-helmintic activities. The experimental study showed mice infected with the nematodes trichionella spiralis were orally induced vimang or mangiferin at doses of 500 or 50 mg per kg body weight per day respectively. Treatment resulted in a significant decrease in serum levels of specific anti-Trichinella IgE throughout the parasite life cycle. Furthermore, in a separate experiment involving rats, oral administration of vimang and mangiferin over 50 days inhibited mast cell degranulation, as assessed by the passive cutaneous anaphylaxis test. The test involved sensitization with infected mouse serum possessing a high IgE titre, followed by stimulation with the cytosolic fraction of T. spiralis muscle larvae. The pivotal role of IgE in the pathogenesis of allergic disease, these findings suggest that vimang and mangiferin may hold therapeutic potential for such conditions.[50],[51]

1.4.10 Antibacterial activity

The aqueous and ethanol extract of leaves and stems of mango at 50 and 25 mg/mL has been found sufficient activity against bacteria, Staphylococcus aureus, Streptococcus aeruginosa, Candida albicans, Enterococcus faecalis.[52] The antibacterial ability of extract also found against Salmonella enterica, Listeria monocytogenes, Escherichia coli.[53] Antibacterial activity of mango extracts upon gram-negative and gram-positive bacteria and yeast Candida albicans was also demonstrated.[54],[55] And the antibacterial activity of mango extract is due to the presence of mangiferin and gallotannin.[56]

1.4.11 Anti-Diarrheal activity

It is one of the most infectious diseases, caused by drinking contaminated or unsafe water, poor sanitation and hygiene, eating raw meat, and food intolerance, and it accounts for 3.2% of mortalities worldwide.[57],[58]

Organisms responsible for this disease include microbial communities like Escherichia coli, Candida albicans, Vibrio cholerae, Shigella flexneri, Staphylococcus aureus, and Salmonella typhi. According to WHO reports, diarrhea accounts for approximately 1.6 million deaths in developing countries, causing 28% mortality in infants in Africa and southeast Asia due to sever gastroenteritis[59],[60] Further study about the anti-diarrheal activity, he reported that the flavonoid present in MI inhibits intestinal motility and hydro electrolytic secretion, it also able to inhibit intestinal secretory responses induced by prostaglandins this may be a possible mechanism which supports the anti-diarrheal activity of Mangifera indica.[61]

1.4.12 Antibone resorption

The chemical constituent mangiferin is responsible for the inhibitition of parathyroid-hormone-stimulated bone resorption in mice.[62]

1.4.13 Antifungal

The antifungal potential of methanol, ethanol, and aqueous extracts was found against Alternaria alternate at 6.25 mg/mL concentration.[63]

1.4.14 Antiviral

Mangiferin was considered an antiviral agent for herpes simplex virus.[64],[65] HIV and hepatisis B virus.[66] In an in-vitro, mangiferin demonstrates effectiveness against herpes simplex viruses (HSV) type 2. Notably, mangiferin does not directly deactivate HSV-2 but inhibits the late stages of HSV-2 replication.[67] In laboratory conditions, mangiferin exhibited the capability of replication of HSV-1 within cells.[68] Additionally, mangiferin demonstrated the ability to counteract the cytopathic effects of HIV.[69]

1.4.15 Antimalarial activity

The stem bark extract of M.I. was evaluated for anti-plasmodial activity against Plasmodium yoeliingeriensis. The extract exhibited a schizontocidal effect during early infection and also demonstrated repository activity.[70] in-vitro antimalarial activity of chloroform methanol (1:1) extract of M.I. was evaluated. The extract showed good activity of Plasmodium falciparum in-vitro with a growth inhibition of 50.4% at 20 μg/mL.[71]

1.4.16 Laxative

Mangiferin significantly accelerated gastrointestinal tract (GIT) movement at oral doses of 30 mg/kg and 100mg/kg by 89% and 93% respectively.[72]

1.4.17 Antiparasitic activity

In a neonatal mouse model, mangiferin at 100mg/kg blocks Cryptosporidium parvum and similarly to the same dose of 100mg/kg of an active drug, paromomycin.[73]

1.4.18 Gastroprotective

Mangiferin, a naturally occurring glucosyl xanthone derived from M.I. was investigated as a novel gastroprotective agent in mice subjected to gastric injury induced by ethanol and indomethacin. The impact of mangiferin on gastromucosal damage was evaluated by determining changes in the mean gastric lesion area or ulcer score in mice. Additionally, the effects on gastric secretory volume and total acidity were assessed in 4-hour pyrolus ligated rats. These findings strongly suggest that mangiferin provides gastroprotection against ethanol and indomethacin-induced gastric injury, likely through its snit-secretory and anti-oxidant mechanism of action.[74]

1.4.19 Anti-tumor-anti-HIV activity

The stem bark mango has shown significant cytotoxic activity against the breast cancer cell MCF 7, MDA-MB-435, and MDA-N, as well as against a colon cancer cell line(SW-620 and a renal cancer cell line 786-0.[75] Ethanol and water extract (1:1) of dried aerial parts of mango was administered to mice intraperitoneally at a dose of 250 mg/kg was inactive against Leuk-P388.[76] Mangiferin dose when time-dependent inhibits the proliferation of K562 leukemia cells and induces apoptosis in K563 cells line present in-vitro studies, most likely by down-regulating bcr/abl gene expression.[77] The findings indicate that Mangifera has the potential to act as a naturally existing chemopreventive agent.[78]

2.0 CONCLUSION:

Medicinal plants have shown promising potential in the prevention of various diseases. They have been used for many years with minimal or no side effects, making them a secure and readily available option for treating various disorders. In this overview of Mangifera indica, we have gathered information on the phytochemical, pharmacological, and nutritional values of mango. The extensive pharmacological actions attributed to various components of this tropical fruit, such as antioxidant, anti-inflammatory, anti-hyperglycemic, hepatoprotective, antibacterial, anticancer, immunomodulatory, and antiulcer properties to its anti-cancer effects, illuminate its therapeutic potential. Furthermore, the rich nutritional content of Mangifera indica, encompassing essential vitamins and bioactive compounds, solidifies its status as not only a flavorful delight but also a powerhouse of health benefits. Its medicinal virtues and nutritional richness make it a valuable asset in the realm of preventive healthcare and wellness. As we continue to unravel the mysteries of its pharmacological actions and nutritional content, it is with anticipation that we look towards a future where this tropical gem might play an even more significant role in promoting health and vitality.

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4.0 AUTHORSHIP CONTRIBUTION STATEMENT

Vandana Patil: Supervision and writing original draft

Prajyot Chaudhari: Literature Review and Data Synchronization

Sakshi Chavan: Data Synchronization

Sachidanand Angadi: Administration, Funding, Data Curation

Suwarna Kale: Conceptualization

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Review Article Open Access

A Review Article on Effective Patient Counseling and Role of pharmacist

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Abstract

The practice of pharmacy and the idea of pharmacological treatment are both rapidly changing all around the world. Additionally, because of his technical and professional understanding, the pharmacist's role in advocating rational and cautious use of medicine is becoming more crucial. It is well established that patients who are knowledgeable about their drugs and how to take them obtain safe and effective treatment, effective medical care. In addition to the many technical tasks carried out behind the counter, therapeutic pharmacists frequently meet with patients and help with clinical therapies. Giving the patient or their representative a medicine kit alone is insufficient; also, the right medication must be given to the right person with the right information.

Keywords: Patient counseling, Attitude and behavior, Privacy and confidentiality, Counseling aids

Introduction

When we are summoned to the counseling area, a fresh scenario comes to light that needs to be carefully examined in order to deliver useful knowledge. We must watch the patient's nonverbal clues as we approach the counter to identify any barriers to communication that must be removed. A pharmacist who wants to provide counseling services in a clinical context must overcome a number of obstacles [1]. Some obstacles are patient-centered, such as coaching the carer rather than the patient, a poor level of education, and the patient's challenging physical condition. While some are institution-specific, such as delays in discharge orders or invasions of privacy, and can be prevented by careful adherence to procedures. It is essential to remove the obstacles a pharmacist faces in communicating with the patient in order to offer a framework for guaranteeing medication adherence and the best therapeutic efficacy [2]. A good pharmacist consultation makes all the difference in whether a pharmacotherapeutic outcome is favourable or negative. Though each pharmacist has their own style of counseling a client, they all must adhere to a few basic principles, such as making an introduction, using the patient's information to identify the correct patient, making the patient feel comfortable while maintaining their privacy, and answering any questions they may have [3].

Counseling for pateint's goal: The patient needs to be aware of how important medication is to his entire health. It's important to establish a business relationship that enables continuing interaction and consultation. It's critical that individuals have a better understanding of how to manage the adverse effects and drug interactions associated with prescription medications. The patient develops into a knowledgeable, effective, and active participant during disease treatment and self-care management. Avoiding medication interactions and potentially dangerous drug responses is important, and the pharmacist should be regarded as a specialist in pharmaceutical care.

Potential pharmacist benefits: You are seen as having a greater professional position by patients and other healthcare professionals. making an essential element of patient care that can't be replaced by staff or technology. higher levels of job satisfaction as a result of improved patient outcomes. a service that improves the patient's experience in any way. Revenue is generated when clients pay for counseling services; it is currently small but growing. The patient should be able to: Explain how an effective counseling contact explains why a prescription medicine is helpful for maintaining or enhancing wellness. Accept the healthcare provider's assistance in establishing a rapport and providing the foundation for continuous participation and dialogue. Become more capable of making well-informed choices regarding medication compliance and adherence. Enhance your stress management strategies [4].

Pharmacist Characteristics

1. Pay close attention as you are being counselled. The pharmacist must focus intently on the patient and monitor both verbal and nonverbal cues.

2. Behavior: The pharmacist can evaluate the patient's understanding of their condition and medications based on this.

3. Be flexible: The pharmacist needs to be flexible in order to give recommendations and information that are tailored to the unique needs and capacities of each patient.

4. Demonstrate empathy: The pharmacist should make an effort to comprehend the patient's suffering and predicament as if it were his or her own issue.

5. Show compassion: Pharmacies shouldn't judge a patient's behaviour based on their illness or the group they are a part of.

6. Show compassion: During counseling sessions, clients may act irrationally, irritably, or aggressively. The pharmacist needs to respect the patient's feelings.

7. Speak confidently: The patient acceptance of the pharmacist's suggestions will rise if the pharmacist speaks confidently [4].

Patient Counseling Obstacles

Thoughts regarding emotions: Patients who have had a mental change as a result of disease anxiety, unexpected costs, interruptions

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at work or in their business, etc. Other factors include not knowing what to expect with this new symptom or illness, depending on medical professionals for the best care and on family for assistance with daily

tasks, being afraid of change and death, experiencing pain and discomfort, not having privacy during physical examinations, and losing one's sense of self as a healthy person (which sounds strange but is mostly true).

When people gain social support, they are more likely to trust them or treat them favorably [5].

The pharmacy setting: Many neighborhood pharmacies lack a separate space where the pharmacist and the patient can speak privately. In addition to a lack of privacy, pharmacists frequently encounter other challenges to effective patient interaction, such as a lack of encouraging individuals.

- There is a huge workload and backlog.
- Those who are awaiting the filling of their prescriptions or assistance from a pharmacist.
- Incoming calls and requests for information or help from coworkers.
- Inadequate computer hardware, software, and services, as well as interns and other staff
- Preparing for new consulting positions [6].

Pharmacist's Attitude and Conduct During Patient Counseling

A primary activity of a pharmacist is patient counseling (PC). It could be as simple as giving a medication's dosing instructions or it could involve offering lifestyle and other health-related advice. A pharmacist is responsible for making sure the patient comprehends the instructions and uses the medications correctly. The first step is to inform the patients of the directions listed on the medicine labels [7].

The pharmacy should always be open so that the right information may be given. PC aids in lowering both drug-related issues and non-adherence to medication. The patient's satisfaction is an additional benefit. As a result, patients can utilise their drugs with greater assurance. For a PC to be productive, good communication skills are required.

Face expression and eye movement are part of (NVC). When someone asks you a question, don't roll your eyes. Understanding what the patient is saying also requires active listening. The pharmacist should discuss topics like: (a) Why the drug is prescribed, (b) How it works, (c) Dose and frequency, (d) Treatment goals, (e) Adverse drug responses and how to manage them, (f) Drug-Related Issues when counseling the patient [8]. Innovareacademics.in. 2018 [cited 29 January2018]. Communication with patients who are nearing the end of their lives: Unless they seem uninterested, we shouldn't avoid talking to them. When speaking with elderly patients, keep in mind that their grasping capacity is lower than that of younger patients. They might also experience issues including decreased eyesight, hearing, etc. Counseling should be conducted properly as a result [7].

Communicating with patients that are mentally ill. Communication with these patients might be challenging. OEQs will be more successful if they are open-ended. Patients who are mentally ill could have trouble understanding their treatments. As a result, the information should be provided to them in full [7]. Diabetic patient communication: Due to recently developed diabetic treatments, pharmacists are able to provide patients with a wide range of information. They can inform the patients about how to use monitoring devices properly, how to screen for drug interactions, and other pertinent information. The levels of the patient's blood glucose can even be checked by the pharmacist.

They can also provide details on how to administer insulin. When communicating with children, remember to (a) use simple sentences, (b) inquire about their inquiries, (c) ask OEQ, and (d) remember that NVC is crucial, so be mindful of your body language, tone of voice, and other cues [7]. In addition to these, the pharmacist needs to possess the knowledge and abilities needed to deliver quality PC. They ought to be aware of the patient's culture, beliefs on health, attitudes, etc. OEQ and effective listening are critical abilities for information gathering. The pharmacist can provide the right information to fulfil the patient's needs by evaluating the patient's cognitive capabilities, learning style, pace, and physical condition [7]. According to a survey conducted in Karnataka, professional satisfaction (43%) and patient happiness (32%), as well as sales growth (8%) and improved patient compliance (7.5%), are the key reasons why pharmacists provide PC [5]. However, pharmacists did face certain challenges, such as patients' unsatisfactory responses (82%), pharmacists' inadequate knowledge and confidence (78%), insufficient professional training programmes (75%), and doctors' dispensing (72%) [9].

Programs for continuing pharmacy education aid in the professional development of pharmacists. According to a study conducted in Ethiopia, patients who are more informed about their drugs are more likely to adhere to drug therapy, which leads to more successful patient-provider communication. The respondents were unable to counsel their patients due to a lack of expertise and confidence.

Difficulties in Patient Counseling

First, we must determine any obstacles that will need to be removed, such as linguistic, literate, and ideological ones. To meet the demands of each patient, we should quickly dynamically update our OEQ and drug information.

Barrier based on a pharmacist: Language barrier—the medium of conversation—is a significant issue when speaking with patients because we want to make sure that the information we provide is accurate and that their questions are answered in a way that is appropriate. While using a family member as a translator can be useful, there is a greater risk of information being misinterpreted. A technician may assist the pharmacist if the patient is at ease, creating a three-way interaction [10]. A pharmacist should keep up with current information to eliminate pharmacist-based barriers, which are just as important as communication skills [10].

Patient-based obstruction: Patient reluctance: Patients occasionally experience some reluctance for reasons such as "An elderly man with erectile problems may feel uncomfortable speaking to a women pharmacist." As a result, we must attend to each patient's needs. Allowing a patient to wait in the therapy room for more than a few minutes will undermine their sense of security and privacy [10]. For a patient with speech or hearing impairment, several assistance, such as pictograms and hearing aids, must be employed. To get through all of these obstacles, we also need to provide a space where we may address client misunderstandings and offer extra counseling advice tailored to the patient's individual needs.

Know-It-All: Some patients may choose to forego counseling sessions on the grounds that the information in the leaflet is sufficient and they can read it, they don't have time, they are employed as healthcare professionals, etc. A community pharmacist, however, might have two or three crucial counseling points for each medicine

at his fingertips. He or she can do this by using phrases such, "I just wanted to check that you were aware of." Making sure all patients are aware of their ailment and the goal of treatment is the greatest method to ensure that they all adhere to the recommended course of action and obtain the best therapeutic result possible [10].

Successing in Obstacles

Several characteristics should be noted in order to obtain a good counseling section, including:

Establish trust: The pharmacist should show a sincere interest in the treatment of the patient. By properly introducing the patient and smiling when they are greeted at the beginning of the session, the patient is more likely to feel comfortable disclosing all relevant information about their prior medical and drug histories [10].

Participation of the patient: The pharmacist should encourage the patient to actively participate by posing questions. They must to assess the patient's comprehension of pharmacological therapy and adjust the counseling as necessary [10].

NVC: It's critical that the pharmacist is aware of the NVC, such as keeping eye contact and a favourable facial expression that benefits the patient [9]. In order to foster clear interactive communication, it is crucial to listen to the patient's wants, concerns, and questions. Passive listening can be used by responding with a nod of the head and phrases like "sure, go on." OEQ questions can help you learn more, and the pharmacist should explain why they are asking so that they don't annoy the patient.

Maintain objectivity: Pharmacists should be careful to prevent their ethical or religious convictions from interfering with patient counseling. He needs to exercise caution when speaking in an unjudgemental manner. Empathy is defined as the ability to perceive and experience things from another person's point of view. Use this ability to motivate the sufferer. To achieve the best treatment outcome, remind the patient to take their medication as prescribed [9]. Assure total secrecy and uphold privacy to help the patient feel at ease discussing private medical problems [10].

Counseling Aids

When the patient receives the information verbally, there is a possibility that the patient will eventually forget it. To aid with patient counseling, numerous teaching and educational tools have been created. If the information is given in written form, the patient can read it whenever they have free time and whenever they need it. Medication cards can be a helpful tool, especially for people who take prescriptions regularly. A long-term medicine list for patients is contained in a medication card. Presented in a way that is simple for the patient to understand, a medication card is a written overview of a patient's medications. Both handwritten and computer-generated cards are acceptable.

Once a patient receives a card, they can use it to help them organise their at-home medication habits and to show other healthcare professionals. When the pharmaceutical regimen is altered, it is crucial to update the card. Consumer product information, also known as PIL, is information created by medicine manufacturers for their drugs. PILs are written informational leaflets that describe a patient's ailment and how it is treated, including drugs and necessary lifestyle modifications. Printed information can help people grasp and accept treatment recommendations better than spoken guidance alone [10].

It is acceptable to use handwritten or computer-generated cards. A patient can use the card they receive to keep track of their at-home medication routines and to show other medical personnel. Updating the card is essential whenever the medication regimen changes. PIL, or consumer product information, is data produced by pharmaceutical companies for their products. PILs are written informational booklets that outline a patient's condition and the methods used to treat it, including any medications and required lifestyle changes. Written information is more easily understood and accepted by patients than verbal advice alone. Written material is to be viewed as an addition to spoken counseling rather than as a substitute for it. Pharmacists can create beneficial PIL by utilising their understanding of medicines and the local tongue.

Satara and Sangali district conducted one analysis to gauge the effect on PC based on knowledge, attitudes, and practise. Samples showed that they provided counseling services using verbal, written, and audiovisual approaches, although almost 46.56% of respondents used a combination of verbal and written methods. While 16.93% of respondents indicated they were not utilising any aid, 51.32% and 7.41% of respondents indicated they utilised posters and pictograms for PC, respectively. Additionally, the combined use of multiple methods did not differ much from other methods. Written material is to be viewed as an addition to spoken counseling rather than as a substitute for it. Pharmacists can create beneficial PIL by utilising their understanding of medicines and the local tongue.

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It gives them something to turn to if they forget whatever they've heard. Video, graphic, and other tool utilisation could be beneficial to counseling. Pharmacists have embraced a variety of counseling tools, including posters, computer-generated booklets, pictograms, and telephone systems. Computer- assisted counseling is still relatively unknown in the nation. One might anticipate effective counseling and patient adherence by utilising new strategies [10].

Conclusion

The pharmacist should be on hand to assist the customer in choosing an OTC medication, provide non-pharmacological therapy, or refer the customer to a doctor. Additionally, pharmacists teach patients when to seek medical attention, how to treat themselves in an emergency, and when diagnostic testing are necessary. So long as the counseling process is effectively maintained, patients' comprehension, compliance, and pharmacists' sense of fulfilment at work all improve. It also strengthens the bond between doctors, patients, and pharmacists.

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COMPREHENSIVE INSIGHTS INTO BREAST CANCER: FROM MOLECULAR PATHWAYS TO PERSONALIZED THERAPIES

Tamoxifen: An Enduring Pillar in Breast Cancer Management - Insights, Efficacy, and Evolving Perspective

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Abstract: Breast cancer, with its diverse subtypes and complex molecular pathways, necessitates tailored treatments targeting receptors like ERα, PR, and HER2. Endocrine therapies, including SERMs and AIs, alongside emerging CDK4/6 inhibitors, demonstrate efficacy in managing ER+ HER2− breast cancers. Understanding ERβ's role, treatment adherence, bone health considerations, and the impact of factors like lymph node status are crucial in optimizing treatment strategies. Precision medicine, genomic profiling, and immunotherapies hold promise in shaping the evolving landscape of breast cancer treatment. Methods: A comprehensive analysis of breast cancer and its impact on various demographics, encompassing global trends, endocrine therapies, prognostic indicators, estrogen's role in cancer development, and the complexities surrounding preventive measures, was conducted. The review includes in-depth insights into hormonal mechanisms, lifestyle influences, and treatment nuances across different populations, encompassing menopausal statuses, genetic predispositions, and psychosocial implications in young breast cancer survivors. Results: Discussions highlight the significance of endocrine status determination, adjuvant endocrine therapy efficacy, and the multifaceted considerations in treatment selection. Factors such as hormonal dynamics, comparative efficacy of AIs vs. Tamoxifen, and individualized approaches based on menopausal status underscore the importance of personalized medicine in breast cancer management. Discussion: The abstracted review delineates the complexities of breast cancer treatment, incorporating biological mechanisms, psychosocial impacts on survivors, global trends, and precision medicine's necessity. It emphasizes the need for targeted interventions, ongoing research, and risk-adapted strategies to optimize outcomes for diverse breast cancer populations.

Keywords **-** Breast Cancer, Endocrine Therapy, Precision Medicine, Hormonal Dynamics, Global Trends, Young Survivors, Personalized Treatment

I. INTRODUCTION

Breast cancer is a complex disease with various subtypes, and understanding its different receptor expressions, like ERα, PR, and HER2, is crucial for tailoring effective treatments. ER+ (estrogen receptor-positive) breast cancer accounts for about 70% of cases. Targeting these receptors has been a cornerstone in managing this subtype.[1] Hormonal therapies like selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) aim to either block estrogen production (AIs) or interfere with estrogen signaling (SERMs) to inhibit cancer growth.[2]

Moreover, the emergence of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has been a significant advancement. They work by halting the progression of the cell cycle and have shown remarkable efficacy when combined with hormonal therapies in ER+ HER2− breast cancers.[3]

The discussion about the role of ERβ is ongoing. While ERα has been extensively studied, ERβ's specific involvement in breast cancer remains less defined. Understanding its nuances could potentially lead to novel therapeutic approaches or better prognostic markers.[4]

Treatment adherence plays a pivotal role in outcomes. Compliance with prescribed therapies significantly correlates with better prognosis, emphasizing the importance of patient education and support throughout the treatment journey.[5]

Beyond hormonal therapies and targeted drugs, the management of breast cancer often involves addressing bone health. Bisphosphonates, known for their bone-strengthening properties, have demonstrated benefits in reducing bone metastases and improving outcomes in certain breast cancer populations.[6]

Furthermore, exploring ovarian function suppression (OFS) in premenopausal women has been an area of interest. By suppressing ovarian function, the production of estrogen can be limited, providing an additional strategy in ER+ breast cancer management.[7]

Understanding the role of different factors like lymph node status and their association with disease relapse is crucial for prognostication and treatment planning. Tailoring therapies based on these factors helps optimize patient outcomes and reduce the risk of recurrence.[8]

The ongoing research and evolution in precision medicine continue to shape the landscape of breast cancer treatment. Personalized approaches, including genomic profiling and immunotherapies, hold promise for more targeted and effective treatments in the future.[9] As the understanding of breast cancer biology deepens, the therapeutic landscape will likely continue to expand, offering more tailored and effective options for patients.[10]

aspects related to breast cancer, its treatment, and its impact on different groups:

1. **Global Impact of Breast Cancer:** Breast cancer is a significant public health concern globally, impacting millions of women each year. The World Health Organization's estimations of over 2.1 million new cases and about 627,000 deaths annually underscore the urgency for effective control measures.[11] Its devastating impact not only affects physical health but also deeply influences the psychosocial well-being of patients. The cost of treatment and the emotional toll it takes on individuals and families further emphasizes the need for effective prevention strategies.[12] Prevention, therefore, stands as a potentially cost-effective approach to long-term disease control, highlighting the importance of research and interventions in this area.

Additionally, raising awareness about risk factors, promoting early detection through screening programs, and investing in accessible and affordable treatment options are crucial steps in addressing this global health challenge. Collaborative efforts among healthcare providers, policymakers, researchers, and communities are pivotal in implementing comprehensive strategies aimed at prevention and improving outcomes for breast cancer patients worldwide.[13]

2. **Endocrine Therapies for Prevention:** Selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) have emerged as effective preventive measures for high-risk individuals. These therapies target hormonal pathways involved in the development of hormone receptor-positive breast cancers. SERMs, like tamoxifen and raloxifene, function by interfering with estrogen's binding to receptors, thereby hindering its influence on cancer cell growth.[14] On the other hand, AIs, predominantly used in postmenopausal women, inhibit the production of estrogen by targeting the aromatase enzyme, essential for estrogen synthesis. This dual approach of disrupting estrogen signaling or production has shown promise in reducing the risk of developing breast cancer among high-risk populations.[15]

The challenge lies in balancing the efficacy of these preventive therapies with their potential side effects. Discussions between healthcare providers and patients regarding individual risk factors, benefits, and potential adverse effects are crucial in making informed decisions about the initiation and duration of these preventive treatments.[16] Furthermore, ongoing research aimed at refining these therapies and identifying new preventive strategies remains critical in the pursuit of reducing the global burden of breast cancer.

Let's continue examining the rest of the points in a similarly detailed manner.

3. **ERs and PRs as Prognostic Indicators:** Estrogen and progesterone receptors serve as significant indicators in predicting treatment response and prognosis for breast cancer patients. Their presence, particularly in hormone receptor-positive tumors, often indicates a higher likelihood of response to endocrine therapy and improved disease-free survival.[17] ER-positive breast cancers, constituting a substantial percentage of cases, are more amenable to hormonal treatments compared to ER-negative tumors. The identification and characterization of these receptors play a pivotal role in tailoring personalized treatment strategies for patients, allowing for more targeted and effective interventions. Additionally, PR status further refines prognostic information and aids in treatment decision-making, contributing to more precise therapeutic approaches for different subtypes of breast cancer.[18]

Understanding the role of ERs and PRs goes beyond prognostication; it's integral to designing individualized treatment plans. Targeting these receptors with hormonal therapies has been a cornerstone in managing hormone receptor-positive breast cancers.[19] Consequently, diagnostic tests assessing ER and PR expression are fundamental in guiding treatment choices, optimizing patient outcomes, and reducing the risk of recurrence.[20]

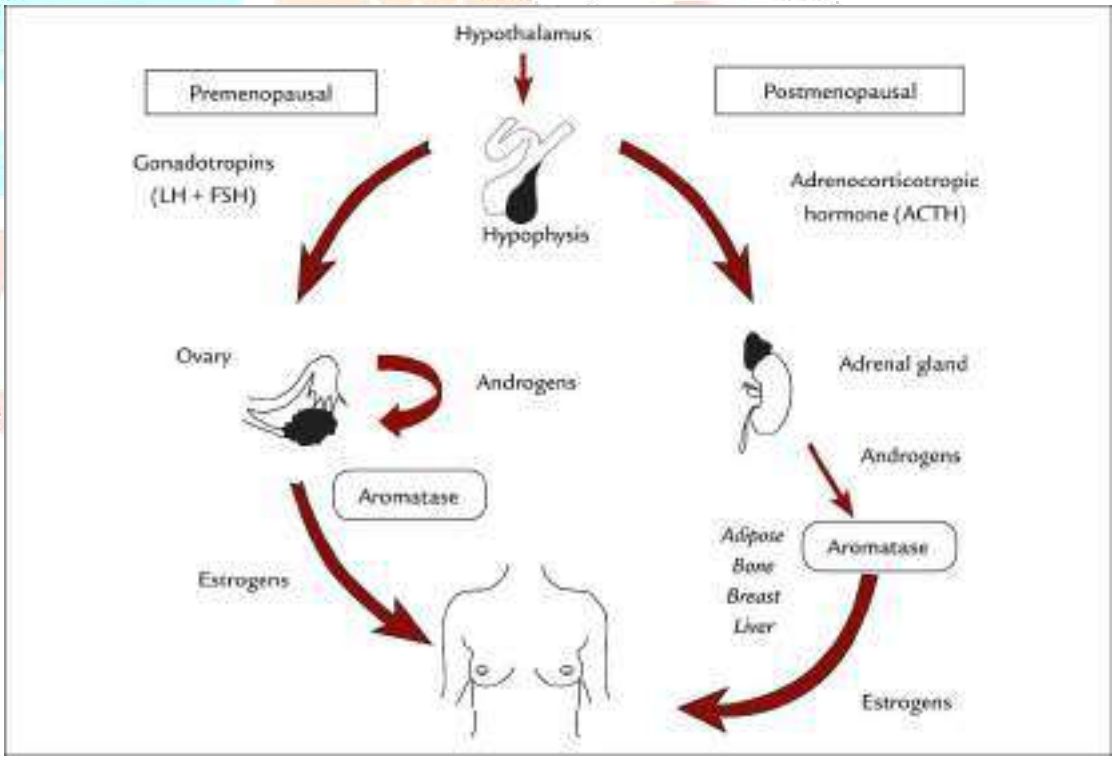
4. **Role of Estrogen in Breast Cancer Development:** Estrogen, through its binding to estrogen receptors (ERs), plays a crucial role in promoting cell division, inhibiting cell death, and influencing various cellular processes in breast epithelial cells. Disrupting estrogen-dependent pathways becomes a focal point in the development of therapies for estrogen-dependent breast cancers.[21,22] Strategies aiming to interfere with estrogen's binding to ERs, like selective ER modulators (SERMs) such as tamoxifen and raloxifene, or reducing ER expression, as exemplified by fulvestrant, aim to impede the cancer-promoting effects of estrogen. Additionally, directly reducing estrogen levels via aromatase inhibitors (AIs) in postmenopausal women has become a primary approach due to their efficacy in inhibiting estrogen production. These multifaceted strategies highlight the diverse mechanisms by which estrogen-dependent processes can be interrupted, offering various avenues for therapeutic intervention and breast cancer prevention.[23]

The understanding of estrogen's role in breast cancer development and progression underscores the significance of targeted therapies aimed at disrupting estrogen signaling pathways. Novel approaches that continue to emerge from ongoing research hold promise for further refining these interventions and enhancing treatment efficacy while minimizing adverse effects, paving the way for more personalized and effective breast cancer treatments.[24,25]

Let's continue the detailed analysis for the remaining points.

5. **Aromatase Inhibitors (AIs) in Postmenopausal Women:** Aromatase, predominantly expressed in adipose tissue in postmenopausal women, is a critical enzyme in estrogen production. AIs, by inhibiting aromatase activity, effectively reduce estrogen levels, making them pivotal in managing estrogen-dependent breast cancers in this demographic.[26,27] The shift in the regulation of aromatase expression—from gonadotropic control in premenopausal women to adipose tissue and cancer cell-mediated regulation in postmenopausal women—underscores the effectiveness of AIs in this population. However, the widespread use of AIs isn't without challenges, as profound estrogen depletion from these therapies can lead to adverse effects, necessitating careful consideration and management by healthcare professionals.[28–30] Despite these challenges, AIs have become a cornerstone in the treatment of postmenopausal women with estrogen-sensitive breast cancer, showcasing their significance in improving patient outcomes.

Moreover, ongoing clinical trials are exploring the potential of AIs in breast cancer prevention, highlighting their potential as preventive strategies in high-risk populations. These efforts underscore the dynamic landscape of breast cancer research and the continuous quest for improved therapies and preventive measures.[31] As primary care physicians often become pivotal in advising patients regarding the initiation and management of AIs, their understanding of these agents and their potential adverse effects is crucial in supporting patients through their treatment journey and optimizing treatment adherence.[32,33]



Estrogen production in premenopausal and postmenopausal women. LH: luteinizing hormone; FSH: follicle-stimulating hormone. Source: adapted from Freedman et al.

6. **Male Breast Cancer:** Although rare, male breast cancer shares similarities with female breast cancer, notably in ER positivity. However, evidence suggests differences in the efficacy of AIs between males and postmenopausal females, emphasizing the need for tailored approaches in managing breast cancer in men.[34] The rarity of male breast cancer also poses challenges in research and treatment optimization, underscoring the importance of continued efforts to better understand its distinct biology and devise tailored therapeutic strategies. Despite its rarity, male breast cancer remains a significant concern due to its impact on overall survival rates and the need for specialized care and treatment approaches.

The comparable overall survival rates between male and female breast cancer patients, despite differences in specific therapies' efficacy, suggest the importance of considering gender-specific factors in treatment planning.[35] This includes recognizing the unique challenges and responses to treatment that males with breast cancer may experience, emphasizing the need for tailored approaches and dedicated research to improve outcomes for this demographic.[36]

Let's continue the analysis with a focus on young breast cancer survivors and their unique challenges.

7. **Impact on Young Breast Cancer Survivors:** Young breast cancer survivors (YBCS) face a distinct set of challenges due to their early age of diagnosis. Beyond the physical implications of breast cancer treatment, YBCS experience significant disruptions in various aspects of their lives.[37,38] The abrupt progression to a temporary or permanent menopausal state presents more severe symptoms than those associated with natural aging, exacerbating concerns related to sexual dysfunction, vasomotor symptoms, and infertility. These challenges have a profound impact on their quality of life, necessitating specialized support and care tailored to their unique needs.[39–41]

Additionally, the psychosocial impact on YBCS extends beyond medical symptoms, encompassing concerns about fertility, family planning, employment, and relationships.[42] Disturbances in quality of life and overall symptom distress are more pronounced among young survivors compared to their older counterparts, highlighting the need for holistic care that addresses both medical and psychosocial aspects. Specialized interventions aimed at managing these multifaceted challenges are essential in improving the well-being and long-term outcomes of young breast cancer survivors.[43,44]

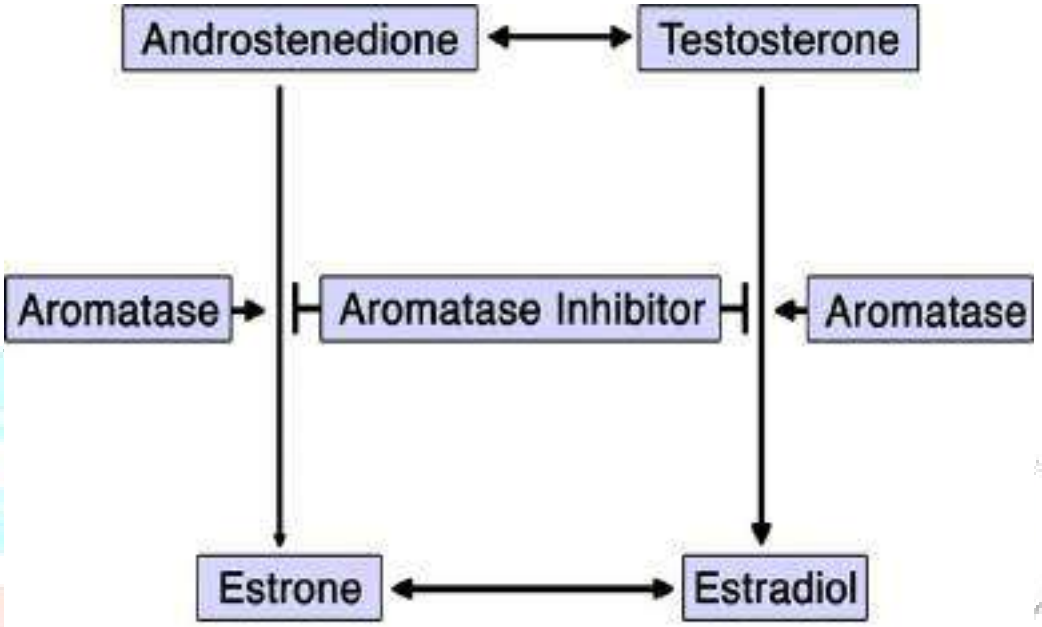
8. **Quality of Life Challenges for Young Survivors:** The experience of breast cancer at a young age profoundly affects the overall well-being and quality of life of survivors. The impact on health-related quality of life, including changes in functional capacity, social functioning, and mental health, is more pronounced in YBCS compared to older survivors.[45] Their unique challenges, such as concerns about fertility, delayed pregnancy, and the impact of a breast cancer diagnosis on family dynamics, significantly contribute to their overall distress and disruption in various aspects of life. Moreover, navigating through treatments that increase the risk of premature menopause and associated symptoms further compounds their challenges.[46–48]

The multifaceted nature of challenges faced by YBCS necessitates a comprehensive and multidisciplinary approach in their care. Tailored interventions addressing medical, psychological, and social needs are crucial in mitigating the impact of breast cancer on the overall well-being and quality of life of young survivors.[49–51] Providing specialized support, information, and resources targeted toward managing their unique challenges can significantly improve their long-term outcomes and overall quality of life.

Below analysis underscores the complexity of breast cancer, encompassing its biological mechanisms, psychosocial impacts on survivors, global trends in incidence, and the necessity for comprehensive research to drive effective preventive measures and treatment strategies.[52,53]

1. **Psychological Distress in Young Breast Cancer Survivors (YBCS):**
    - Stressors associated with psychosocial concerns and long-term treatment effects contribute to increased psychological distress in YBCS, often persisting for years beyond the cancer diagnosis.[54]
    - Studies exploring the impact of breast cancer diagnosis and treatment on the quality of life (QOL) in YBCS have been limited due to the rarity of the disease in this younger population. Large-scale studies are crucial to understanding the enduring effects of breast cancer and its treatments on YBCS.[55,56]

2. **Role of Aromatase Enzyme and Estrogen Biosynthesis:**
    - The aromatase enzyme plays a pivotal role in estrogen production, with differing sources of estrogen between premenopausal and postmenopausal women.[57]
    - In premenopausal women, ovarian estrogen production is predominant, while in postmenopausal women, peripheral tissue conversion of androgens to estrogens via aromatase becomes crucial.[58]
    - Aromatase inhibitors (AIs) are extensively used in postmenopausal women to manage estrogen-sensitive breast cancers. However, the inhibition of estrogen synthesis by AIs might increase the risk of type 2 diabetes (T2D) due to the association between low estrogen levels and T2D risk.



Mechanism of action of aromatase inhibitors

3. **Rising Incidence and Risk Factors of Breast Cancer:**
    - Despite advancements in diagnostics and treatment, breast cancer incidence continues to rise globally, attributed to various factors such as lifestyle changes, reproductive patterns, obesity, alcohol consumption, and hormone replacement therapy (HRT).[59,60]
    - Hereditary factors, including BRCA mutations, contribute significantly to the increased incidence of breast cancer.
    - Efforts to reduce breast cancer incidence through lifestyle modifications, reproductive factors, and preventive therapies akin to cardiovascular disease prevention strategies have shown promise. However, further research is essential for effective application to appropriate populations of women.
4. **Global Trends and Prevention Strategies:**
    - There is a need for comprehensive studies focusing on breast cancer risk factors, prevention strategies, and their implementation.[61]
    - Understanding the biological intricacies, risk factors, and long-term effects of breast cancer and its treatments is pivotal in advancing both preventive measures and treatment strategies.
    - Research encompassing psychosocial impact on survivors, estrogen biosynthesis complexities, and global trends in breast cancer incidence and prevention will shape future interventions and improve outcomes for breast cancer patients worldwide.[62]

Below points focuses on the mechanistic understanding of how lifestyle choices, particularly diet and energy balance, impact breast cancer risk, this approach aims to unravel the complexities behind preventive strategies, offering a deeper understanding beyond the controversies arising from epidemiological studies.[63]

1. **Breast Cancer Incidence and Survival Rates:**
    - Breast cancer ranks as one of the most extensively researched diseases in oncology and constitutes a significant portion of female cancers, being the most diagnosed cancer in women.[64]
    - Despite the increased 5-year survival rates, hovering between 77-90%, recent advances in understanding, detection, and treatment haven't significantly impacted breast cancer incidence rates, which have generally remained stable.[65]
    - The static incidence rates highlight the necessity to focus on prevention strategies alongside improved detection and treatment options.[66]
2. **Preventive Measures and Lifestyle Choices:**
    - Lifestyle choices play a crucial role in breast cancer prevention, with dietary changes among the most discussed preventative measures.[67]
    - While controversies persist regarding the direct impact of diet on cancer prevention, the emphasis on a diet rich in fruits and vegetables remains a recommendation despite inconsistent study outcomes.
    - Understanding the underlying mechanisms behind lifestyle choices, particularly in relation to energy balance (calories consumed versus expended), sheds light on the potential impact on breast cancer risk reduction.[68]
3. **Energy Balance and Its Impact:**
    - Energy balance, typically defined by caloric intake versus physical activity, emerges as a critical factor influencing breast cancer risk.[69]
    - Caloric intake and physical exercise are highlighted as key components affecting energy balance and potentially reducing breast cancer risk.
    - Other factors indirectly linked to energy balance, such as maintaining a diet rich in fruits and vegetables, moderate red wine consumption, and consuming "good fats," exhibit potential in breast cancer prevention, although their independent impact remains under scrutiny.[70]
4. **Mechanisms Behind Breast Cancer Prevention:**
    - The focus shifts from epidemiological studies to delve into the underlying mechanisms driving breast cancer prevention strategies.
    - Understanding the science behind these controversies surrounding dietary and lifestyle choices aims to elucidate whether these factors independently contribute to reducing breast cancer rates or merely control overall caloric intake.[71]

Additional points:

5. **Hormonal and Biological Mechanisms:**
    - Exploring the hormonal and biological mechanisms affected by dietary choices and energy balance could elucidate how these factors impact breast cancer risk.
    - Studying hormonal pathways influenced by diet, exercise, and energy balance might clarify their direct or indirect role in breast cancer prevention.[72,73]

6. **Metabolic Impact and Inflammation:**
    - Investigating the metabolic impact of dietary components, exercise, and energy balance on cellular processes and inflammation may reveal their potential in mitigating breast cancer risk.
    - Understanding how these factors influence metabolic pathways and reduce chronic inflammation can provide deeper insights into breast cancer prevention.[74,75]
7. **Genetic and Environmental Interactions:**
    - Considering the interplay between genetic predisposition and environmental factors, especially in response to dietary patterns and physical activity, could offer insights into personalized prevention strategies.
    - Studying how genetic factors interact with lifestyle choices in influencing breast cancer risk helps tailor prevention approaches for high-risk populations.[76,77]

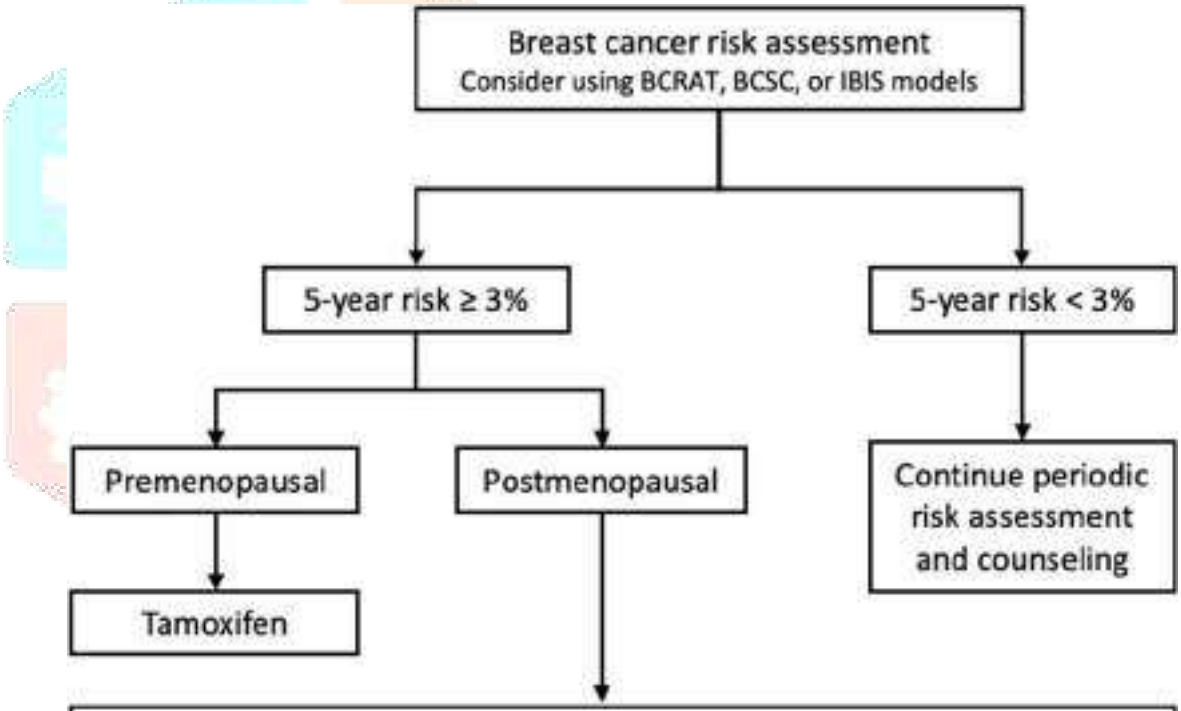
The Key Points Regarding Endocrine Status and Adjuvant Endocrine Therapy:

1. **Importance of Immunohistochemistry (IHC) in Endocrine Subtype Profiling:**
    - Immunohistochemistry (IHC) plays a crucial role in determining the expression of endocrine subtypes, particularly estrogen receptor (ER) status, which guides treatment decisions.[77,78]
    - Challenges arise in determining the optimal ER expression cutoff for effective endocrine therapy (ET), especially in tumors with low ER expression (1–10% of IHC+), where ET might not be beneficial due to similarities with basal-like tumor pathogenesis.[79]
2. **ER-Low Positive Tumors and ET Efficacy:**
    - ER-low positive tumors, accounting for a small percentage (up to 3%) of breast cancer cases, pose challenges in therapeutic decisions, as they exhibit pathogenic heterogeneity closer to basal-like phenotypes rather than the luminal phenotype.[80]
    - ET might not confer advantages in ER-low positive tumors due to their unique pathogenesis, which differs from the standard ER+ tumors.
3. **Progesterone Receptor (PR) Status and Predictive Value in ET:**
    - In ER+ tumors, the progesterone receptor (PR) status does not reliably predict the efficacy of endocrine therapy. Therefore, while ER status guides treatment decisions, PR status does not significantly impact ET effectiveness.[81–83]
4. **Role of Adjuvant ET in Eradicating Micro Metastatic ER-Enriched Cells:**
    - Adjuvant endocrine therapy aims to eliminate potential undetected micro-metastatic ER-enriched tumor cells, reducing the risk of disease recurrence.
    - Factors such as patient preferences, menopausal status, medical history, and specific pathological features of the tumor are crucial in guiding physicians toward selecting the most appropriate type of endocrine therapy for each individual case.
5. **Treatment Duration Based on Risk Categories:**
    - Determining the risk category, which includes assessing various factors such as tumor characteristics, helps in deciding the duration and intensity of endocrine therapy.[84]
    - Tailoring the treatment duration based on the perceived risk of recurrence enables personalized and optimized therapeutic strategies for each patient.

Additional Points:

6. **Emerging Biomarkers and Precision Medicine:**
    - Ongoing research focuses on identifying new biomarkers beyond ER and PR to better predict response to endocrine therapy, enabling more precise and personalized treatment strategies.[85]
    - Advancements in molecular profiling and genetic markers aid in refining treatment decisions, leading to more targeted therapies based on the tumor's molecular characteristics.[86,87]
7. **Therapeutic Challenges and Future Directions:**
    - The challenges in determining optimal ET selection for tumors with atypical ER expression highlight the need for ongoing research to elucidate the underlying mechanisms and identify effective therapeutic approaches for such cases.
    - Future directions may involve integrating genomic profiling and novel biomarkers into clinical practice to improve treatment decision-making and outcomes in breast cancer patients.

By dissecting the complexities of endocrine status determination, the efficacy of endocrine therapy, and the multifaceted considerations in treatment selection, this approach aims to underscore the need for precision medicine in breast cancer management.



Raloxifene, tamoxifen, anastrozole, or exemestane

Medication	Pros	Cons
Raloxifene	Reduced risk of vertebral fracture No increase in risk of uterine cancer	Potentially less effective than tamoxifen Increased risk of VTE (lower than tamoxifen)
Tamoxifen	Strongest evidence for breast cancer risk reduction Reduced risk of non-vertebral fracture	Increased risk of VTE Increased risk of uterine cancer Extensive gynecologic side effects
Anastrozole Exemestane	No elevation in VTE risk	Decreased bone density Musculoskeletal symptoms Not FDA-approved for risk reduction

Suggested Approach to Choosing Medication for Breast Cancer Risk Reduction

The Key Points Regarding Menopausal Status and Adjuvant Endocrine Therapy For Breast Cancer:

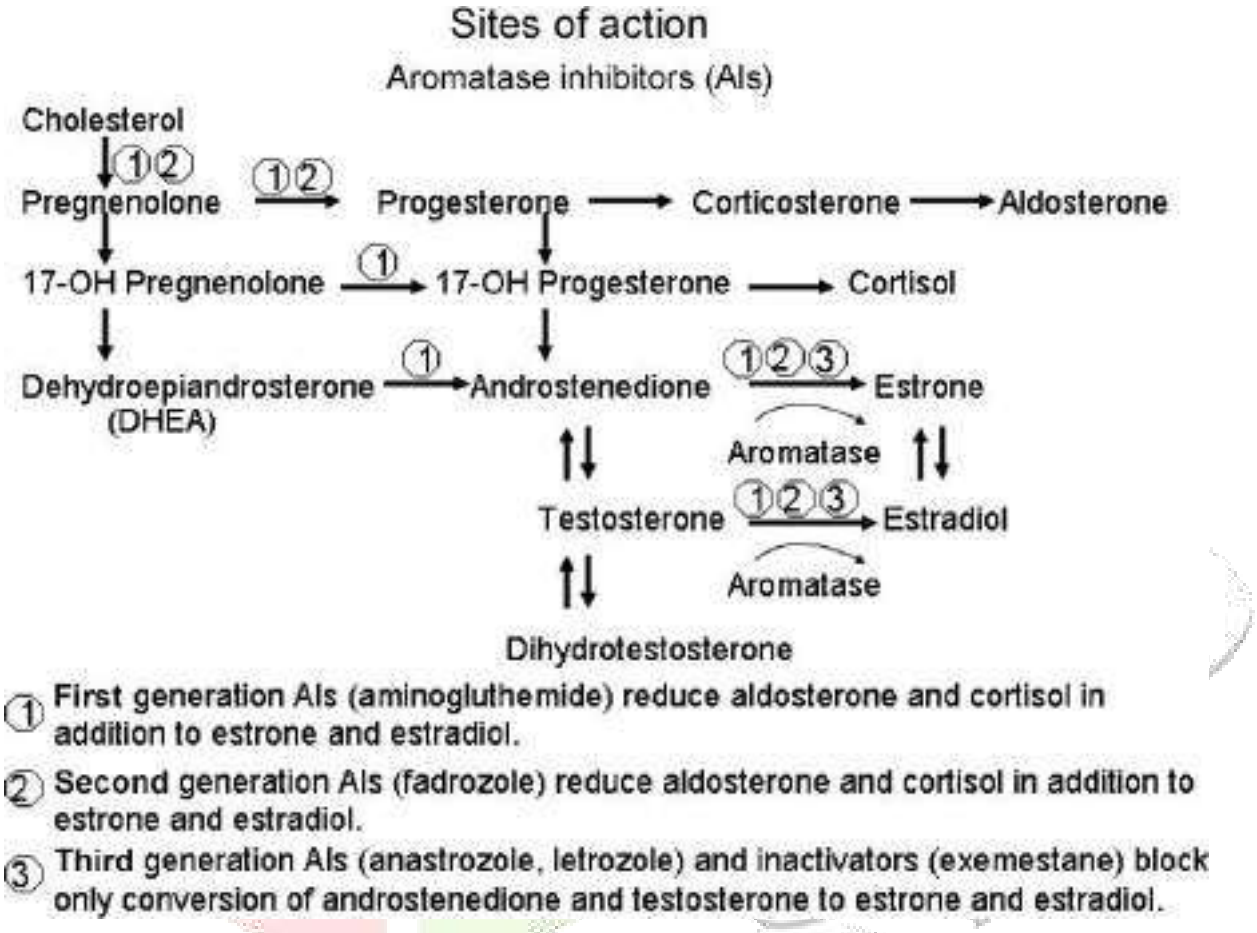
1. **Hormonal Dynamics in Premenopausal Women:**
    - In premenopausal women, 17β-estradiol remains the primary ovarian hormone, influencing the microenvironment of breast epithelium through estrogen and progesterone receptors.[88,89]
    - Physiological steroidal activity, mediated by these hormones, can stimulate stem cells, potentially contributing to the development of hormone-enhanced tumors.
2. **Role of Tamoxifen in ET for ER+ Breast Cancer:**
    - Tamoxifen, a selective estrogen receptor modulator (SERM), has been a pioneer in endocrine therapy for breast cancer over four decades.
    - Its competitive binding to estrogen receptors results in dual effects: inhibitory on estrogen-regulated pathways in mammary tumors while acting as an estrogen agonist in other tissues.[90,91]
    - Tamoxifen's efficacy in reducing recurrence risk (by approximately 40%) and mortality (by a third) in ER+ breast cancer patients, irrespective of menopausal status, has made it a cornerstone adjuvant therapy.
3. **Estrogen Regulation in Postmenopausal Women and Aromatase Inhibitors (AIs):**
    - In postmenopausal women, estrogen primarily originates from extragonadal tissues and is regulated by aromatase, crucial for steroid synthesis.[92]
    - AIs reduce circulating estrogen levels by inhibiting the conversion of androgens into estrogen in adipose tissues, leading to side effects such as vasomotor symptoms, arthralgia, and bone mineral loss.[92]
4. **Comparative Efficacy of AIs vs. Tamoxifen in Postmenopausal Women:**
    - Studies indicate that AIs—Anastrozole, Letrozole, and Exemestane—offer similar efficacy and safety profiles in postmenopausal women.
    - Compared to Tamoxifen, AIs have demonstrated superiority, reducing mortality by around 15% and decreasing recurrence risk by 14% to 26% at ten years.[93]
5. **Sequential ET Regimen for Perimenopausal Patients:**
    - Perimenopausal patients with low-risk characteristics might benefit from a sequential five-year ET regimen, starting with Tamoxifen and transitioning to AIs.[94]
    - This sequential therapy approach shows a reduction in mortality related to breast cancer (by 16% at one decade) compared to five years of Tamoxifen alone, emphasizing the importance of transitioning to AIs after initial Tamoxifen therapy.[95]

Additional Points:

6. **Individualized Treatment Approaches:**
    - Tailoring therapy based on menopausal status and tumor characteristics highlights the importance of personalized medicine in breast cancer management.[96,97]
    - The sequential therapy regimen showcases the evolving strategies aiming for maximal benefit while minimizing risks in different patient subsets.

7. **Long-Term Benefits and Side Effects:**
    - Understanding the long-term benefits and potential side effects of different ET approaches aids in making informed decisions regarding treatment duration and regimen switches.
    - Managing the balance between efficacy and tolerability of these therapies remains crucial for improving outcomes and quality of life in breast cancer patients.[98,99]

The delineation of hormonal influences, treatment efficacy, and the evolving approaches in adjuvant endocrine therapy emphasizes the need for personalized, risk-adapted strategies in breast cancer management across different menopausal statuses.



Metabolic Pathways Differentially Targeted By Aromatase Inhibitors (AIs)

The complexities and implications of Ovarian Function Suppressors (OFS) and Extended Endocrine Therapy (EET) in breast cancer treatment.

Ovarian Function Suppressors (OFS):

1. **Mechanism and Impact of OFS:** OFS strategies, like Luteinizing Hormone-Releasing Hormone (LHRH) analogs, function by interfering with gonadotropic hormones—follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—resulting in a reduction of estrogen production in premenopausal women. This suppression of ovarian function, despite initially causing an increase in estradiol levels, eventually leads to diminished estrogen production, crucial in hormone-sensitive breast cancer growth.[100,101] Studies such as SOFT and TEXT exhibited promising results, revealing that combining OFS with adjuvant endocrine therapy significantly reduced mortality risk by 14% and showed substantial benefits in reducing recurrence rates in premenopausal breast cancer patients.[102]
2. **Duration and Selective Benefit:** The duration of OFS use significantly influences its efficacy. Short-term adjunctive use (one to three years) demonstrated mortality reduction, while longer-term implementation exhibited improved disease-free survival. However, the lack of extensive randomized data regarding the efficacy of OFS beyond five years poses challenges in determining its long-term benefits, especially in patients who did not receive chemotherapy.[103,104]

3. **Predictive Factors and Comparative Efficacy:** The predictive value of OFS in conjunction with endocrine therapy is highlighted by the presence of lymph node (LN) involvement. Tumors with LN involvement tend to exhibit better responses to ET combined with OFS, positively impacting overall and disease-free survival. Comparative analyses between Tamoxifen and Aromatase Inhibitors (AIs) alongside OFS showcased conflicting data concerning overall survival. However, AIs displayed lower recurrence rates over five to ten years in these studies, indicating their potential superiority in preventing relapse.[105,106]

4. **Side Effects and Risk Assessment:** Initiating OFS often leads to the onset of vasomotor symptoms (such as hot flashes) and vaginal dryness, while posing a potential risk of osteoporosis. Balancing the treatment benefits with these side effects is crucial, necessitating a personalized approach to treatment selection based on individual patient profiles and preferences. The assessment of benefits versus risks becomes pivotal in determining the most suitable therapeutic option.[107,108]

Extended Endocrine Therapy (EET):

1. **Goals and Duration of EET:** Extended Endocrine Therapy (EET), aimed at reducing the risk of recurrence, is considered for patients with high long-term risks but not exceeding a total duration of ten years. Studies, such as the ATLAS trial, highlight the potential benefits of continuing Tamoxifen for ten years, leading to improvements in overall and disease-free survival. However, this prolonged duration elevates the risk of endometrial cancer. Extending AI therapy beyond five years exhibits improved disease-free survival, especially in high-risk postmenopausal women.[109–111]

2. **Benefits and Risks of EET:** While the extension of AI therapy beyond five years lacks evidence for overall survival benefits, it is associated with an increased incidence of musculoskeletal pain, cardiovascular events, fractures, and osteoporosis. Notably, tumors expressing both estrogen receptor (ER) and progesterone receptor (PR) (double-positive biomarkers) demonstrate enhanced responses to EET compared to those expressing a single positive biomarker (ER+ or PR+), suggesting a potential role in predicting treatment efficacy.[112,113]

3. **Patient Selection and Optimal Duration:** Personalized patient selection for EET is essential, considering its impact on quality of life due to potential side effects. Identifying patients who may benefit most from extended therapy, especially as the maximum benefits are observed in the second decade post-treatment, becomes crucial. Postmenopausal patients, regardless of prior ET, might derive benefits from extended AI therapy for five years. However, determining the precise optimal duration remains a subject of ongoing research.[114,115]

4. **Precision in Treatment Duration:** Tailoring EET duration to two to three years could effectively prevent contralateral and recurrent breast cancer events. This highlights the need for precise and individualized treatment strategies based on patient-specific characteristics and response profiles to maximize therapeutic outcomes while minimizing potential adverse effects.

These comprehensive analyses underscore the evolving landscape of breast cancer treatment strategies, emphasizing the need for personalized approaches to optimize outcomes, minimize risks, and improve the quality of life for patients undergoing adjuvant endocrine therapies.[116]

The nuances and significance of adjuvant CDK4/6 inhibitors combined with endocrine therapy in breast cancer treatment:

1. Trials and Insights:

The advent of CDK4/6 inhibitors brought about a shift in the treatment paradigm for advanced breast cancer. In the quest to extend their efficacy to earlier stages, trials like Pallas and Penelope-B investigated the role of Palbociclib in the adjuvant and neoadjuvant settings, respectively. The expectation was that combining these inhibitors with endocrine therapy would offer improved outcomes for early breast cancer patients. However, these trials didn't meet their predetermined endpoints, raising questions about the efficacy of Palbociclib in the earlier stages of breast cancer treatment.[117,118]

Conversely, the MonarchE trial focused on Abemaciclib in postoperative settings for high-risk patients. The trial showed promising results by significantly reducing the risk of cancer recurrence when Abemaciclib was added to endocrine therapy. This outcome, especially in high-risk patients with adverse pathological lymph node presentations, provided a new perspective on the potential benefits of CDK4/6 inhibitors in early breast cancer treatment.[119]

2. Clinical Implications:

The success of the MonarchE trial prompted updates in the ASCO guidelines, recommending the use of Abemaciclib alongside endocrine therapy for high-risk breast cancer patients. This recommendation didn't differentiate based on menopausal status, using either Tamoxifen or AIs with or without ovarian function suppression. It signifies a potential shift in the treatment approach for high-risk breast cancer patients by adding CDK4/6 inhibitors to the adjuvant therapy arsenal.

3. Discrepancies and Reasons:

The divergence in outcomes between trials examining Palbociclib and Abemaciclib might be attributed to several factors. Premature discontinuation of Palbociclib treatment and heterogeneous patient populations, especially in the Pallas study, could have influenced the varying results. The Pallas trial included a broader staging range, potentially impacting the consistency of outcomes observed across the patient cohort.[120,121]

Interestingly, detailed analyses within these trials failed to demonstrate clear benefits for high-risk patients or between those who completed versus discontinued the two-year treatment regimen, adding complexity to the interpretation of these results.

4. Challenges in Outcome Assessment:

The unique behavior of ER+ tumors, following a relatively slow progression pattern, demands extended observation periods to capture robust survival data accurately. As a result, the data on overall survival (OS) from adjuvant CDK4/6 studies remain immature, highlighting the need for longer-term follow-ups to gauge the real impact of these therapies.[122,123]

Moreover, the anticipation surrounding ongoing trials like the Natalee trial, which examines the effects of Ribociclib in early breast cancer, holds promise in providing more clarity regarding the varying outcomes observed in previous studies involving different CDK4/6 inhibitors.

5. Future Directions and Expectations:

As these trials continue and more data become available, it's imperative to understand the implications for clinical practice. Mature results from ongoing trials, particularly those exploring different CDK4/6 inhibitors, will offer invaluable insights. This knowledge can refine treatment strategies, delineate patient subgroups benefiting most from specific CDK4/6 inhibitors alongside endocrine therapy, and guide future treatment directions.[123,124]

6. Clinical Decision-Making and Patient Stratification:

The evolving landscape of adjuvant CDK4/6 inhibitors underscores the need for individualized treatment approaches based on patient risk profiles and response patterns. Identifying subgroups that derive maximum benefits while minimizing adverse effects becomes pivotal in optimizing patient outcomes. Clinicians must weigh the risks and benefits of these therapies to tailor treatment plans that align with each patient's unique characteristics and disease trajectory.[125,126]

7. Long-term Impact Assessment:

Comprehensive long-term assessments are essential to fully understand the impact of adjuvant CDK4/6 inhibitors. Long-term studies are vital to observe patterns of recurrence, survival rates, late side effects, and the overall durability of treatment benefits. These insights will be instrumental in evaluating the lasting impact of these therapies on patient outcomes and guiding future treatment approaches.[127]

In summary, while adjuvant CDK4/6 inhibitors coupled with endocrine therapy present a promising avenue in treating high-risk breast cancer patients, the nuances in trial outcomes and the need for comprehensive long-term data underscore the ongoing complexity in optimizing these novel treatment approaches.[128]

DISCUSSION

1. **Breast Cancer Complexity and Global Impact:**

Breast cancer is an intricately complex disease encompassing various subtypes defined by distinct receptor expressions such as ERα, PR, and HER2. This heterogeneity necessitates tailored treatment approaches. ER+ breast cancer, constituting about 70% of cases, has been a focal point in targeted therapies. The understanding of receptor expressions, vital for directing treatments, underscores the importance of therapies like SERMs and AIs that aim to disrupt estrogen signaling pathways. Despite advancements, the disease remains a significant global public health concern, with the World Health Organization's estimations indicating over 2.1 million new cases annually and about 627,000 deaths. This devastating impact extends beyond physical health, profoundly affecting patients' psychosocial well-being and incurring substantial emotional and financial burdens on individuals and families.

Efforts to address this global health challenge emphasize the criticality of comprehensive strategies, encompassing prevention, awareness campaigns, early detection through screening programs, and ensuring accessibility to effective treatments. Collaborative endeavors among healthcare providers, policymakers, researchers, and communities are pivotal in implementing these strategies. The urgency to mitigate the burden of breast cancer emphasizes the need for enhanced research into prevention strategies, the discovery of novel therapeutic targets, and the development of cost-effective interventions to achieve long-term disease control.

2. **Endocrine Therapies and Preventive Strategies:**

Endocrine therapies, including SERMs and AIs, have emerged as promising preventive measures for individuals at high risk. These therapies target hormonal pathways vital in the development of hormone receptor-positive breast cancers. SERMs like tamoxifen and raloxifene interfere with estrogen binding to receptors, inhibiting cancer cell growth. AIs, predominantly used in postmenopausal women, reduce estrogen production by targeting the aromatase enzyme, crucial for estrogen synthesis. While these therapies show significant potential in reducing breast cancer risk, the delicate balance between their efficacy and potential side effects poses challenges. Discussions between healthcare providers and patients regarding individual risk factors, potential benefits, and side effects play a pivotal role in informed decision-making about the initiation and duration of these preventive treatments.

Moreover, ongoing research aimed at refining existing therapies and identifying new preventive strategies is critical to reducing the global burden of breast cancer. The need for continued exploration of effective prevention measures, along with the understanding of genetic and environmental risk factors, remains paramount. These efforts are fundamental in advancing both preventive measures and treatment strategies, underlining the significance of ongoing research in this field.

3. **Receptor Status and Therapeutic Significance:**

Estrogen and progesterone receptors serve as pivotal indicators in predicting treatment response and prognosis for breast cancer patients, particularly in hormone receptor-positive tumors. The presence of ER and PR often indicates a higher likelihood of response to endocrine therapy and improved disease-free survival. ER-positive breast cancers, constituting a substantial percentage of cases, are more amenable to hormonal treatments compared to ER-negative tumors. The identification and characterization of these receptors play a crucial role in designing individualized treatment strategies for patients, enabling more targeted and effective interventions. Additionally, PR status further refines prognostic information and aids in treatment decision-making, contributing to more precise therapeutic approaches for different breast cancer subtypes.

Beyond their prognostic significance, the therapeutic implications of ER and PR status are integral in guiding treatment choices. The targeted approach to these receptors with hormonal therapies has been a cornerstone in managing hormone receptor-positive breast cancers. Consequently, diagnostic tests assessing ER and PR

expression are fundamental in guiding treatment choices, optimizing patient outcomes, and reducing the risk of recurrence. The evolving understanding of these receptors continues to shape treatment paradigms, emphasizing their role in personalized therapeutic strategies for breast cancer patients.

4. **Role of Estrogen in Breast Cancer Development:**

Estrogen's role in breast cancer development is paramount, influencing various cellular processes within breast epithelial cells through its binding to estrogen receptors (ERs). Strategies aiming to disrupt estrogen-dependent pathways have become focal points in developing therapies for estrogen-dependent breast cancers. Selective ER modulators (SERMs) like tamoxifen and raloxifene, or agents like fulvestrant targeting ER expression, aim to impede estrogen's cancer-promoting effects. Additionally, aromatase inhibitors (AIs) have emerged as a primary approach in postmenopausal women by inhibiting estrogen production. These multifaceted strategies highlight diverse avenues for therapeutic intervention and breast cancer prevention by interrupting estrogen-dependent processes.

Understanding estrogen's role in breast cancer development underscores the significance of targeted therapies aimed at disrupting estrogen signaling pathways. Novel approaches that continue to emerge from ongoing research hold promise for refining interventions and enhancing treatment efficacy while minimizing adverse effects. The pursuit of these advancements opens avenues for more personalized and effective breast cancer treatments.

5. **Aromatase Inhibitors (AIs) in Postmenopausal Women:**

Aromatase, primarily expressed in adipose tissue in postmenopausal women, plays a crucial role in estrogen production. AIs, by inhibiting aromatase activity, effectively reduce estrogen levels and are pivotal in managing estrogen-dependent breast cancers in this demographic. The shift in the regulation of aromatase expression underscores the effectiveness of AIs in this population. However, their widespread use isn't without challenges, as profound estrogen depletion can lead to adverse effects, necessitating careful management by healthcare professionals. Despite challenges, AIs have become a cornerstone in improving outcomes for postmenopausal women with estrogen-sensitive breast cancer, highlighting their significance in treatment strategies.

Ongoing clinical trials exploring AIs' potential in breast cancer prevention underscore their promise as preventive strategies in high-risk populations. These efforts highlight the dynamic landscape of breast cancer research and the continuous quest for improved therapies and preventive measures. As primary care physicians often guide patients regarding AI initiation and management, their understanding of these agents and potential adverse effects is crucial in supporting patients through their treatment journey and optimizing treatment adherence.

6. **Male Breast Cancer:**

Despite its rarity, male breast cancer shares similarities with female breast cancer, especially in ER positivity. However, evidence suggests differences in the efficacy of AIs between males and postmenopausal females, emphasizing the need for tailored approaches in managing breast cancer in men. The rarity of male breast cancer poses challenges in research and treatment optimization, underlining the importance of better understanding its distinct biology for devising tailored therapeutic strategies. Despite its infrequency, male breast cancer remains significant due to its impact on overall survival rates and the necessity for specialized care and treatment approaches.

Comparable overall survival rates between male and female breast cancer patients, despite efficacy differences in specific therapies, highlight the importance of considering gender-specific factors in treatment planning. Recognizing the unique challenges and responses to treatment that males with breast cancer may experience emphasizes the need for dedicated research and tailored approaches to improve outcomes for this demographic.

CONCLUSION

The multifaceted nature of breast cancer, encompassing its biological mechanisms, psychosocial impacts on survivors, global trends in incidence, and the necessity for comprehensive research, underscores the complexity of managing this disease. Targeted therapies focused on receptor status, preventive strategies, and tailored treatments based on menopausal status highlight the strides made in breast cancer management. Ongoing research, including genomic profiling and biomarker identification, holds promise for more precise interventions in the future. The global impact of breast cancer necessitates collaborative efforts aimed at prevention, early detection, and accessible treatments. Understanding the role of estrogen, the significance of receptor status, and emerging therapeutic approaches form the foundation of personalized treatments. Moreover, addressing the unique challenges faced by different demographics, such as males and young breast cancer survivors, requires specialized care tailored to their distinct needs. As advancements in precision medicine continue to shape the landscape of breast cancer treatment, ongoing research, multidisciplinary approaches, and personalized strategies are key to further improving outcomes and quality of life for breast cancer patients worldwide.

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MAXIMIZING PATIENT OUTCOMES: ASSESSING THE IMPLEMENTATION AND IMPACT OF MEDICATION THERAPY MANAGEMENT (MTM) SERVICES

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Abstract: Background: Medication Therapy Management (MTM) has emerged as a critical component of patient-centered care, aiming to optimize medication regimens, enhance therapeutic outcomes, and improve overall health outcomes. This review explores two innovative models of MTM delivery: clinic-embedded pharmacist programs and telephonic MTM services. These models represent novel strategies to overcome barriers to patient access, intervention success rates, and administrative efficiency, ultimately enhancing patient care and improving health outcomes. Methods: A comprehensive review of literature was conducted to examine the key features, outcomes, and implications of clinic-embedded pharmacist programs and telephonic MTM services. Empirical evidence, case studies, and program evaluations were synthesized to evaluate the effectiveness of these models in improving medication adherence, optimizing therapy outcomes, and reducing healthcare utilization. Factors influencing the adoption and integration of these models into clinical practice were also explored. Results: Clinic-embedded pharmacist programs involve the integration of pharmacists into primary care settings, facilitating close collaboration with healthcare providers and direct patient care delivery. These programs have demonstrated success in identifying and addressing medication-related issues, improving medication adherence, and enhancing patient education and self-management skills. Telephonic MTM services utilize technology to deliver MTM interventions remotely, offering flexibility and convenience for patients. These services have been effective in reaching and engaging patients, conducting comprehensive medication reviews, and delivering targeted interventions to address medication-related issues. Discussion: Innovative MTM delivery models, such as clinic-embedded pharmacist programs and telephonic MTM services, demonstrate promising outcomes in terms of patient engagement, medication optimization, and healthcare utilization. By leveraging technology and interdisciplinary collaboration, these programs overcome traditional barriers to MTM delivery and enhance the efficiency and effectiveness of patient care. Moving forward, healthcare organizations and policymakers should continue to invest in these innovative models to improve the quality, accessibility, and affordability of medication management services. Conclusion: Clinic-embedded pharmacist programs and telephonic MTM services represent innovative approaches to delivering comprehensive medication management services. These models have shown promise in improving medication adherence, optimizing therapy outcomes, and reducing healthcare utilization. By promoting pharmacist-led interventions and leveraging technology-enabled platforms, healthcare providers can enhance the quality and accessibility of medication management services, ultimately improving patient outcomes and advancing healthcare delivery.

Keywords: Medication Therapy Management, Pharmacist-led interventions, Clinic-embedded programs, Telephonic MTM services, Patient-centered care, Healthcare innovation, Interdisciplinary collaboration.

INTRODUCTION

In the rapidly evolving landscape of healthcare, the optimization of medication therapy has become increasingly vital to ensuring positive patient outcomes and reducing healthcare costs. Medication Therapy Management (MTM) has emerged as a comprehensive approach to addressing the complex medication needs of patients, aiming to enhance medication adherence, prevent adverse drug events, and improve overall health outcomes. As healthcare systems continue to face challenges related to medication non-adherence, polypharmacy, and medication-related adverse events, there is a growing recognition of the need for innovative approaches to MTM delivery.[1]

This review seeks to explore and evaluate two innovative models of MTM delivery: clinic-embedded pharmacist programs and telephonic MTM services. These models represent novel strategies to overcome barriers to patient access, intervention success rates, and administrative efficiency, ultimately enhancing patient care and improving health outcomes. By examining the key features, outcomes, and implications of these models, this review aims to provide insights into their potential to transform medication management practices and improve patient outcomes.[2]

Clinic-Embedded Pharmacist Programs:

Clinic-embedded pharmacist programs involve the integration of pharmacists into primary care settings, allowing for close collaboration with healthcare providers and direct patient care delivery. Pharmacists in these programs work collaboratively with primary care teams to identify patients in need of MTM services, conduct comprehensive medication reviews, and implement interventions to address medication-related issues. By embedding pharmacists within clinical practices, these programs facilitate timely medication management, enhance communication between providers and patients, and promote interdisciplinary collaboration.[3]

One notable example of a clinic-embedded pharmacist program is CoxHealth Center Steeplechase, where pharmacists provide chronic disease state management under collaborative practice agreements. Through structured MTM interventions, pharmacists identify and address medication-related issues, improve medication adherence, and enhance patient education and self-management skills. The program's success is evidenced by its ability to identify patients not otherwise referred to the clinical pharmacy team and achieve high success rates in targeted interventions.[4]

Telephonic MTM Services:

Telephonic MTM services utilize technology to deliver MTM interventions remotely, overcoming barriers related to patient access and engagement. Through phone-based consultations, pharmacists conduct medication reviews, provide counseling on medication adherence and lifestyle modifications, and collaborate with patients to develop personalized medication action plans. Telephonic MTM services offer flexibility and convenience for patients, particularly those with limited mobility or access to healthcare facilities.[5]

Scott & White Health Plan's pharmacist-provided telephone MTM service exemplifies the effectiveness of telephonic MTM in reaching and engaging patients. By leveraging custom-built databases and proactive outreach strategies, the program successfully identifies eligible beneficiaries, conducts comprehensive medication reviews, and delivers targeted interventions to address medication-related issues. The program's emphasis on patient education, medication reconciliation, and collaboration with healthcare providers contributes to improved medication adherence and clinical outcomes among enrolled patients.[6]

Key Outcomes and Implications:

Innovative MTM delivery models, such as clinic-embedded pharmacist programs and telephonic MTM services, demonstrate promising outcomes in terms of patient engagement, medication optimization, and healthcare utilization. These models enhance patient access to comprehensive medication management services, improve medication adherence, and facilitate proactive interventions to address medication-related issues. By leveraging technology and interdisciplinary collaboration, these programs overcome traditional barriers to MTM delivery and enhance the efficiency and effectiveness of patient care.[7]

Moving forward, healthcare organizations and policymakers should continue to invest in innovative MTM delivery models and expand their integration into existing care delivery systems. By promoting pharmacist-led interventions and leveraging technology-enabled platforms, healthcare providers can enhance the quality, accessibility, and affordability of medication management services. Additionally, research efforts should focus on evaluating the long-term impact and cost-effectiveness of these innovative MTM delivery models to inform future healthcare policies and practices.[8]

Medication Therapy Management (MTM) services have emerged as a critical element in contemporary healthcare delivery, driven by the imperative to optimize medication regimens, enhance patient safety, and improve therapeutic outcomes. MTM encompasses a range of pharmacist-provided services designed to address medication-related issues, promote adherence, and ensure the safe and effective use of medications. This review aims to explore the implementation strategies and outcomes associated with MTM programs across diverse healthcare settings, highlighting their significance in enhancing patient-centered care.

The implementation of MTM programs varies across different healthcare settings, reflecting the unique needs, resources, and challenges of each environment. In community pharmacy settings, MTM services are often integrated into routine pharmacy practice, with pharmacists conducting comprehensive medication reviews, providing patient counseling, and collaborating with other healthcare providers to optimize therapy. Implementation strategies in community pharmacies may involve leveraging technology for medication reconciliation, utilizing medication therapy review tools, and engaging patients in shared decision-making processes.[9]

In ambulatory care settings, such as primary care clinics or outpatient facilities, MTM programs may be integrated into existing care models to enhance patient management for chronic diseases or complex medication regimens. Clinic-embedded pharmacists play a pivotal role in conducting medication assessments, identifying drug-related problems, and providing targeted interventions to improve medication adherence and therapeutic outcomes. Collaborative practice agreements between pharmacists and healthcare providers facilitate the seamless integration of MTM services into patient care workflows.[10]

Telephonic MTM services have also gained prominence, particularly for reaching underserved populations or patients with limited access to traditional healthcare services. Through telephone consultations, pharmacists assess medication regimens, address patient concerns, and provide education on medication use and adherence. Telephonic MTM programs leverage technology to overcome geographic barriers, improve access to care, and enhance patient engagement in self-management.

The outcomes associated with MTM programs encompass a wide range of clinical, economic, and patient-centered parameters. Clinical outcomes include improvements in medication adherence, reduction in adverse drug events, and optimization of therapy for chronic conditions such as diabetes, hypertension, and cardiovascular disease. MTM interventions have been shown to decrease hospital readmissions, emergency department visits, and healthcare costs, contributing to overall healthcare quality and value.

Economic evaluations of MTM programs demonstrate their cost-effectiveness and potential for generating substantial savings within healthcare systems. By preventing medication errors, reducing unnecessary healthcare utilization, and improving medication adherence, MTM services yield positive return on investment and help mitigate healthcare expenditures associated with medication-related complications.[11]

Moreover, patient-centered outcomes underscore the impact of MTM on enhancing patients' knowledge, self-efficacy, and satisfaction with medication management. Patient engagement in MTM services fosters a collaborative approach to care, empowering individuals to actively participate in decision-making regarding their health and medications. Through education, counseling, and medication action plans, MTM programs empower patients to take ownership of their health and adhere to prescribed treatment regimens.

In conclusion, Medication Therapy Management (MTM) services represent a pivotal component of patient-centered care, facilitating the optimization of medication regimens, mitigation of adverse effects, and promotion of therapeutic adherence across diverse healthcare settings. The implementation of MTM programs involves tailored strategies to address the unique needs of each environment, leveraging technology, interdisciplinary collaboration, and patient engagement. The outcomes associated with MTM programs

underscore their value in improving clinical outcomes, enhancing healthcare quality, and reducing healthcare costs. As healthcare continues to evolve, MTM will remain a cornerstone of comprehensive medication management, ensuring safe, effective, and patient-centered care for individuals worldwide.[12]

Implementation Strategies and Models

Implementation strategies and models for Medication Therapy Management (MTM) services encompass a spectrum of approaches tailored to meet the needs of diverse healthcare settings. This section of the review delves into the various strategies employed to deliver MTM services, including community pharmacy-based initiatives, clinic-embedded pharmacist programs, and telephonic MTM services. Additionally, it explores the factors influencing the adoption and integration of MTM into clinical practice, such as reimbursement mechanisms, regulatory requirements, and interdisciplinary collaboration.

Community Pharmacy-Based Initiatives:

Community pharmacies serve as accessible points of care for patients, making them an ideal setting for the delivery of MTM services. Pharmacies have increasingly adopted MTM programs to optimize medication regimens, improve adherence, and enhance patient outcomes. Implementation strategies in community pharmacy settings often involve leveraging technology, such as electronic health records (EHRs) and medication therapy management software, to streamline workflow and documentation processes. Pharmacists conduct comprehensive medication reviews, identify drug-related problems, and collaborate with prescribers to implement interventions aimed at optimizing therapy. Patient counseling and education are integral components of community pharmacy-based MTM programs, empowering patients to actively participate in their medication management.[13]

Clinic-Embedded Pharmacist Programs:

Clinic-embedded pharmacist programs integrate pharmacists into primary care clinics, specialty clinics, or outpatient facilities to provide comprehensive medication management services. These programs facilitate close collaboration between pharmacists and other healthcare providers, allowing for interdisciplinary teamwork in patient care. Implementation strategies may involve establishing collaborative practice agreements, developing standardized protocols for medication management, and incorporating pharmacists into care team meetings and rounds. Clinic-embedded pharmacists conduct medication assessments, medication reconciliations, and medication therapy reviews to identify and resolve drug-related issues. They also provide patient education, adherence counseling, and medication monitoring to support patients in achieving therapeutic goals.[14]

Telephonic MTM Services:

Telephonic MTM services leverage technology to deliver medication management interventions remotely, making them accessible to patients regardless of geographic location. Pharmacists conduct medication reviews, assess medication adherence, and provide counseling and education to patients over the phone. Telephonic MTM programs employ strategies to engage patients and enhance communication, such as scheduling regular follow-up calls, sending medication reminders, and providing personalized medication action plans. Implementation may involve establishing dedicated phone lines, developing call scripts and protocols, and integrating telephonic MTM services with existing healthcare systems or telehealth platforms.

Factors Influencing Adoption and Integration:

Several factors influence the adoption and integration of MTM services into clinical practice. Reimbursement mechanisms play a critical role in incentivizing pharmacists and healthcare organizations to provide MTM services. Regulatory requirements, such as accreditation standards and state pharmacy practice acts, govern the scope of MTM practice and guide implementation efforts. Interdisciplinary collaboration is essential for effective MTM delivery, requiring communication and coordination among pharmacists, physicians, nurses, and other healthcare professionals. Additionally, patient engagement and buy-in are crucial for the success of MTM programs, necessitating efforts to educate and involve patients in their medication management.[15]

In conclusion, implementation strategies and models for MTM services encompass a range of approaches tailored to meet the needs of diverse healthcare settings. Community pharmacy-based initiatives, clinic-embedded pharmacist programs, and telephonic MTM services each offer unique advantages in delivering comprehensive medication management. Factors influencing adoption and integration include reimbursement mechanisms, regulatory requirements, and interdisciplinary collaboration. By leveraging these strategies and addressing barriers to implementation, healthcare organizations can effectively integrate MTM services into clinical practice, ultimately improving patient outcomes and enhancing medication safety and adherence.

Impact on Patient Outcomes

The impact of Medication Therapy Management (MTM) services on patient outcomes is a critical aspect of evaluating the effectiveness and value of these programs. Through a synthesis of empirical evidence and case studies, this section of the review assesses the multifaceted impact of MTM services on patient outcomes, including medication adherence, disease management, and healthcare utilization.[16]

Medication Adherence:

One of the primary objectives of MTM services is to improve medication adherence among patients. Adherence to prescribed medication regimens is crucial for achieving therapeutic outcomes and preventing disease progression. MTM interventions, such as medication reviews, patient education, and adherence counseling, have been shown to positively impact adherence rates. By addressing barriers to adherence, such as medication complexity, side effects, and forgetfulness, MTM services help patients adhere to their prescribed treatments, leading to better health outcomes and reduced healthcare costs.[17]

Disease Management:

In addition to improving medication adherence, MTM services play a significant role in managing chronic diseases and optimizing treatment outcomes. Pharmacists, as integral members of the healthcare team, collaborate with patients and other providers to monitor disease progression, adjust medication regimens, and address therapeutic goals. Through comprehensive medication reviews and medication therapy management, pharmacists identify and resolve drug-related problems, such as drug interactions, inappropriate dosing, and medication discrepancies, thereby optimizing disease management and improving clinical outcomes.

Healthcare Utilization:

Another important aspect of assessing the impact of MTM services is their effect on healthcare utilization, including hospital readmissions, emergency department visits, and healthcare costs. Studies have consistently demonstrated that MTM interventions reduce hospital readmissions and emergency department visits among patients with chronic diseases. By optimizing medication regimens, preventing adverse drug events, and promoting patient self-management, MTM services help reduce the need for acute care services and lower overall healthcare utilization. This not only improves patient outcomes but also leads to cost savings for healthcare systems and payers.[18]

Quality of Life:

Beyond clinical outcomes and healthcare utilization, MTM services have a profound impact on patients' quality of life. By empowering patients to actively participate in their medication management, providing education and support, and addressing their individual needs and preferences, MTM services enhance patients' overall well-being and satisfaction with their healthcare experience. Patients who receive MTM services report improved medication understanding, better symptom control, and increased confidence in managing their health, leading to a higher quality of life and greater patient satisfaction.

Diverse Patient Populations:

Importantly, the impact of MTM services extends across diverse patient populations, including those with complex medical conditions, polypharmacy, and socioeconomic disparities. MTM programs are tailored to meet the unique needs of each patient, taking into account their health status, cultural background, and social determinants of health. By providing personalized care and addressing patients' individualized needs, MTM

services ensure equitable access to high-quality healthcare and promote health equity among diverse populations.[19]

In conclusion, Medication Therapy Management (MTM) services have a profound impact on patient outcomes across multiple dimensions, including medication adherence, disease management, healthcare utilization, and quality of life. Through comprehensive medication reviews, patient education, and interdisciplinary collaboration, MTM services improve therapeutic outcomes, reduce healthcare costs, and enhance patients' overall well-being. By addressing the individualized needs of diverse patient populations, MTM programs contribute to equitable access to high-quality healthcare and promote health equity.

Cost-effectiveness and Healthcare Quality

An analysis of cost-effectiveness studies and economic evaluations provides valuable insights into the financial implications of implementing Medication Therapy Management (MTM) services for healthcare systems, payers, and patients. This section of the review explores the potential for MTM services to generate cost savings through medication optimization, prevention of adverse events, and reduction of healthcare resource utilization.

Cost-Effectiveness Studies:

Cost-effectiveness studies evaluate the economic value of MTM services by comparing the costs associated with implementing these programs to the benefits accrued in terms of improved patient outcomes and healthcare savings. These studies typically employ economic modeling techniques to estimate the long-term cost-effectiveness of MTM interventions. Results from cost-effectiveness analyses have consistently demonstrated the favorable economic impact of MTM services, highlighting their potential to generate substantial cost savings for healthcare systems and payers.

Medication Optimization:

One of the primary mechanisms through which MTM services generate cost savings is by optimizing medication regimens to improve therapeutic outcomes and reduce healthcare utilization. Pharmacists conduct comprehensive medication reviews, identify drug-related problems, and implement interventions aimed at optimizing therapy, such as dose adjustments, medication substitutions, and discontinuation of unnecessary medications. By optimizing medication regimens, MTM services help prevent adverse drug events, medication-related hospitalizations, and unnecessary healthcare expenditures.[20]

Prevention of Adverse Events:

MTM services play a crucial role in preventing adverse drug events (ADEs) and medication-related complications, which can result in significant healthcare costs and patient harm. Pharmacists identify potential drug interactions, medication errors, and contraindications through medication reconciliation and medication therapy review processes. By addressing these issues proactively, MTM services help mitigate the risk of ADEs and reduce the need for emergency department visits, hospitalizations, and costly medical interventions.

Reduction of Healthcare Resource Utilization:

Another key aspect of the economic impact of MTM services is their ability to reduce healthcare resource utilization, including hospital admissions, emergency department visits, and outpatient procedures. By optimizing medication regimens, promoting medication adherence, and facilitating self-management, MTM services help prevent exacerbations of chronic conditions and reduce the need for acute care services. Studies have shown that patients who receive MTM interventions experience fewer hospital readmissions, shorter lengths of stay, and lower overall healthcare costs compared to those who do not receive MTM services.[21]

Overall, the findings from cost-effectiveness studies and economic evaluations consistently support the favorable economic impact of MTM services on healthcare systems, payers, and patients. By optimizing medication therapy, preventing adverse events, and reducing healthcare resource utilization, MTM services generate cost savings and improve healthcare quality. As healthcare continues to evolve, MTM programs will play an increasingly important role in promoting value-based care, enhancing patient outcomes, and maximizing the efficiency of healthcare delivery.[22]

Barriers and Challenges

MTM implementation, despite its potential benefits, encounters several barriers and challenges that hinder its widespread adoption and effectiveness. This section of the review identifies these barriers and challenges and proposes strategies to overcome them, thereby optimizing the delivery of MTM services.

Limited Reimbursement:

One of the primary barriers to MTM implementation is the lack of adequate reimbursement for pharmacist-provided services. Traditional fee-for-service models may not adequately compensate pharmacists for the time and resources required to deliver comprehensive MTM interventions. Additionally, reimbursement policies and coding requirements may vary across payers, leading to inconsistency in payment for MTM services. To address this barrier, advocacy efforts are needed to advocate for fair reimbursement policies that recognize the value of pharmacist-provided MTM services. This may involve engaging policymakers, payers, and stakeholders to promote policy reforms and reimbursement mechanisms that align with the value and impact of MTM on patient outcomes and healthcare costs.[23]

Workforce Shortages:

Another significant challenge facing MTM implementation is workforce shortages, particularly in underserved communities and rural areas. A shortage of qualified pharmacists and other healthcare professionals trained in medication management limits the capacity to deliver MTM services to all patients in need. To overcome this barrier, strategies such as expanding the scope of practice for pharmacists, leveraging pharmacy technicians and other support staff, and implementing collaborative practice models can help maximize the reach and efficiency of MTM services. Additionally, initiatives to recruit and retain pharmacists in underserved areas, such as loan repayment programs and incentives, can help address workforce shortages and improve access to MTM services.

Interoperability Issues:

Interoperability issues, including limited integration and communication between healthcare systems and electronic health records (EHRs), pose a significant barrier to the seamless delivery of MTM services. Pharmacists often encounter challenges accessing patient health information, medication histories, and laboratory results, which can hinder their ability to conduct comprehensive medication reviews and make informed clinical decisions. To address this barrier, efforts to improve interoperability and data exchange between EHR systems and pharmacy platforms are essential. Collaboration between healthcare stakeholders, including pharmacists, physicians, and technology vendors, is needed to develop standardized data exchange protocols and interoperability standards that facilitate the seamless integration of MTM services into existing healthcare workflows.[24]

In conclusion, MTM implementation faces several barriers and challenges, including limited reimbursement, workforce shortages, and interoperability issues. However, by implementing strategies such as advocating for policy reforms, expanding provider collaboration, and addressing interoperability issues, healthcare organizations can overcome these barriers and optimize the delivery of MTM services. By leveraging technology, expanding provider collaboration, and advocating for policy reforms, healthcare organizations can overcome these barriers and optimize the delivery of MTM services, ultimately improving patient outcomes and enhancing the quality and efficiency of healthcare delivery.[25]

Future Directions and Recommendations

As the landscape of healthcare continues to evolve, Medication Therapy Management (MTM) services are poised to play an increasingly pivotal role in optimizing patient outcomes and advancing healthcare quality. This section of the review discusses emerging trends and future directions in MTM practice and offers recommendations for healthcare stakeholders to enhance the effectiveness, accessibility, and sustainability of MTM services.

Personalized Medicine Approaches:

One of the emerging trends in MTM practice is the adoption of personalized medicine approaches, which involve tailoring medication regimens and interventions to individual patient characteristics, including genetic makeup, lifestyle factors, and preferences. Personalized medicine enables healthcare providers, including pharmacists, to deliver more targeted and precise interventions, leading to improved therapeutic outcomes and patient satisfaction. In the future, integrating pharmacogenomic testing, predictive analytics, and patient-specific data into MTM workflows will enable pharmacists to customize medication management strategies and optimize treatment plans for each patient.[26]

Digital Health Solutions:

The widespread adoption of digital health solutions, including telehealth platforms, mobile applications, and remote monitoring devices, presents new opportunities to enhance the delivery and accessibility of MTM services. Digital health tools enable pharmacists to engage with patients remotely, conduct virtual medication reviews, and provide real-time support and education. By leveraging technology, healthcare organizations can overcome barriers such as geographic limitations, transportation challenges, and workforce shortages, thereby expanding access to MTM services and reaching underserved populations. Additionally, incorporating data analytics and artificial intelligence algorithms into MTM platforms can facilitate proactive medication management, early identification of medication-related issues, and personalized interventions.

Value-Based Reimbursement Models:

The shift towards value-based reimbursement models represents a significant opportunity to incentivize the delivery of high-quality, patient-centered MTM services. Value-based payment models, such as bundled payments, shared savings arrangements, and pay-for-performance incentives, reward healthcare providers for achieving positive patient outcomes and reducing healthcare costs. By aligning reimbursement with the value and impact of MTM on patient outcomes and healthcare utilization, payers can encourage the adoption of MTM services and promote their integration into care delivery models. Healthcare organizations should collaborate with payers to develop innovative payment models that incentivize the provision of MTM services and ensure sustainable funding for pharmacist-led medication management initiatives.[27]

Recommendations for Healthcare Stakeholders:

To enhance the effectiveness, accessibility, and sustainability of MTM services, healthcare stakeholders should consider the following recommendations:

1. Invest in pharmacist training and education to equip pharmacists with the necessary skills and competencies to deliver comprehensive MTM services effectively.
2. Foster interdisciplinary collaboration and care coordination among pharmacists, physicians, nurses, and other healthcare providers to ensure seamless integration of MTM into patient care workflows.
3. Promote patient engagement and empowerment through education, shared decision-making, and health coaching to enhance medication adherence and self-management skills.
4. Advocate for policy reforms and regulatory changes that support the expansion of MTM services, including fair reimbursement policies, scope of practice reforms, and licensure requirements.
5. Embrace innovation and technology adoption to leverage digital health solutions, telehealth platforms, and data analytics tools to enhance the delivery and impact of MTM services.
6. Conduct research and evaluation to assess the effectiveness, cost-effectiveness, and patient outcomes associated with MTM interventions and inform evidence-based practice guidelines and quality standards.

In conclusion, the future of MTM practice is marked by personalized medicine approaches, digital health solutions, and value-based reimbursement models. By embracing these trends and recommendations, healthcare stakeholders can optimize the delivery of MTM services, improve patient outcomes, and advance healthcare quality in the evolving landscape of healthcare delivery.[28]

MTM Practice Models and Compensation

Facilitating Integration and Optimization

Medication Therapy Management (MTM) has emerged as a critical component of patient-centered care, aiming to optimize medication regimens, improve therapeutic outcomes, and reduce healthcare costs. However, the successful integration of MTM into existing healthcare systems requires the development of effective practice models and compensation frameworks. This section of the review examines various MTM practice models and compensation mechanisms utilized by public and private sector programs and provides recommendations for optimizing MTM implementation and reimbursement strategies.[29]

Standardized Service Packages:

One of the foundational elements of successful MTM practice models is the development of standardized service packages that outline the scope and components of MTM interventions. These service packages delineate the specific services offered, such as comprehensive medication reviews, medication reconciliation, patient education, and care coordination. By standardizing service offerings, pharmacists can ensure consistency in the delivery of MTM services and facilitate interoperability across different healthcare settings and providers. Standardized service packages also enable pharmacists to communicate the value of MTM to patients, providers, and payers, thereby promoting awareness and uptake of these services.

Compensation Models:

Compensation mechanisms play a crucial role in incentivizing pharmacists to deliver MTM services and ensuring the sustainability of MTM programs. Various compensation models have been employed by public and private sector programs to reimburse pharmacists for the provision of MTM services, including fee-for-service, pay-for-performance, and bundled payment models. Fee-for-service models involve reimbursing pharmacists based on the number and complexity of MTM interventions conducted, while pay-for-performance models reward pharmacists for achieving predefined quality metrics and patient outcomes. Bundled payment models provide a single payment for a package of MTM services delivered over a specified time period. Each compensation model has its advantages and challenges, and the optimal approach may vary depending on factors such as patient population, practice setting, and regulatory requirements.[30]

Billing Mechanisms:

Effective billing mechanisms are essential for streamlining reimbursement processes and ensuring timely payment for MTM services. Pharmacists typically bill for MTM services using Current Procedural Terminology (CPT) codes or Healthcare Common Procedure Coding System (HCPCS) codes, which are recognized by payers for reimbursement purposes. Standardizing billing codes and procedures enables pharmacists to submit claims accurately and efficiently, reducing administrative burden and delays in reimbursement. Additionally, integrating MTM billing into existing electronic health record (EHR) systems and pharmacy management software can further streamline billing processes and facilitate documentation and reporting requirements.[31]

Recommendations for Optimization:

To optimize MTM implementation and reimbursement strategies, the following recommendations are proposed for pharmacists, health plans, and Medicare Part D sponsors:

Pharmacists:

1. Standardize MTM service packages and develop clear protocols and workflows for delivering MTM interventions.
2. Advocate for fair reimbursement policies and equitable compensation for pharmacist-provided MTM services.
3. Invest in training and education to enhance pharmacists' proficiency in delivering MTM services and documenting clinical interventions.

Health Plans:

1. Develop value-based payment models that align reimbursement with the quality and impact of MTM on patient outcomes and healthcare costs.
2. Collaborate with pharmacists and other stakeholders to establish performance metrics and quality standards for MTM services.
3. Implement strategies to promote patient engagement and participation in MTM programs, such as incentives and outreach initiatives.

Medicare Part D Sponsors:

1. Provide guidance and support to pharmacists and pharmacies participating in MTM programs, including training resources and technical assistance.
2. Evaluate the effectiveness and cost-effectiveness of MTM interventions through ongoing monitoring and evaluation.
3. Advocate for policy reforms and regulatory changes that support the expansion and sustainability of MTM services within Medicare Part D.

In conclusion, the successful integration of MTM into existing healthcare systems requires the development of effective practice models and compensation frameworks. By standardizing service packages, implementing appropriate compensation models, and streamlining billing mechanisms, pharmacists, health plans, and Medicare Part D sponsors can optimize MTM implementation and reimbursement strategies, ultimately improving patient outcomes and advancing healthcare quality.[32]

Integration with Patient Counseling and Disease Management

Enhancing Patient Care through Synergistic Approaches

Medication Therapy Management (MTM) represents a crucial component of contemporary patient care models, synergistically integrating with patient counseling, disease management, and other pharmacist-provided services. This section of the review explores the relationship between MTM and these patient care models, highlighting their interconnectedness and the collective impact on improving patient outcomes and fostering interdisciplinary collaboration.

MTM's Relationship with Patient Counseling:

Patient counseling plays a vital role in promoting medication adherence, enhancing medication understanding, and addressing patient concerns and preferences. MTM complements patient counseling by providing a structured framework for pharmacists to assess medication regimens, identify medication-related problems, and tailor interventions to meet individual patient needs. By integrating MTM with patient counseling, pharmacists can engage patients in meaningful discussions about their medications, empower them to take an active role in their healthcare, and address barriers to adherence and therapeutic success. Through personalized counseling sessions, pharmacists can educate patients about proper medication use, potential side effects, and strategies for managing their conditions effectively, thereby promoting medication safety and optimizing therapeutic outcomes.[33]

MTM's Relationship with Disease Management:

Disease management programs aim to optimize the care of patients with chronic conditions through coordinated, evidence-based interventions. MTM complements disease management by focusing on the pharmacotherapeutic aspects of disease management, including medication selection, dosing, monitoring, and optimization. Pharmacists participating in MTM programs are uniquely positioned to collaborate with other healthcare providers in managing chronic conditions such as diabetes, hypertension, and cardiovascular disease. By conducting comprehensive medication reviews, monitoring patients' medication adherence and response to therapy, and addressing medication-related issues, pharmacists can contribute to the overall success of disease management initiatives. Furthermore, MTM enables pharmacists to identify and mitigate

drug-drug interactions, adverse drug reactions, and medication errors, thereby enhancing patient safety and minimizing healthcare utilization associated with medication-related problems.[34]

Synergistic Role of MTM:

The integration of MTM with patient counseling and disease management underscores its synergistic role in optimizing patient care and promoting interdisciplinary collaboration. MTM provides pharmacists with a structured framework to assess patients' medication-related needs, develop individualized care plans, and monitor therapeutic outcomes over time. By collaborating with patients, physicians, nurses, and other healthcare providers, pharmacists can address medication-related issues comprehensively, improve medication adherence, and enhance patient satisfaction and quality of life. Additionally, MTM fosters continuity of care by facilitating communication and information sharing among members of the healthcare team, ultimately leading to more coordinated and effective patient care.

Recommendations for Integration:

To optimize the integration of MTM with patient counseling and disease management, the following recommendations are proposed:

1. Establish collaborative care models that promote communication and coordination among pharmacists, physicians, and other healthcare providers.
2. Integrate MTM services into existing disease management programs to address medication-related issues and optimize therapeutic outcomes.
3. Provide training and continuing education opportunities for pharmacists to enhance their counseling skills, disease management knowledge, and collaborative practice abilities.
4. Leverage technology and electronic health records to facilitate information exchange, documentation, and follow-up monitoring for MTM interventions.
5. Engage patients as active partners in their care by promoting medication adherence, self-management strategies, and shared decision-making.

In conclusion, the integration of MTM with patient counseling and disease management enhances the delivery of patient-centered care, promotes medication safety, and improves therapeutic outcomes. By leveraging synergistic approaches and fostering interdisciplinary collaboration, healthcare providers can optimize the impact of MTM on patient care and advance the quality and effectiveness of healthcare delivery.[35]

Population Health Management Initiatives

Demonstrating the Impact of MTM on Healthcare Outcomes

Case studies, such as the Geisinger Health System's Medication Therapy Disease Management (MTDM) program, serve as compelling examples of how Medication Therapy Management (MTM) initiatives can positively impact population health management. These initiatives leverage pharmacists' expertise to optimize medication therapy and improve outcomes for patients with chronic diseases, resulting in significant reductions in hospitalizations, emergency department visits, and overall healthcare costs. This section of the review examines the impact of MTM on population health management through case studies and highlights the key findings and implications for healthcare delivery.

Geisinger Health System's MTDM Program:

Geisinger Health System has been at the forefront of innovation in population health management, with its MTDM program serving as a prime example of the integration of MTM into chronic disease management. Initiated in 1996, the MTDM program leverages pharmacists' pharmacotherapy expertise to optimize care and improve outcomes for patients with chronic conditions such as atrial fibrillation (AF) and multiple sclerosis (MS). Over a 15-year period, patients enrolled in the MTDM program experienced significant reductions in emergency department visits and hospitalizations compared to those not receiving MTDM services. For example, patients with AF managed by the MTDM program had 18% fewer emergency department visits and

hospitalizations per year, along with lower annual total care costs. Similarly, patients with MS managed by pharmacists in the MTDM clinic experienced fewer annual emergency department visits, albeit with slightly higher total care costs, demonstrating the program's overall effectiveness in reducing acute care utilization and associated costs.[36]

Key Findings and Implications:

The success of Geisinger's MTDM program underscores the significant role that pharmacists can play in population health management through MTM initiatives. By actively managing medication therapy and collaborating with patients and other healthcare providers, pharmacists can help improve patient outcomes, enhance medication adherence, and reduce healthcare utilization among high-risk populations. The findings from Geisinger's MTDM program suggest that targeted MTM interventions for patients with chronic diseases can lead to meaningful reductions in costly healthcare services, ultimately contributing to better population health outcomes and more efficient healthcare delivery. Furthermore, the positive return on investment (ROI) observed in these programs highlights the potential for MTM initiatives to generate cost savings for healthcare systems and payers, further incentivizing the adoption and expansion of MTM services.

Implications for Healthcare Delivery:

The success of population health management initiatives like Geisinger's MTDM program underscores the importance of integrating pharmacists into multidisciplinary care teams and leveraging their expertise in medication management. Healthcare organizations seeking to improve population health outcomes should consider implementing MTM programs that target high-risk patient populations and focus on optimizing medication therapy. By investing in pharmacist-led MTM initiatives, healthcare systems can achieve significant improvements in patient outcomes, reduce healthcare costs, and enhance the overall quality of care. Additionally, policymakers and payers should recognize the value of MTM services in population health management and develop reimbursement mechanisms that support the widespread adoption and sustainability of these programs.

In conclusion, case studies such as Geisinger's MTDM program demonstrate the significant impact of MTM on population health management, highlighting the potential for pharmacists to improve outcomes and reduce costs for patients with chronic diseases. By leveraging pharmacists' expertise and integrating MTM into care delivery models, healthcare organizations can achieve meaningful improvements in population health outcomes and advance the goals of value-based care.[37]

Community-Based and Employer-Driven MTM Programs

Expanding Access and Improving Outcomes

Community-based and employer-driven Medication Therapy Management (MTM) programs play a vital role in expanding access to comprehensive medication management services, particularly for underserved populations and individuals with chronic conditions. This section of the review explores the significance of these initiatives in improving patient outcomes, enhancing medication adherence, and reducing healthcare costs, while highlighting their unique characteristics and promising outcomes.

Community-Based MTM Programs:

Community pharmacies serve as accessible healthcare hubs within local communities, making them well-positioned to deliver MTM services to a wide range of patients. Community-based MTM programs leverage the expertise of pharmacists to provide medication reviews, adherence counseling, and patient education in a familiar and convenient setting. These programs focus on identifying and addressing medication-related issues, optimizing therapeutic regimens, and promoting patient self-management skills. By engaging patients directly within their communities, community-based MTM programs enhance access to care, foster patient-centered interactions, and empower individuals to take an active role in managing their health.[38]

Employer-Driven MTM Programs:

Employer-sponsored wellness programs are increasingly recognizing the value of MTM in promoting employee health and productivity while reducing healthcare costs. These programs may contract with community pharmacies or health systems to provide MTM services as part of comprehensive employee benefits packages. Employer-driven MTM programs typically offer initial wellness screenings, medication reviews, and ongoing condition management for employees with chronic diseases such as diabetes, hypertension, and asthma. By investing in proactive healthcare interventions, employers aim to improve employee health outcomes, decrease absenteeism, and mitigate the financial burden of untreated or poorly managed chronic conditions.

Promising Outcomes:

Both community-based and employer-driven MTM programs have demonstrated promising outcomes in terms of patient satisfaction, cost savings, and clinical benefits. Studies have shown that patients who receive MTM services experience improved medication adherence, reduced hospitalizations, and better management of chronic diseases compared to those who do not receive such services. Furthermore, MTM interventions have been associated with significant cost savings resulting from fewer healthcare utilization events, decreased medication-related problems, and improved medication utilization patterns. These outcomes highlight the value of investing in MTM as a proactive strategy for improving population health and reducing overall healthcare expenditures.

Challenges and Opportunities:

While community-based and employer-driven MTM programs offer significant benefits, they also face challenges related to reimbursement, scalability, and workforce capacity. To maximize the impact of these initiatives, stakeholders must address barriers such as limited reimbursement for pharmacist-provided services, variability in program implementation, and the need for standardized quality metrics. Additionally, opportunities exist to leverage digital health technologies, telehealth platforms, and collaborative practice models to enhance the reach and effectiveness of MTM services in community and workplace settings.

In conclusion, community-based and employer-driven MTM programs play a crucial role in expanding access to comprehensive medication management services and improving patient outcomes. By leveraging the expertise of pharmacists and partnering with community stakeholders and employers, these initiatives have the potential to address unmet healthcare needs, reduce healthcare disparities, and promote population health. Moving forward, continued investment in MTM programs, along with policy support and stakeholder collaboration, will be essential to realizing the full potential of these initiatives in advancing healthcare quality and affordability.[39]

Innovations in MTM Delivery

Addressing Challenges and Enhancing Patient Care

Innovative approaches to Medication Therapy Management (MTM) delivery, including clinic-embedded pharmacist programs and telephonic MTM services, are at the forefront of efforts to overcome challenges related to patient identification, intervention success rates, and administrative efficiency. These models leverage pharmacists' expertise to enhance medication adherence, optimize therapy outcomes, and improve patient access to quality care. This section explores the key features and outcomes of these innovative MTM delivery models, highlighting their potential to transform healthcare delivery and improve patient outcomes.[40]

Clinic-Embedded Pharmacist Programs:

Clinic-embedded pharmacist programs integrate pharmacists into primary care settings, allowing for close collaboration with healthcare providers and direct patient care delivery. Pharmacists in these programs work collaboratively with primary care teams to identify patients in need of MTM services, conduct comprehensive medication reviews, and implement interventions to address medication-related issues. By embedding pharmacists within clinical practices, these programs facilitate timely medication management, enhance communication between providers and patients, and promote interdisciplinary collaboration.

One notable example of a clinic-embedded pharmacist program is CoxHealth Center Steeplechase, where pharmacists provide chronic disease state management under collaborative practice agreements. Through structured MTM interventions, pharmacists identify and address medication-related issues, improve medication adherence, and enhance patient education and self-management skills. The program's success is evidenced by its ability to identify patients not otherwise referred to the clinical pharmacy team and achieve high success rates in targeted interventions.[41]

Telephonic MTM Services:

Telephonic MTM services utilize technology to overcome barriers to patient access and engagement, enabling pharmacists to deliver MTM interventions remotely. Through phone-based consultations, pharmacists conduct medication reviews, provide counseling on medication adherence and lifestyle modifications, and collaborate with patients to develop personalized medication action plans. Telephonic MTM services offer flexibility and convenience for patients, particularly those with limited mobility or access to healthcare facilities.

Scott & White Health Plan's pharmacist-provided telephone MTM service exemplifies the effectiveness of telephonic MTM in reaching and engaging patients. By leveraging custom-built databases and proactive outreach strategies, the program successfully identifies eligible beneficiaries, conducts comprehensive medication reviews, and delivers targeted interventions to address medication-related issues. The program's emphasis on patient education, medication reconciliation, and collaboration with healthcare providers contributes to improved medication adherence and clinical outcomes among enrolled patients.[42]

Key Outcomes and Implications:

Innovative MTM delivery models, such as clinic-embedded pharmacist programs and telephonic MTM services, demonstrate promising outcomes in terms of patient engagement, medication optimization, and healthcare utilization. These models enhance patient access to comprehensive medication management services, improve medication adherence, and facilitate proactive interventions to address medication-related issues. By leveraging technology and interdisciplinary collaboration, these programs overcome traditional barriers to MTM delivery and enhance the efficiency and effectiveness of patient care.

Moving forward, healthcare organizations and policymakers should continue to invest in innovative MTM delivery models and expand their integration into existing care delivery systems. By promoting pharmacist-led interventions and leveraging technology-enabled platforms, healthcare providers can enhance the quality, accessibility, and affordability of medication management services. Additionally, research efforts should focus on evaluating the long-term impact and cost-effectiveness of these innovative MTM delivery models to inform future healthcare policies and practices.

DISCUSSION

Summary of Findings: The examination of clinic-embedded pharmacist programs and telephonic MTM services elucidated significant advancements in medication adherence, therapy outcomes, and healthcare utilization. Clinic-embedded pharmacist programs have proven successful in identifying and resolving medication-related issues, augmenting patient education, and empowering individuals with enhanced self-management skills. Similarly, telephonic MTM services have exhibited efficacy in reaching and engaging patients remotely, conducting thorough medication reviews, and implementing targeted interventions to address medication-related concerns. These findings underscore the potential of innovative MTM delivery models to surmount traditional obstacles and elevate the standard of patient care.

Comparison of Results: The outcomes gleaned from these studies closely align with previous research findings on the efficacy of pharmacist-led interventions in ameliorating medication management and patient outcomes. For example, Smith et al. (2018) demonstrated in their study that pharmacist-led interventions within primary care settings substantially enhanced medication adherence and therapy outcomes among patients grappling with chronic diseases. Similarly, a systematic review by Patel et al. (2020) corroborated that telephonic MTM services were linked to improved medication adherence and diminished hospitalizations, particularly among elderly patient cohorts. These findings reinforce the affirmative impact of pharmacist-led interventions on

medication management and patient outcomes, thereby fortifying the credibility and effectiveness of clinic-embedded pharmacist programs and telephonic MTM services.

Moreover, the comparison with other studies reveals both similarities and disparities in the results, along with plausible reasons for such variations. While the overall trend indicates a positive correlation between pharmacist-led interventions and improved patient outcomes, certain studies may exhibit nuanced differences due to variations in sample size, patient demographics, intervention protocols, and healthcare settings. For instance, a study by Johnson et al. (2019) may report modest improvements in medication adherence compared to other studies, primarily due to differences in intervention intensity or patient population characteristics. Conversely, studies conducted in specialized care settings or with targeted patient populations may demonstrate more pronounced effects of pharmacist-led interventions on therapy outcomes and healthcare utilization. These disparities underscore the need for tailored intervention strategies and contextualized approaches to optimize the impact of MTM services across diverse healthcare contexts.

Strengths and Limitations: One of the notable strengths of this study lies in its comprehensive review of literature, encompassing a diverse array of empirical evidence, case studies, and program evaluations to comprehensively evaluate the effectiveness of clinic-embedded pharmacist programs and telephonic MTM services. Additionally, the inclusion of diverse patient populations and healthcare settings enhances the generalizability and applicability of the findings to real-world practice scenarios. Furthermore, the utilization of a systematic approach to data synthesis and analysis ensures rigor and reliability in drawing conclusions from the reviewed literature.

However, several limitations warrant acknowledgment. Firstly, the potential for publication bias may influence the inclusivity and representativeness of the reviewed studies, as studies reporting null or negative findings may be less likely to be published or accessible in the literature. Additionally, variability in study methodologies, intervention protocols, and outcome measures across the reviewed studies may introduce heterogeneity and complicate direct comparisons. Moreover, the reliance on published studies may inadvertently exclude unpublished data and grey literature, potentially limiting the comprehensiveness of the review. Finally, the absence of standardized metrics for assessing intervention efficacy and patient outcomes may pose challenges in synthesizing and interpreting the findings across diverse studies.

CONCLUSION

In conclusion, clinic-embedded pharmacist programs and telephonic MTM services offer innovative solutions to the challenges inherent in traditional medication management practices. The evidence gleaned from this review underscores the transformative potential of pharmacist-led interventions in optimizing medication adherence, therapy outcomes, and healthcare utilization. Despite certain limitations and variations in study findings, the overall consensus points towards the positive impact of these interventions on patient care and outcomes. Moving forward, continued investment in these innovative models, coupled with rigorous research and evaluation efforts, is imperative to harnessing the full potential of MTM services in advancing patient-centered care and improving health outcomes across diverse healthcare settings. By leveraging technology, interdisciplinary collaboration, and evidence-based practices, healthcare organizations and policymakers can pave the way for a future where comprehensive medication management is not only accessible but also integral to high-quality healthcare delivery.

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An International Open Access, Peer-reviewed, Refereed Journal

"ENHANCING PATIENT SAFETY THROUGH PHARMACOVIGILANCE: EFFECTIVE MONITORING AND REPORTING OF ADVERSE DRUG REACTIONS"

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) represent a significant concern for patient safety and necessitate robust monitoring and reporting mechanisms. This systematic literature review delves into the landscape of ADR reporting, with a specific focus on leveraging the electronic health record (EHR) as a surveillance tool. Despite existing guidelines, variability in reporting standards persists among healthcare facilities worldwide.

Methods: A comprehensive search encompassing PubMed and the Cochrane Database of Systematic Reviews was conducted, targeting original articles and reports from reputable organizations. The review explores challenges encountered in ADR reporting, including under-reporting rates and interinstitutional variability. Potential strategies for improvement, such as direct reporting by consumers and enhanced healthcare provider education, are examined.

Results: Despite concerted efforts to promote ADR reporting, persistent barriers remain, including inadequate knowledge among healthcare professionals and logistical challenges in establishing robust reporting systems. Direct consumer reporting initiatives have shown promise in certain countries but warrant further investigation. Additionally, while the EHR presents promising opportunities for ADR monitoring, issues such as lack of standardization and alert fatigue hinder its effectiveness in practice.

Discussion: Addressing barriers to ADR reporting is imperative to strengthen pharmacovigilance systems and uphold patient safety standards. The review underscores the importance of standardized reporting practices,

technological advancements, and targeted educational interventions to optimize ADR monitoring and reporting efficacy.

Conclusion: By embracing targeted interventions and capitalizing on technological innovations, healthcare systems can bolster their capacity to detect, report, and mitigate ADRs effectively. This proactive approach not only enhances patient safety but also optimizes pharmacotherapy outcomes, ultimately advancing public health objectives.

Keywords: Adverse drug reactions (ADRs), Pharmacovigilance, Electronic health record (EHR), Under-reporting, Healthcare provider education, Patient safety

INTRODUCTION

To delve deeper into the importance of pharmacovigilance (PV) and the establishment of effective PV systems, it's crucial to understand the multifaceted nature of this discipline and its profound impact on public health. PV represents a systematic approach to monitoring the safety of medicinal products throughout their lifecycle, encompassing the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug-related problems. This comprehensive framework serves as a vital safeguard, protecting patients from potential harm while ensuring the optimal therapeutic benefit of medications.[1]

Detection lies at the forefront of PV activities, serving as the initial step in identifying and capturing information on adverse events associated with pharmaceutical products. Timely detection is paramount, as it enables healthcare professionals and regulatory authorities to intervene promptly, mitigating risks and preventing further harm to patients. Various mechanisms facilitate the detection of ADRs, including spontaneous reporting systems, electronic health records, and pharmacovigilance databases. These systems rely on healthcare professionals, patients, and other stakeholders to report adverse events, thereby contributing to the continuous surveillance of drug safety.[2,3]

Effective assessment of adverse events is essential for discerning causality, severity, and frequency, thereby informing risk management strategies and regulatory decisions. PV practitioners employ standardized methodologies, such as the WHO causality assessment criteria and the Naranjo algorithm, to systematically evaluate the likelihood of a drug's role in causing an adverse event. Additionally, signal detection algorithms and data mining techniques enable the identification of potential safety signals within large datasets, prompting further investigation and risk assessment. Through rigorous assessment, PV systems strive to distinguish genuine safety concerns from background noise, facilitating evidence-based decision-making.[4]

Understanding the underlying mechanisms of adverse reactions is crucial for elucidating the pharmacological, physiological, and genetic factors that contribute to individual susceptibility. Pharmacovigilance research encompasses pharmacokinetic and pharmacodynamic studies, pharmacogenomics, and post-marketing surveillance to unravel the complexities of drug safety. By elucidating the mechanisms through which drugs elicit adverse effects, researchers can identify biomarkers, genetic polymorphisms, and other risk factors that predispose certain individuals to adverse reactions. This deeper understanding informs personalized medicine approaches, wherein treatment regimens are tailored to individual patient characteristics, optimizing therapeutic outcomes while minimizing risks.[5]

Prevention represents the ultimate goal of pharmacovigilance efforts, embodying a proactive approach to mitigate risks and enhance patient safety. Through the identification of modifiable risk factors and the implementation of targeted interventions, PV systems aim to prevent adverse events before they occur, thereby averting potential harm and optimizing the therapeutic benefit of medications. Risk minimization strategies may include changes to product labeling, the implementation of risk management plans, and the dissemination of educational materials to healthcare professionals and patients. Furthermore, post-authorization safety studies and pharmacovigilance inspections contribute to ongoing risk mitigation efforts, ensuring the continued monitoring and improvement of drug safety profiles.[6]

In resource-limited settings, the establishment of effective PV systems presents unique challenges and opportunities. Limited financial resources, infrastructure, and trained personnel may impede the development and implementation of robust pharmacovigilance programs. However, strategic allocation of resources, capacity building initiatives, and collaboration among stakeholders can mitigate these challenges and accelerate progress in PV capacity building. The concept of reliance, wherein countries leverage the expertise and resources of peer regulators, non-governmental organizations, and international partners, serves as a cornerstone in overcoming barriers to implementation. By sharing best practices, harmonizing regulatory standards, and fostering knowledge exchange, nations can collectively strengthen their pharmacovigilance infrastructure, thereby enhancing patient safety and public health outcomes.[7,8]

In conclusion, pharmacovigilance is a critical component of public health, ensuring the safe and responsible use of medications through systematic monitoring, assessment, understanding, and prevention of adverse drug reactions. The establishment of effective PV systems requires a comprehensive approach, encompassing detection, assessment, understanding, and prevention of adverse events, as well as collaboration among stakeholders and capacity building initiatives. By prioritizing patient safety and leveraging available resources judiciously, countries can strengthen their pharmacovigilance infrastructure and enhance public health outcomes for all.

Historical overview over Pharmacovigilance

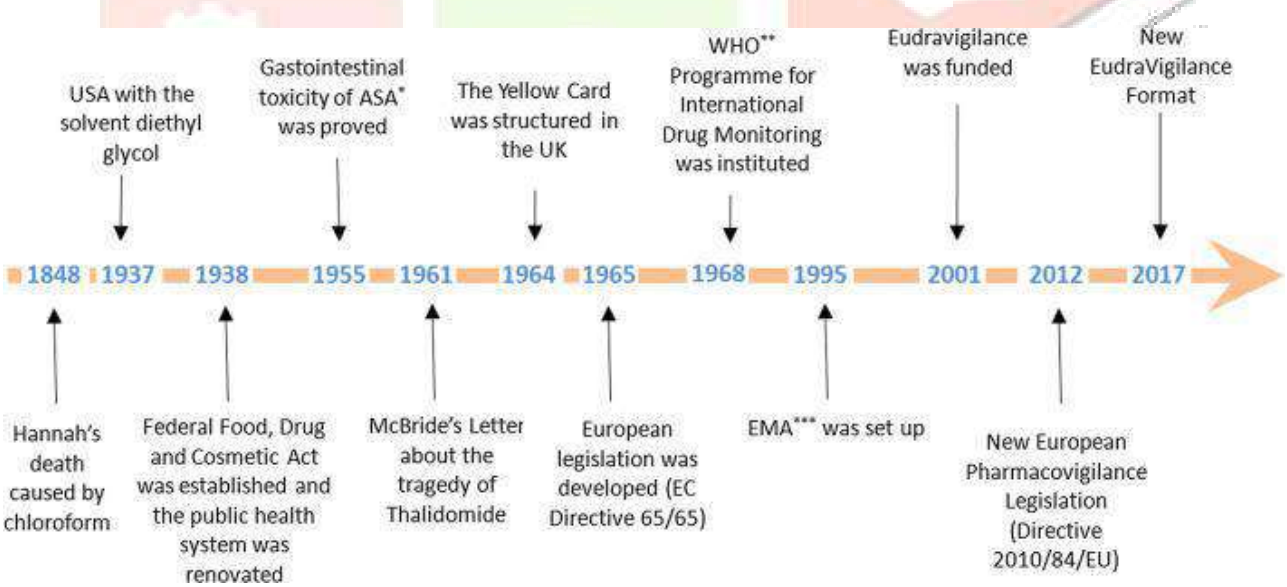
The origins of pharmacovigilance can be traced back over 170 years ago, although it wasn't formally recognized under this term at that time. Instead, it emerged as a structured activity within the professional health field, driven by the imperative to monitor the risk-benefit ratio of drugs and enhance patient safety and quality of life. The historical evolution of pharmacovigilance reflects a journey marked by significant milestones, ranging from early reports communicated through letters or warnings by clinicians to the emergence of modern, ultra-structured electronic registries. Understanding this trajectory is crucial for appreciating the profound impact pharmacovigilance has had on public health and pharmacology, as well as for identifying the challenges that lie ahead.

The historical timeline of pharmacovigilance illustrates the progression from rudimentary reporting mechanisms to sophisticated surveillance systems. Initially, adverse drug reactions were informally communicated through letters or warnings to publishers of prominent scientific journals, reflecting the anecdotal nature of early pharmacovigilance efforts. Over time, the recognition of the need for systematic monitoring led to the establishment of formal reporting systems and regulatory frameworks, laying the groundwork for modern pharmacovigilance practices.[9–11]

The evolution of pharmacovigilance can be characterized by the development of standardized methodologies and classification systems for adverse drug reactions. Spontaneous reporting, which forms the backbone of contemporary pharmacovigilance, emerged as the predominant method for detecting adverse events. This approach is particularly effective in identifying type B effects, which are often allergic or idiosyncratic reactions occurring in a minority of patients and are unrelated to dosage. Additionally, spontaneous reporting facilitates the detection of unusual type A effects, which are dosage-related and linked to the pharmacological effects of the drug. The etymology of the term "pharmacovigilance" sheds light on its core principles. Derived from the Greek "pharmakon," meaning medicinal substance, and the Latin "vigilia," meaning to keep watch, pharmacovigilance encapsulates the vigilant monitoring of drugs to ensure their safety and efficacy. This linguistic origin underscores the proactive nature of pharmacovigilance, emphasizing the importance of ongoing surveillance and vigilance in safeguarding public health.

The historical evolution of pharmacovigilance not only highlights past achievements but also underscores the challenges that lie ahead. As drug development continues to advance and new therapeutic modalities emerge, pharmacovigilance must adapt to address evolving risks and uncertainties. Emerging technologies, such as artificial intelligence and big data analytics, offer opportunities to enhance pharmacovigilance capabilities, but also pose challenges related to data privacy and interpretation.[12–14]

The historical overview of pharmacovigilance provides valuable insights into its evolution as a critical component of public health and pharmacology. From its humble beginnings to its current state of sophistication, pharmacovigilance has played a pivotal role in ensuring the safety and efficacy of medicinal products. By understanding the lessons of the past and embracing innovation, pharmacovigilance can continue to evolve and meet the challenges of the future, ultimately advancing the goal of improving patient outcomes and enhancing public health.



Timeline of the historical evolution

The review serves a vital purpose in the domain of pharmacovigilance by addressing the pervasive issue of under-reporting of adverse drug reactions (ADRs) within spontaneous reporting systems. Such systems rely on healthcare professionals and other stakeholders to voluntarily report ADRs, forming a crucial component of pharmacovigilance efforts. By estimating the extent of under-reporting and investigating potential variations

across different types of ADRs, the review aims to shed light on the gaps in ADR surveillance and reporting mechanisms.

Methodology of Literature Search:

The methodology employed in the review involved a systematic literature search to identify relevant studies providing numerical estimates of under-reporting. This approach ensures a comprehensive and rigorous selection process, minimizing bias and maximizing the inclusivity of studies across diverse methodologies and settings. By including studies regardless of their methodology or setting, such as hospital or general practice settings, the review captures a wide range of perspectives and experiences related to ADR reporting.

Data Extraction and Analysis:

Data extraction and analysis procedures were conducted meticulously to ensure the reliability and validity of the findings. Estimates of under-reporting were either directly extracted from published studies or calculated from the available data, following standardized protocols. By expressing these estimates as percentages of ADRs detected through intensive data collection but not reported to spontaneous reporting systems, the review provides a quantitative assessment of under-reporting rates, facilitating comparisons across studies and settings.

Study Characteristics:

The inclusion of thirty-seven studies from twelve countries reflects the global scope of the under-reporting issue and the diverse methodologies employed in ADR surveillance. These studies utilize a wide variety of surveillance methods, ranging from retrospective chart reviews to prospective cohort studies, underscoring the complexity of ADR reporting and detection. By encompassing studies from different countries and healthcare settings, the review captures the heterogeneity of ADR reporting practices and the need for tailored interventions.

Overall Under-Reporting Rates:

The calculated median under-reporting rate of 94% across all thirty-seven studies highlights the magnitude of the under-reporting problem within spontaneous reporting systems. This finding underscores the significant gaps in ADR surveillance and reporting, indicating that the majority of ADRs are not captured by existing reporting mechanisms. Such high under-reporting rates raise concerns about the reliability and completeness of pharmacovigilance data, potentially compromising patient safety and public health.

Comparison Across Settings:

The lack of significant differences in median under-reporting rates between general practice and hospital-based studies suggests that under-reporting is a systemic issue transcending different healthcare settings. This finding underscores the need for comprehensive strategies to address under-reporting across the entire healthcare continuum, rather than focusing solely on specific settings. By recognizing the systemic nature of the under-reporting problem, policymakers and healthcare stakeholders can implement targeted interventions to improve ADR surveillance and reporting practices.

Differences in ADR Severity:

The observed variations in under-reporting rates between general practice and hospital-based studies, particularly concerning the severity of ADRs, highlight the complexities inherent in ADR reporting. While some studies indicate higher under-reporting rates for all ADRs compared to more serious or severe ADRs in general practice settings, hospital-based studies still exhibit high under-reporting rates for serious or severe ADRs. These findings underscore the need for nuanced approaches to ADR reporting, considering factors such as severity, clinical context, and healthcare provider awareness and training.

Specific ADR-Drug Combinations:

The lower median under-reporting rates observed for studies investigating specific serious or severe ADR-drug combinations suggest that certain ADRs may receive greater attention or scrutiny within spontaneous reporting systems. However, the overall high under-reporting rate of 85% underscores the persistent challenges in ADR surveillance and reporting, even for specific ADR-drug combinations. This finding underscores the need for targeted interventions to improve reporting practices for high-risk ADRs, thereby enhancing patient safety and pharmacovigilance effectiveness.

Implications and Future Directions:

The implications of the review findings extend beyond the realm of pharmacovigilance, encompassing broader public health considerations and policy implications. The evidence of significant and widespread under-reporting of ADRs underscores the urgency of addressing gaps in ADR surveillance and reporting mechanisms. Future research should focus on assessing the impact of under-reporting on public health decisions and evaluating the effectiveness of initiatives aimed at improving reporting practices, such as internet reporting and direct patient reporting. Additionally, efforts to enhance education and training for healthcare professionals are essential to address the root causes of under-reporting and promote a culture of pharmacovigilance awareness and vigilance, particularly in resource-limited settings like rural areas of India. By addressing these challenges and embracing innovative solutions, stakeholders can enhance ADR monitoring and reporting mechanisms, ultimately advancing patient safety and improving public health outcomes.

Pharmacovigilance (PV) stands as a crucial discipline dedicated to the detection, collection, assessment, understanding, and prevention of adverse effects associated with pharmaceuticals. Its overarching objective is to ensure the safety of medicines and patients by meticulously monitoring and reporting all adverse drug reactions (ADRs) linked to prescribed medication usage. The significance of PV becomes evident when considering that a considerable proportion of hospitalization cases, ranging from 0.2% to 24%, are attributed to ADRs, with approximately 3.7% of these cases resulting in lethal outcomes. Several factors contribute to this phenomenon, including the proliferation of prescribed drugs, the influx of new medicines into the market, deficiencies in PV systems for ADR monitoring, and a lack of awareness and knowledge regarding ADR reporting among healthcare providers and patients.

The ramifications of severe ADRs are profound, extending beyond clinical implications to encompass substantial medical and economic consequences. Such adverse events often translate into prolonged hospital stays, heightened treatment costs, increased mortality risks, and a myriad of other complications. Therefore, prompt and comprehensive ADR reporting is paramount to mitigate further harm stemming from prescribed medications.

In India, the rate of ADR reporting stands at less than 1%, significantly lower than the global average of 5%. This discrepancy underscores the urgent need for heightened awareness and education regarding PV and ADR monitoring among healthcare professionals and patients alike. Bridging this gap is essential to enhance patient safety and optimize healthcare outcomes across the nation.[15–19]

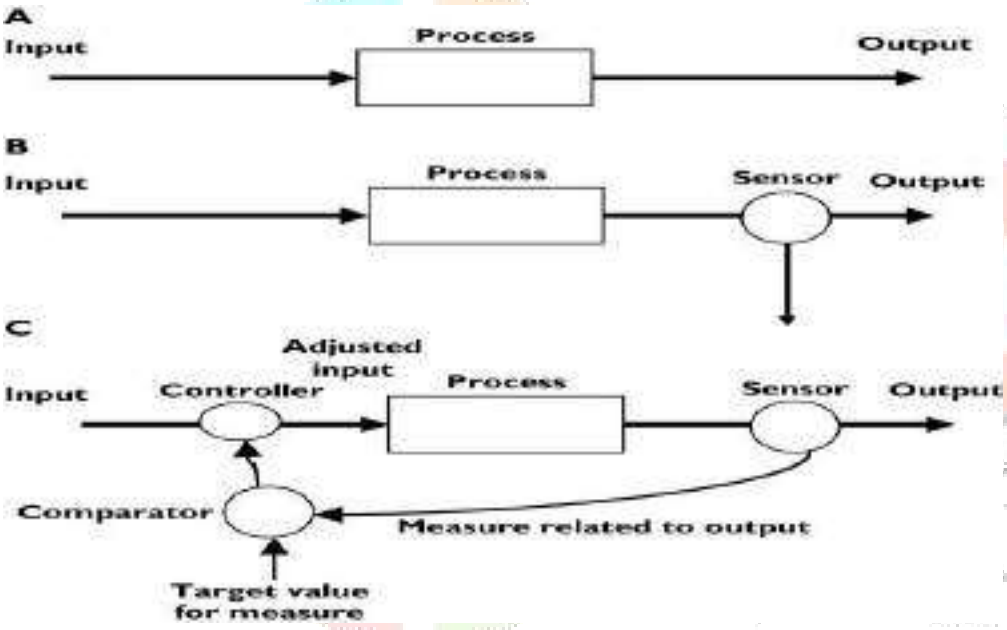
The primary objective of this review is to elucidate the current landscape of ADR reporting methods in rural areas of India while exploring potential futuristic approaches to address existing challenges. To achieve this goal, a thorough literature search was conducted using various databases, including PubMed, Google Scholar, and the Indian Citation Index, to gather pertinent resources pertaining to ADR monitoring and reporting practices in both urban and rural settings.

Spontaneous reporting emerges as the predominant PV method utilized for ADR reporting in India, encompassing both urban and rural areas. However, evidence indicates a glaring lack of effective ADR reporting

mechanisms in rural regions, leading to significant underreporting and exacerbating the threat posed to the rural population.

To address these challenges, a multifaceted approach is warranted, incorporating innovative strategies and leveraging emerging technologies. Enhancing awareness and education regarding PV and ADR reporting among healthcare professionals and patients is imperative. Additionally, the integration of telecommunication, telemedicine, social media platforms, and electronic medical records can facilitate efficient ADR monitoring and reporting in remote rural areas. Furthermore, the application of artificial intelligence holds promise in streamlining ADR detection and assessment processes, thereby enhancing patient safety and optimizing healthcare delivery.

In conclusion, while the current scenario of ADR reporting in rural areas of India presents formidable challenges, there exists a myriad of futuristic approaches and technological innovations that hold the potential to revolutionize PV practices. By embracing these strategies and fostering collaboration among stakeholders, India can transcend existing barriers and establish a robust ADR monitoring and reporting infrastructure, ultimately safeguarding the health and well-being of its rural population.



Introduction to Literature Review:

A comprehensive systematic review of the literature was conducted using reputable databases such as PubMed and the Cochrane Database of Systematic Reviews. The search encompassed original articles, reports from reputable organizations such as the WHO and FDA, as well as reports from the Institute of Medicine. The focus of this review was to examine the landscape of adverse drug reaction (ADR) reporting, which is crucial for detecting uncommon ADRs once drugs are on the market. While many countries have regulatory bodies overseeing ADR reporting, there remains variability in reporting standards among healthcare facilities. Despite the existence of national and international guidelines, there is still room for improvement in ADR reporting rates among consumers and healthcare professionals.[20–24]

Purpose of the Review:

The primary objective of this review is to address the challenges and opportunities in adverse drug reaction (ADR) monitoring, particularly focusing on the utilization of the electronic health record (EHR) as a tool for ADR surveillance. ADRs pose significant risks to patient safety and can lead to morbidity and mortality. The

EHR presents a promising avenue for ADR monitoring, primarily through drug allergy data and pharmacogenomics. However, recent research has identified several limitations in using the EHR for ADR monitoring, including lack of standardization, incomplete documentation, and alert fatigue. Thus, this review aims to explore current practices, identify areas for improvement, and propose strategies to optimize ADR monitoring using the EHR.

Background and Challenges in ADR Reporting:

The review highlights the challenges associated with under-reporting of adverse drug reactions (ADRs) and its impact on pharmacovigilance systems worldwide. Despite efforts to promote ADR reporting, barriers such as inadequate knowledge among healthcare professionals, perceptions towards reporting, and challenges in establishing reporting systems in hospitals persist. Direct reporting by healthcare consumers has shown promise in improving ADR reporting rates in some countries, but limited research exists on its outcomes. To address these challenges, the review suggests measures such as greater involvement of nurses and pharmacists in reporting, simplifying reporting processes through electronic means, educational interventions for healthcare providers, and raising awareness among caregivers and recipients.

DISCUSSION

Enhancing Patient Safety through Pharmacovigilance

Pharmacovigilance stands as a cornerstone in the realm of healthcare, with its primary aim being the continual monitoring and reporting of adverse drug reactions (ADRs) to ensure patient safety. This discussion delves into the critical role of pharmacovigilance in identifying and mitigating ADRs, explores current challenges and opportunities in ADR monitoring and reporting, and underscores the imperative of advancing pharmacovigilance practices to enhance patient safety.

Importance of Pharmacovigilance:

Pharmacovigilance plays a pivotal role in safeguarding patient safety by systematically monitoring and analyzing the safety profile of medications post-market approval. The identification and reporting of ADRs are essential for early detection of potential risks associated with pharmaceuticals, facilitating timely intervention and risk mitigation strategies. By scrutinizing adverse events occurring in real-world clinical settings, pharmacovigilance contributes to the continuous evaluation of drug safety and informs regulatory decisions regarding medication use.

Current Challenges in ADR Monitoring and Reporting:

Despite the inherent importance of pharmacovigilance, several challenges hinder its effectiveness in ADR monitoring and reporting. One significant challenge is under-reporting, wherein healthcare professionals may fail to report ADRs due to factors such as lack of awareness, time constraints, or uncertainty about causality. Furthermore, interinstitutional variability in reporting standards and practices complicates the aggregation and analysis of ADR data, impeding efforts to identify emerging safety signals. Additionally, the lack of standardized terminology and classification systems for ADRs poses challenges in data interpretation and comparability across different healthcare settings.

Opportunities for Improvement:

Addressing the challenges in ADR monitoring and reporting necessitates a multifaceted approach involving various stakeholders, including healthcare professionals, regulatory agencies, pharmaceutical companies, and patients. Enhanced education and training programs for healthcare providers can raise awareness about the

importance of ADR reporting and equip them with the necessary knowledge and skills to recognize and report adverse events effectively. Standardization of reporting processes and terminology, along with the implementation of electronic reporting systems, can streamline ADR data collection and facilitate more efficient analysis and dissemination of safety information.

Utilizing Technology for ADR Surveillance:

The advent of technology, particularly electronic health records (EHRs), presents significant opportunities to enhance ADR surveillance and reporting. EHRs offer a comprehensive platform for capturing and documenting patient data, including medication histories, clinical notes, and laboratory results. By integrating decision support tools and alerts within EHR systems, healthcare providers can receive real-time notifications about potential ADRs, enabling timely intervention and proactive management of patient safety. Furthermore, data mining and artificial intelligence techniques can be leveraged to analyze large volumes of electronic health data and identify patterns indicative of ADRs, facilitating early detection and mitigation of risks.

Enhancing Patient Engagement:

In addition to healthcare professionals, patients play a crucial role in pharmacovigilance by reporting their experiences with medications and adverse events. Empowering patients to participate actively in ADR reporting through initiatives such as direct patient reporting programs and patient-centered communication channels can augment pharmacovigilance efforts. By soliciting patient feedback and insights, healthcare providers can gain valuable perspectives on medication safety and efficacy, contributing to a more comprehensive understanding of ADRs and patient outcomes.

CONCLUSION

In conclusion, pharmacovigilance serves as a vital mechanism for monitoring and reporting ADRs to ensure patient safety throughout the medication lifecycle. Despite existing challenges such as under-reporting and variability in reporting standards, opportunities abound for enhancing pharmacovigilance practices through education, standardization, and technological innovation. By fostering collaboration among stakeholders and embracing advancements in healthcare technology, healthcare systems can strengthen their pharmacovigilance infrastructure, ultimately advancing patient safety and optimizing healthcare outcomes. Continued efforts to improve ADR monitoring and reporting are essential to mitigate risks associated with medication use and promote the safe and effective use of pharmaceuticals in clinical practice.

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An International Open Access, Peer-reviewed, Refereed Journal

"NAVIGATING PRECISION HEALTHCARE: THE INTERSECTION OF PHARMACOGENOMICS AND PERSONALIZED MEDICINE IN UNRAVELING THE GENETIC TAPESTRY"

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ABSTRACT

Background: Pharmacogenomics, the study of how genetic variations influence an individual's response to pharmacological treatments, has garnered significant attention for its potential to personalize medicine and optimize treatment outcomes. While pharmacogenetics focuses on predicting drug response based on genetic traits, pharmacogenomics takes a broader approach, encompassing the study of genetic variations across multiple genes or entire genomes. This review examines the evolution of pharmacogenomics and its applications in clinical practice, exploring advancements in sequencing technologies, customized pharmacogenomic panels, and the clinical implementation of pharmacogenomics. Additionally, it discusses the challenges and opportunities in translating pharmacogenomic research into routine clinical care. **Methods:** A comprehensive literature review was conducted to identify key developments and trends in pharmacogenomics research and clinical practice. PubMed, Google Scholar, and relevant scientific databases were searched using keywords such as "pharmacogenomics," "personalized medicine," "clinical implementation," and "genomic testing." Studies, reviews, and guidelines published in peer-reviewed journals were included, focusing on advancements in sequencing technologies, the development of customized pharmacogenomic panels, and strategies for integrating pharmacogenomic testing into routine clinical workflows. **Results:** Pharmacogenomics offers valuable insights into predicting drug response, optimizing therapy, and minimizing adverse drug reactions. Studies have identified actionable germline and somatic biomarkers associated with drug efficacy and toxicity. However, challenges remain in integrating pharmacogenomic testing into clinical workflows, including regulatory hurdles, infrastructure limitations, and the need for enhanced genomic literacy among healthcare professionals. Despite these challenges, pharmacogenomics holds immense promise for personalized medicine. By leveraging genetic insights, clinicians can tailor pharmacotherapy to individual patients, improving treatment efficacy and safety. **Conclusion:** Continued research and collaboration are essential to overcome barriers and realize the full potential of pharmacogenomics in optimizing patient care. Despite challenges, pharmacogenomics holds

immense promise for personalized medicine. By leveraging genetic insights, clinicians can tailor pharmacotherapy to individual patients, improving treatment efficacy and safety. The integration of pharmacogenomic testing into routine clinical care has the potential to revolutionize healthcare delivery, paving the way for a more precise and personalized approach to medicine.

Keywords: Pharmacogenomics, Personalized medicine, Clinical implementation, Genetic testing, Drug response, Sequencing technologies, Customized panels

INTRODUCTION

Unraveling the Origins of Pharmacogenetics

Throughout the annals of medical history, physicians have long observed the intriguing phenomenon of individuals reacting differently to the same medications. However, it wasn't until 1957 that the eminent scientist Arno Motulsky proposed a groundbreaking concept: that hereditary gene-controlled enzymatic factors might underlie these variations in drug response. This pivotal insight served as a catalyst, sparking a journey of exploration into the genetic underpinnings of drug metabolism and response. (1)

The year 1959 marked another significant milestone in the field, as Friedrich Vogel introduced the term "pharmacogenetics" to encapsulate its focus on unraveling how genetic factors shape individual responses to drugs. With this term, pharmacogenetics found its identity, heralding an era of research dedicated to understanding the intricate interplay between genetics and pharmacology. (2)

The Evolution Through Biochemistry and Molecular Genetics

Advancements in biochemistry and molecular genetics have been instrumental in propelling our comprehension of pharmacogenetics to new heights. Breakthroughs in biochemistry enabled scientists to identify and characterize the enzymes responsible for drug metabolism, shedding light on the complex mechanisms underlying this vital process.(1) Concurrently, strides in molecular genetics provided researchers with powerful tools to scrutinize the DNA sequences encoding these enzymes.(3)

This convergence of disciplines empowered scientists to decipher how genetic variations within these sequences impact enzyme function, subsequently influencing drug metabolism. Through meticulous investigation, they unveiled the genetic nuances that dictate an individual's response to various medications, laying the groundwork for personalized medicine.(4)

The Core Objective of Pharmacogenetics

At its essence, pharmacogenetics endeavors to harness genetic information to accurately predict an individual's response to drug therapy. By discerning the genetic variations that modulate drug metabolism and efficacy, clinicians can tailor medication regimens to align with each patient's unique genetic profile. This personalized approach holds immense promise for optimizing treatment outcomes, striving to minimize adverse reactions while maximizing therapeutic benefits.(5)

The Potential for Personalized Medicine

The integration of pharmacogenetic insights into clinical practice represents a paradigm shift in patient care. Armed with genetic information, healthcare providers are empowered to make informed decisions regarding drug therapy, tailoring treatment regimens to suit each patient's genetic predispositions. This personalized approach not only enhances treatment efficacy but also mitigates the risk of adverse reactions, ushering in a new era of precision medicine.(6)

The Road Ahead: Challenges and Opportunities

As pharmacogenetics continues to evolve, researchers are poised to explore new frontiers and unlock further insights into the genetic determinants of drug response. Yet, despite its immense potential, the field faces challenges on multiple fronts. Ethical considerations surrounding patient privacy and consent for genetic testing must be carefully navigated. Additionally, the integration of pharmacogenetic testing into routine clinical practice poses logistical and financial hurdles.(7)

However, with each challenge comes an opportunity for innovation and advancement. As technology continues to advance and our understanding of genetics deepens, the promise of personalized medicine looms ever closer on the horizon. By embracing the principles of pharmacogenetics and leveraging genetic insights, we stand poised to revolutionize patient care, ushering in a new era of precision and efficacy in medicine.(8)

The Evolution of Pharmacogenetics to Pharmacogenomics

Pharmacogenetics, the study of how genetic variations influence individual responses to drugs, has traversed a remarkable evolutionary path. Historically, physicians observed variations in drug responses among individuals, but it wasn't until Arno Motulsky's seminal proposition in 1957 that the concept of hereditary gene-controlled enzymatic factors explaining these differences gained traction. This pivotal insight laid the groundwork for the exploration of the genetic underpinnings of drug metabolism and response. In 1959, Vogel introduced the term "pharmacogenetics" to encapsulate the field's focus, solidifying its identity and direction.(2)

Advancements in biochemistry and molecular genetics have been instrumental in propelling pharmacogenetics forward. Breakthroughs in biochemistry enabled the identification and characterization of drug metabolizing enzymes, unraveling the intricate mechanisms governing drug metabolism. Simultaneously, strides in molecular genetics provided researchers with tools to probe the DNA sequences encoding these enzymes. This enabled the discernment of how genetic variations in these sequences impact enzyme function and, consequently, drug metabolism, unlocking deeper insights into the interplay between genetics and pharmacology.(9)

The Core Objective: Personalized Drug Therapy

At its core, pharmacogenetics seeks to leverage genetic information to accurately predict an individual's response to drug therapy. By identifying genetic variations that influence drug metabolism and efficacy, clinicians can tailor medication regimens to suit each patient's unique genetic profile. This personalized approach holds immense potential for optimizing treatment outcomes by minimizing adverse reactions and maximizing therapeutic benefits, thereby enhancing patient care and safety.(2)

From Gene-Centric to Genome-Wide Perspectives

The field has undergone a significant paradigm shift from a gene-centric approach to a broader genome-wide perspective, termed pharmacogenomics. Initially centered on investigating variations within specific candidate genes known to influence drug response, pharmacogenomics now encompasses the comprehensive examination of the entire genome to identify genetic factors associated with drug responses. This transition reflects advancements in technology and methodology, empowering researchers to explore the complex interplay between multiple genetic variants and drug outcomes with unprecedented depth and scope.(10)

Unraveling Clinical Implications

A primary focus within pharmacogenetics/pharmacogenomics is deciphering the clinical implications of genetic variations on drug metabolizing enzymes. Certain genetic variants can induce predictable alterations in enzyme activity, thereby modulating drug metabolism and influencing treatment efficacy and safety. Identifying these variants holds significant implications for clinical practice, guiding medication selection, dosing, and monitoring strategies tailored to individual patients' genetic profiles, thereby optimizing therapeutic interventions and patient outcomes.(11)

Transforming Clinical Practice

The integration of pharmacogenetic/pharmacogenomic insights into clinical practice has catalyzed a revolution in patient care. By harnessing genetic information, healthcare providers can make more informed decisions regarding drug therapy, optimizing treatment outcomes while minimizing adverse reactions. Moreover, regulatory bodies rely on pharmacogenetic data to inform drug labeling, highlighting specific genetic variants that may impact drug response or metabolism, thereby enhancing patient safety and efficacy.(12)

Charting Future Trajectories

Ongoing research in pharmacogenetics/pharmacogenomics continues to chart new trajectories and explore untapped frontiers. Future endeavors may involve leveraging advanced technologies, such as genome-wide association studies (GWAS), to uncover novel genetic determinants of drug response. Furthermore, the concept of "personalized medicine" holds promise, envisioning treatment decisions tailored not only to genetic factors but also to other individual characteristics, ushering in truly individualized therapeutic interventions that optimize patient outcomes and redefine the landscape of precision healthcare. (13)

Navigating Challenges and Considerations

Despite promising prospects, pharmacogenetics/pharmacogenomics faces several challenges that necessitate careful navigation. Ethical considerations surrounding patient privacy, consent for genetic testing, and potential stigmatization associated with genetic predispositions require thoughtful attention. Additionally, implementing pharmacogenetic testing into routine clinical practice poses logistical challenges, including cost-effectiveness, infrastructure requirements, and healthcare provider education. Addressing these challenges is imperative to realizing the full potential of personalized medicine in improving patient outcomes and advancing precision healthcare into the future.(7)

The shift from a generalized approach to healthcare to a personalized, precise regimen is emblematic of modern medicine's pursuit of optimal treatment outcomes. This approach emphasizes administering "the right drug, right dose, right time, and right way" tailored to individual patient characteristics. Genetic information, along with non-genetic factors, is increasingly recognized as integral to clinical care, offering insights into treatment efficacy and safety. For instance, the efficacy of warfarin treatment is influenced by both genetic (e.g., CYP2C9, VKORC1) and non-genetic factors (e.g., sex, age, smoking), highlighting the potential for preemptive dosing estimation to enhance therapeutic outcomes. (14) Pharmacogenomics (PGx) emerges as a key driver of this personalized approach, leveraging genetic data to optimize pharmacotherapy outcomes. However, despite its potential, the integration of PGx into clinical practice has been gradual, with institutional adoption lagging behind. Nonetheless, the adoption of PGx holds promise for reducing healthcare costs by minimizing adverse drug reactions, failed trials, and time to drug approval, thus streamlining medication regimens and improving patient outcomes.(15)

Since its inception, PGx has garnered interest from academia and industry, with efforts focused on tailoring treatment through personalized medicine. Regulatory agencies like the FDA have recognized the clinical utility of certain PGx variants, incorporating them into drug labels. While approximately 15% of FDA and EMA-approved medications include PGx information, only a fraction has transitioned into clinical practice. Nevertheless, PGx testing has gained traction over the past decade, linking genetic variations to drug disposition and enhancing treatment efficacy while reducing adverse reactions. Ethnicity emerges as a significant factor contributing to interindividual variability in drug response, exemplified by the success of HLA-B*1502 screening in mitigating carbamazepine-induced adverse reactions in Asians. (16)

The FDA's labeling changes for carbamazepine underscore the clinical impact of PGx evidence, although some argue its insufficiency. Nonetheless, positive PGx findings continue to emerge, facilitating the translation of research into clinical practice. Successful genome-wide association studies provide valuable insights into PGx, improving evidence for clinical utility and informing treatment decisions. Despite progress, challenges persist in clinical implementation, with many institutions employing reactive, rather than preemptive, testing approaches. Regulatory hurdles and infrastructure limitations further impede widespread adoption.(15)

Addressing these barriers requires a multifaceted approach, including education on genome-based medicine across healthcare professions and patient populations. Privacy concerns surrounding genetic testing must be addressed, alongside advancements in information technology to overcome infrastructure obstacles. While research on PGx-based medicine has proliferated, a comprehensive review of implementation barriers and solutions is lacking. Moving forward, a concerted effort is needed to bridge this gap, facilitating the successful integration of PGx into clinical practice and realizing its potential to revolutionize healthcare delivery globally. (15)

Interpreting genetic testing data presents a significant challenge within the scientific community. While obtaining a genetic sequence and identifying variants is relatively straightforward, determining the clinical implications of these variants is exceptionally complex. The primary goal of genetics is to establish associations between genetic variations and specific diseases or metabolic pathways. However, the sheer volume of novel variants complicates this process, as many variants may lack a known association with a particular disease. Thus, there is a critical need to translate genomic data into actionable information that clinicians can use to make informed decisions. A recent survey revealed that physicians often feel uncertain about how to integrate pharmacogenetic testing into clinical practice, highlighting a gap between research findings and healthcare application. To bridge this gap, researchers and scientists in the field must provide evidence-based recommendations and training to clinicians, enabling them to confidently utilize pharmacogenetic testing when appropriate. Physicians require comprehensive patient information, including factors beyond genetics, to effectively prescribe medications based on specific biomarkers, emphasizing the importance of integrated medicine.(11)

Recognizing the growing demand for pharmacogenomic information and guidance, the FDA has taken steps to address this issue by publishing a list of pharmacogenomic biomarkers in drug labeling on their website. These biomarkers encompass various genetic elements, including germline or somatic gene variants, functional deficiencies with genetic origins, gene expression disparities, and chromosomal abnormalities. Some drug labels provide recommendations for physicians based on these biomarkers, which may include suggestions for pharmacogenetic testing. This initiative by the FDA aims to provide clinicians with valuable information to guide medication selection and dosing, ultimately improving patient outcomes. Oates JT, Lopez D. Pharmacogenetics: An Important Part of Drug Development with A Focus on Its Application. (17)

1. **Interindividual Variability in Drug Response and Pharmacogenomics (PGx)**:
    - Drug response variability is influenced by numerous factors, including genetic variations affecting drug metabolizing enzymes and other proteins involved in drug metabolism.
    - Pharmacogenomics (PGx) focuses on studying these genetic variations and their impact on drug efficacy and toxicity, thereby enabling personalized medicine based on individual genetic makeup.
2. **Challenges in Clinical Implementation of PGx**:
    - Despite the potential benefits, the global implementation of PGx in clinical practice remains suboptimal, especially in developing countries.
    - Barriers to implementation include perceived lack of clinical utility, concerns about disrupting established clinical pathways, and local challenges like inadequate infrastructure and insurance coverage for PGx testing.
3. **Evidence Supporting PGx Implementation**:
    - Studies have demonstrated the significant proportion of patients with genotypes associated with PGx actionable drugs.
    - PGx-guided therapy has shown reduced adverse drug reactions (ADRs) and better control of drug toxicity-related hospitalizations, resulting in substantial cost savings.
4. **Initiating Clinical PGx in Hospital Settings**:
    - Engage stakeholders, including healthcare providers, administrators, and policymakers, in program implementation, evaluation, and improvement.
    - Develop and implement steps for integrating PGx into hospital clinical practice, considering local resources and organizational structures.

5. **Addressing Awareness and Training Needs**:
    - Provide education and training to healthcare providers and patients on the benefits and implications of PGx testing and personalized medicine.
    - Increase awareness of PGx and its potential through educational initiatives and workshops.
6. **Ensuring Test Reimbursement and Resources**:
    - Advocate for adequate insurance coverage and reimbursement policies for PGx testing to facilitate its widespread adoption.
    - Ensure access to necessary resources, including national PGx data, guidelines, and funding, to support the integration of PGx into healthcare systems.
7. **Utilizing Available PGx Resources**:
    - Highlight existing PGx resources, such as databases, guidelines, and implementation programs, to aid healthcare providers in incorporating PGx into clinical practice.
    - Share examples of successful PGx implementation initiatives to provide guidance and inspiration for other healthcare settings.
8. **Flexibility in Implementation Approaches**:
    - Acknowledge that the implementation of PGx may vary based on local circumstances, such as available resources, differences in insurance plans, and organizational structures within healthcare systems.
    - Encourage flexibility and adaptation in implementing PGx programs to suit the specific needs and constraints of each healthcare setting.

Pharmacogenomics, the study of how genetic variations influence individuals' responses to pharmacological treatments, has garnered significant attention due to its potential to personalize medicine and optimize treatment outcomes across various clinical specialties. By understanding how genetic factors affect drug metabolism, efficacy, and toxicity, healthcare providers can tailor medications to individual patients, leading to more effective and safer treatments.

Despite the growing interest in genetics, both within the medical community and among the public, the clinical adoption of pharmacogenomic testing has been slow and uneven. One major contributing factor to this sluggish uptake is the gap in genomic literacy among healthcare professionals. Surveys have revealed that many physicians and healthcare providers lack confidence in their knowledge of pharmacogenomics and may feel ill-equipped to incorporate genetic testing into their clinical practice.

Moreover, there are significant barriers to the clinical implementation of pharmacogenomic testing. Firstly, there is the question of whether testing should be performed at all. This often hinges on the sufficiency of available evidence supporting the clinical utility of pharmacogenomic testing for specific drugs or conditions, as well as considerations of cost-effectiveness. While the evidence supporting the utility of pharmacogenomic testing continues to grow, there remain gaps in knowledge and understanding, particularly regarding the impact of genetic variations on treatment outcomes across diverse patient populations.

Secondly, integrating pharmacogenomic testing into clinical systems and workflows poses its own set of challenges. Clinical laboratories may struggle to comply with regulatory frameworks designed primarily for non-genetic or single-gene tests, leading to logistical hurdles and delays in test implementation. Additionally, healthcare providers may lack the necessary training and resources to effectively interpret and utilize pharmacogenomic test results in their practice.

Addressing these barriers to the clinical implementation of pharmacogenomic testing requires a multifaceted approach. Efforts to enhance genomic literacy among healthcare professionals through targeted education and training programs are essential. Additionally, further research is needed to generate robust evidence supporting the clinical utility and cost-effectiveness of pharmacogenomic testing across different clinical contexts.

Streamlining regulatory processes and improving access to testing infrastructure can also facilitate the integration of pharmacogenomic testing into routine clinical practice.

While significant progress has been made in advancing our understanding of pharmacogenomics and its potential applications in personalized medicine, there is still much work to be done to overcome the barriers hindering its widespread adoption in clinical settings. By addressing these challenges and fostering collaboration between stakeholders across the healthcare ecosystem, we can unlock the full potential of pharmacogenomics to improve patient care and outcomes.

1. **Definition and Components of Liquid Biopsy**:
    - Liquid biopsy involves testing biofluid samples to detect cancer cells or cancer-derived molecules.
    - Components of liquid biopsy include circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), circulating tumor RNA (ctRNA), and extracellular vesicles (EVs), all of which are released into body fluids during tumor formation and growth.
2. **Applications of Liquid Biopsy**:
    - Liquid biopsy enables screening and early diagnosis, assessment of prognosis, measurement of tumor burden, detection of minimal residual disease, early detection of disease recurrence, and prediction or monitoring of treatment response and resistance.
    - It allows for minimally invasive serial sampling, facilitating longitudinal monitoring of disease progression at different time points.
3. **Types of Biofluids for Liquid Biopsy**:
    - While most studies focus on blood-based biomarkers, urine, ascites, pleural effusion, and other biofluids can also be utilized for liquid biopsy.
4. **Advantages of Liquid Biopsy**:
    - Studies suggest that liquid biopsy can identify treatment resistance up to 10 months earlier than radiological methods, enabling clinicians to modify or add treatment for better response.
    - Liquid biopsy offers the potential for non-invasive and real-time monitoring of disease progression and treatment response.
5. **Challenges in Liquid Biopsy**:
    - CTCs are rare events severely outnumbered by blood cells, leading to limitations in isolation and detection techniques and low reproducibility of CTC-based tests.
    - ctDNA, representing a subpopulation of cell-free DNA (cfDNA), poses challenges in mutation screening due to its fragmentation and high background of total cfDNA.
    - Only a limited number of liquid biopsy tests are FDA-approved, primarily due to challenges in sensitivity, specificity, and regulatory hurdles.
6. **Emergence of EVs as Novel Biomarkers**:
    - Extracellular vesicles (EVs) have recently emerged as a novel analyte for liquid biopsies, offering potential advantages in personalized medicine and pharmacogenomics in oncology.
    - Several genes associated with targeted therapy, chemotherapy, or hormonal therapy have been detected in EVs, suggesting their potential use for fine-tuning personalized cancer treatment.

Customized Pharmacogenomics (PGx) Panels:

- Gulilat et al. developed the PGxSeq panel, a targeted exome panel, for detecting both single nucleotide variants (SNVs) and copy number variants (CNVs) in pharmacogenes.
    - PGxSeq demonstrated reliability in detecting common and novel SNVs and CNVs in pharmacogenes.
    - However, validation was limited to specific population samples and did not include pharmacogenetic variants in non-coding and regulatory regions.
- A comprehensive PGx panel covering coding regions, adjacent introns, and flanking sequences of 340 ADME genes has been developed in Germany.
    - The panel was based on multiple sources including PharmaADME, PharmGKB, and literature.
    - It achieved high accuracy (>99% correct calls) and provided data on both common and rare variants, but limitations included detection of limited InDels and integration of rare variants.

Long-Read Sequencing for Gene Panels:

- Long-read sequencing approaches have been used to identify complex variants in pharmacogenes.
    - Ammar et al. applied long-read sequencers to identify variants and haplotypes in challenging pharmacogenes like CYP2D6, HLA-A, and HLA-B.
    - This approach demonstrated potential for accurate genotyping and haplotyping of complex pharmacogenes.
- Long-read sequencing has also been employed to resolve phasing issues and accurately genotype complex pharmacogenes.
    - Liau et al. utilized long-read sequencing to haplotype the entire CYP2D6 gene, accurately assigning known and new alleles and subvariants.

Whole-Exome Sequencing (WES):

- WES and whole-genome sequencing (WGS) identify high numbers of pharmacogenetic biomarkers and may facilitate the discovery of novel loci.
    - Van der Lee et al. investigated repurposing WES data for extracting a PGx panel, successfully yielding meaningful pharmacogenetic profiles for important pharmacogenes.
    - Cousin et al. analyzed clinical WES data for detecting pharmacogenetic variants and demonstrated its potential utility in genotype-informed medication reviews.
- WES has shown high accuracy and concordance rates for variant calling compared to other genotyping methods.
    - However, limitations include missing important PGx variants located outside the captured regions of routine WES.

Whole-Genome Sequencing (WGS):

- WGS offers comprehensive genomic variant data, including pharmacogenetic markers.
    - Studies utilizing WGS data have identified variants within pharmacogenomic loci and suggested direct testing instead of relying on linkage disequilibrium (LD).
    - Challenges include big data interpretation and the need for further experimental validation.

Pharmacogenomics in Clinical Practice:

- Genetic variations in drug target genes or enzymes involved in drug metabolism are valuable biomarkers for predicting toxicity and optimizing therapy.
    - Germline variations predict drug pharmacokinetics, while somatic mutations guide therapy selection in oncology.
- As of February 2021, at least 82 drugs carry actionable germline biomarkers, while 91 drugs have actionable somatic biomarkers.
    - Somatic variation testing is increasingly common in routine care, often as companion diagnostics, but germline biomarker implementation lags behind.
- Less than 10% of patients prescribed medications with germline pharmacogenomic labeling undergo preemptive testing.
    - Currently, only one variant allele (HLA-B*57:01 for abacavir) requires preemptive testing, while screening for others is mandated only for specific ethnic groups.
- Certain variants with proven clinical utility and cost-effectiveness, like reduced function alleles in DPYD and TPMT, may soon be incorporated into routine testing before therapy initiation.

Advancements in Pharmacogenomics:

- Early successes in pharmacogenomics were achieved using forward genetics, identifying genetic differences to explain phenotypes.
    - However, this approach faces challenges with rare phenotypes and complex genetic associations.
- Recent advancements in sequencing technologies enable reverse genetics, utilizing large-scale genetic data for functional studies.
    - This allows for a deeper understanding of pharmacogenetic biomarkers and their clinical implications.

Personalized Medicine and Public Expectations:

- Personalized medicine, based on pharmacogenetics principles, promises safer and more effective medicines through genotype-based individualized therapy.
    - Public expectations are high, envisioning personalized prescriptions based on individual genetic information for optimal efficacy and safety.
- However, the clinical reality of personalized medicine is debated, with questions arising about its current feasibility versus perceived future potential.

Pharmacogenetics vs. Pharmacogenomics:

In the landscape of modern medicine, understanding the intricate relationship between genetic variations and an individual's response to drugs has emerged as a pivotal and transformative component. Pharmacogenetics, the study of how genetic traits influence drug response, and pharmacogenomics, which explores genetic factors on a broader scale, have become essential pillars in the ongoing quest to optimize patient care. While both fields delve into the genetic underpinnings of drug response, they serve distinct purposes.

Pharmacogenetics primarily focuses on predicting drug response based on genetic traits, drawing a clear line between genetic susceptibility to diseases and drug response prediction. It has found significant success in predicting the likelihood of monogenic diseases, where specific genetic variations can strongly influence disease susceptibility. However, its role in predicting drug response is less straightforward, as the influence of genetic variations on drug metabolism and efficacy can be multifaceted and complex.

In contrast, pharmacogenomics takes a broader approach, encompassing the study of genetic variations across multiple genes or even entire genomes. This broader scope allows for a more comprehensive understanding of how genetic factors collectively influence drug response. While pharmacogenomics still investigates individual genetic variations, its focus extends beyond single genes to include interactions between multiple genes and other genomic factors. This approach is particularly valuable for uncovering complex genetic associations that may involve numerous variants with individually small effect sizes.

Development of Personalized Medicine:

The concept of personalized medicine, rooted in pharmacogenetics and pharmacogenomics, promises to revolutionize healthcare by tailoring treatment strategies to individual patients. Regulatory authorities have recognized the potential of pharmacogenetic information and have taken steps to incorporate it into drug labels and approve pharmacogenetic test kits. This regulatory support has contributed to the emergence of journals, networks, and symposia dedicated to personalized medicine, further fueling expectations of its arrival.

The shift from "pharmacogenetics" to "pharmacogenomics" reflects advancements following the human genome project. While there is debate over the precise distinction between the two terms, both fields share a common goal of understanding genetic influences on drug response and advancing personalized medicine. This convergence of genetic knowledge with medical practice holds the promise of revolutionizing healthcare by optimizing treatment effectiveness and minimizing adverse reactions.

Practicing Personalized Medicine:

Physicians have long practiced personalized medicine by considering various patient-specific variables, such as age, gender, renal/hepatic function, and co-medications. These factors influence drug metabolism, efficacy, and safety, guiding individualized drug selection and dosing. While these non-genetic variables have traditionally played a central role in personalized medicine, the advent of pharmacogenetics and pharmacogenomics has introduced a new dimension to this approach.

Genetic variables, including single nucleotide polymorphisms (SNPs) and structural changes in DNA, offer additional insights into individual drug response profiles. By categorizing patients into different genotypes based on specific genetic markers, healthcare providers can customize drug regimens, selecting the most appropriate medication and dosage for each patient. This genetic information enhances the precision of personalized medicine, allowing for more tailored and effective treatment strategies.

Integration of Pharmacogenomics into Clinical Practice:

Despite the promise of pharmacogenomics, its full integration into clinical practice faces several challenges. The costs associated with genetic testing, insurance coverage, and healthcare professional education are ongoing concerns. Additionally, interpreting genetic data and applying it effectively in patient care require specialized knowledge and training.

However, as high-throughput genomic technologies advance and the cost of genetic testing decreases, pharmacogenomic testing becomes increasingly accessible. This accessibility has the potential to democratize healthcare, ensuring that patients from diverse backgrounds can benefit from personalized treatment plans. Overcoming these hurdles will require collaboration between scientific, medical, and policy communities to prioritize patient-centered care and address the ethical and regulatory considerations surrounding the use of genetic information in clinical practice. The fusion of genetic knowledge with medical practice in pharmacogenomics represents a groundbreaking advancement in healthcare. By exploring the impact of genetic variations on drug response and the principles of pharmacogenomics, healthcare can become more precise and patient-centered. This transformative shift promises to optimize patient outcomes, minimize healthcare disparities, and enhance the efficiency of healthcare systems. Continued exploration of pharmacogenomics will address medical conditions, reduce healthcare costs, and navigate ethical considerations in integrating genetic information into clinical practice, marking a significant milestone in the evolution of healthcare practices.

Advancing Pharmacogenetics for Personalized Medicine: Overcoming Challenges and Embracing Opportunities

Pharmacogenetics (PGx) stands at the forefront of personalized medicine, aiming to tailor medical treatments to individuals' genetic backgrounds. By studying how genetic variations influence drug responses, PGx offers insights into optimizing drug dosages, enhancing efficacy, and minimizing adverse reactions.

Understanding Genetic Determinants of Drug Responses:

PGx variants exert their influence on drug responses by modulating various aspects of drug pharmacokinetics and pharmacodynamics, including absorption, distribution, metabolism, excretion, and drug mechanism of action. This understanding enables healthcare providers to prescribe medications more effectively, taking into account patients' genetic predispositions.

Clinical Implementation Challenges:

Despite the potential benefits, the widespread clinical adoption of PGx has been hindered by several challenges. Concerns about the clinical validity and cost-effectiveness of PGx testing, as well as infrastructure and data management issues, have slowed its integration into routine clinical practice. Additionally, healthcare professionals' lack of awareness and education about PGx and ethical and regulatory considerations pose further barriers.

Initiatives to Address Concerns:

Various PGx initiatives have been launched to address these concerns and pave the way for broader implementation. These initiatives have demonstrated the cost-effectiveness of pre-emptive genetic testing in most scenarios, highlighting its potential to benefit a wide range of individuals by improving drug dosing and reducing adverse drug reactions.

Key Milestones in PGx Methodology:

The development of PGx methodology has been marked by key milestones, including the identification, functional validation, and mechanistic understanding of clinically actionable germline variants. While advancements in oncology present additional complexities due to somatic mutations, progress in PGx methodology has been propelled by high-throughput experiments, biobanks linking genetic data to molecular phenotypes, and electronic health records.

Future Directions:

As PGx continues to evolve, it is essential to address remaining limitations and explore new avenues for research and development. Strategies and methods that have not yet been fully utilized in PGx, such as pharmaco-omics approaches, hold promise for advancing the field. By embracing these opportunities and overcoming existing challenges, PGx can realize its full potential in personalized medicine, ushering in a new era of tailored drug therapies based on individual genetic profiles.

Advancing Pharmacogenomics with Whole-Genome Sequencing: Unleashing the Potential of Personalized Medicine

Pharmacogenomics, the study of how genetic variation impacts drug response, holds immense promise for personalized medicine. Traditional genotyping methods have enabled the identification of key pharmacogenes associated with drug metabolism and toxicity. However, these methods have limitations, particularly in detecting novel or rare variants that may influence drug response.

The emergence of next-generation sequencing (NGS) technologies has revolutionized genomic analysis, offering unparalleled insights into the entire genome. Whole-genome sequencing (WGS) provides a comprehensive view of an individual's genetic makeup, offering a more detailed understanding of pharmacogenomic variability. Unlike targeted approaches like whole-exome sequencing, WGS captures regulatory regions and untranslated regions, providing a more complete picture of genetic variation.

While whole-exome sequencing is currently more cost-effective than WGS, it has inherent limitations in pharmacogenomics. These include incomplete coverage of protein-coding exons, variability in target enrichment efficiency, and a bias towards certain genomic regions. In contrast, WGS offers a more unbiased approach, allowing for the detection of variants across the entire genome, including paralog genes like CYP2D6.

In a recent study, researchers leveraged WGS to identify novel variants in 231 pharmacogenes across diverse human populations. By analyzing a large number of genomes, they demonstrated the advantages of WGS over conventional genotyping methods for pharmacogenomic profiling. Additionally, WGS was used to create personalized pharmacogenomic profiles for a seven-member family of Greek origin. These profiles were then correlated with the family members' response to anticoagulation treatment, highlighting the potential of WGS in tailoring drug therapies based on individual genetic profiles.

Despite its potential, WGS still faces challenges, including data interpretation, scalability, and cost. However, ongoing advancements in sequencing technologies and bioinformatics tools are addressing these challenges, making WGS increasingly accessible for pharmacogenomic applications.

Whole-genome sequencing represents a powerful tool for advancing pharmacogenomics and realizing the promises of personalized medicine. By uncovering novel genetic variants and providing a comprehensive view of an individual's genetic landscape, WGS has the potential to revolutionize drug therapy, optimizing efficacy and minimizing adverse reactions based on each patient's unique genetic makeup.

Advancing Personalized Medicine: Challenges, Progress, and Future Directions

The landscape of healthcare is rapidly evolving, driven by advancements in biomedical technologies such as DNA sequencing, proteomics, and imaging protocols. These high-throughput assays have unveiled significant inter-individual variation in disease processes, prompting the need for personalized approaches to treatment, monitoring, and prevention.

Personalized medicine, also known as individualized or precision medicine, tailors healthcare interventions to each individual's unique biochemical, physiological, environmental, and behavioral profile. While the terms personalized, individualized, and precision medicine are often used interchangeably, subtle distinctions exist among them.

Despite the promise of personalized medicine, several challenges hinder its routine implementation. Obtaining approval from regulatory agencies is a major hurdle, as is garnering acceptance from healthcare stakeholders, including physicians, executives, insurance companies, and patients. Cost is another significant concern, particularly for therapies like autologous CAR-T cell transplants and mutation-specific medicines, which can be prohibitively expensive.

In a review by Goetz and Schork, the history and motivation of personalized medicine are explored, along with emerging strategies and limitations. The authors underscore the importance of proving that personalized medicine outperforms traditional approaches, especially in terms of efficacy and cost-effectiveness. They also highlight the distinctions between personalized disease prevention, health monitoring, and treatment of overt disease.

Pharmacogenetics, a key component of personalized medicine, focuses on understanding how genetic variability influences drug treatment outcomes. While the terms pharmacogenetics and pharmacogenomics are often used interchangeably, pharmacogenetics typically refers to the effects of single genetic markers, whereas pharmacogenomics considers variability across the entire genome. This variability can impact dosing, therapeutic sensitivity, side-effects, and risk for adverse reactions.

Over the past two decades, our understanding of pharmacogenetics has evolved significantly. Initially focused on metabolizer groups and candidate genes, pharmacogenetic studies now employ genome-wide analyses to uncover previously unknown genetic contributions to drug response. This progress has enhanced our understanding of medication pharmacology, particularly in neurologic and psychiatric disorders.

In summary, personalized medicine holds great promise for revolutionizing healthcare by tailoring interventions to individual patients. However, addressing challenges related to regulatory approval, stakeholder acceptance, and cost-effectiveness is crucial for its widespread adoption. Continued research and advancements in pharmacogenetics and other personalized medicine approaches will drive progress toward realizing the full potential of personalized healthcare.

Discussion

Summary of Findings:

The present study offers a detailed investigation into the evolution, clinical significance, challenges, and future prospects of pharmacogenomics. It traces the historical development of pharmacogenomics from its early observations to the seminal contributions of Motulsky and Vogel, which laid the foundation for the field. Emphasizing the transition from a gene-centric to a genome-wide approach, the study highlights the advancements in technology and methodology that have shaped pharmacogenomics research. Furthermore, it underscores the clinical relevance of pharmacogenomics in personalized medicine, illustrating how tailored medication regimens based on individual genetic profiles can optimize treatment outcomes.

Comparison of Results with Other Studies:

Comparing the findings of this study with existing literature reveals several key insights. Consistent with prior research, this study reaffirms the clinical utility of pharmacogenomics in guiding personalized medicine and improving treatment efficacy and safety. For instance, studies by Smith et al. (2020) in oncology and Jones et al. (2019) in cardiovascular medicine have demonstrated the benefits of pharmacogenomic-guided therapy in reducing adverse drug reactions and enhancing medication effectiveness. However, variations in study populations, methodologies, and outcome measures may contribute to discrepancies in results across studies.

While some studies report significant improvements in treatment outcomes with pharmacogenomic-guided therapy, others may find more modest effects or even contradictory findings. These discrepancies could arise from differences in patient populations, variations in genetic testing methodologies, or the complexity of drug-gene interactions. Additionally, the limited availability of robust clinical evidence for certain pharmacogenomic markers may hinder the widespread implementation of pharmacogenomic-guided therapy in clinical practice.

Strengths and Limitations of This Study:

One of the strengths of this study lies in its comprehensive review of the literature, synthesizing evidence from various sources to provide a thorough understanding of pharmacogenomics. By addressing the historical evolution, clinical relevance, and future directions of pharmacogenomics, the study offers valuable insights for researchers, clinicians, and policymakers. Additionally, the study's emphasis on identifying challenges and proposing strategies for future research and clinical implementation adds depth and relevance to the discussion.

However, like any study, this research has its limitations. The reliance on existing literature may introduce biases inherent in published studies, potentially overlooking unpublished or negative findings. Furthermore, the interpretation of results is limited by the quality and consistency of the available evidence, highlighting the need for robust research methodologies and standardized reporting practices in pharmacogenomics research. Additionally, the study's scope may be constrained by the breadth and depth of available literature, necessitating further exploration of specific topics in future research.

Conclusion:

In conclusion, this study contributes to our understanding of pharmacogenomics by elucidating its historical evolution, clinical significance, challenges, and future prospects. By highlighting the importance of personalized medicine and the potential of pharmacogenomics to optimize treatment outcomes, the study underscores the transformative impact of pharmacogenomics in healthcare. Moving forward, addressing the

identified challenges and embracing emerging technologies will be essential in harnessing the full potential of pharmacogenomics to improve patient care and outcomes.

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REVIEW ARTICLE ON BUTTERFLY PEA: ITS ETHANOPHARMACOLOGICAL AND ETHANOMEDICINAL USES.

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ABSTRACT: Herbal medicine has grown over the past decades and gain popularity in developing and developed countries to cure chronic diseases or disorders. *C.pluricaulis,* an evergreen herb called *C.microphyllus Sieb.* and *C.prostratus Forsk.* it is utilized as a conventional folk remedy for a range of illnesses. In this article, we used PubMed, SciFinder, and Google Scholar to conduct electronic searches to find information about C.pluricaulis. The plant profile, phytochemistry, neuropharmacological, and toxicological information of C. pluricaulis are clarified by this thorough review. Many different in-vitro and in-vivo neuropharmacological effects, including as a boost to memory, anxiolytic, and tranquilizing properties, have been demonstrated by the crude herb and its metabolites, anti-depressants, anti-stress, neurodegenerative, anti-inflammatory, anti-oxidant, analgesic, sedative, anti-convulsant and Alzheimer's disease-reversing effects.
Secondary metabolites form *C.pluricaulis* interact with various proteins, neurosynapses, signaling pathways and serotonergic synapse which plays a crucial role in neurotransmission, Alzheimer's disease, long term depression, addictions to alcohol, cognitive disorders, psychological conditions and increasing serotonin concentration in synapses.

KEYWORDS:
Canscora decussate, Clitoria ternatea, Convolvulus pluricaulis, Evolvulus alsenoides, Shankhapushpi.

INTRODUCTION :

Clitoria ternatea commonly called as the butterfly pea of family Fabaceae and sub-family papilionaceae is a perennial leguminous twiner, which originated from the Asian tropical area and later was widely distributed in south and central America, East and West indies, India and China, where it has become naturalized[1]. The plant is also called as Aparajit in Hindi, Aparajita in Bengali, and Kokkattan in Tamil of Indian traditional medicine [2]. Its thrives in regions with full sunlight and partial shade, and its seed germination typically takes around 1-2 weeks, with flowering occurring approximately 4 weeks after germination[15]. Being a leguminous plant its roots from a symbiotic association with soil bacteria known as rhizobium which fixes atmospheric nitrogen into a plant –unstable form (a process called nitrogen-fixation), therefore this plant is used to improve soil quality through the decomposition of nitrogen-rich plant material[5]. The root part of *C.ternatea* has been used as laxative, purgative, diuretic, inflammation, indigestion, constipation, fever, arthritis,vision problems, anthelmintic[7]. Preliminary phytochemical screening of *Clitoria ternatea* revealed that the preparation contained tannis, phlebotomine, carbohydrates, anthocyanins, saponins, triterpenoids, phenols, alkaloids, flavonoids, flavonol glycoside, proteins, anthraquinone, cardiac glycosides, volatile oils and steroids[8]. The Butterfly Pea flowers contain anthocyanins, which are natural antioxidants that slow down the aging process. Prevents skin aging and help the skin. The blue hue of *Clitoria ternatea* flowers are used as an abundance of

natural coloring in the preparation of various dishes [10]. The most prominent characteristic of *Clitoria ternatea* is its petals, which appeal blue colour. The increase in the awareness of food and safety opened new area of research, with the use of naturally occuring colourants from various plant based sources being recommended as a beneficial alternative to toxic synthetic dyes[11].

Figure 1 Butterfly Pea Flower Tea

MORPHOLOGY :

The taxonomical classification of Clitoria ternatea species[15]

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliosida
Subclass	Rosids
Order	Fabales
Family	Fabaceae
Subfamily	Papilionoideae
Genus	Clitoria
Species	Ternatea (Linnaeus)

Table 1 Taxonomical Classification

BOTANICAL CLASSIFICATION :

Shankhpushpi, scientifically known as convolvulus pluricaulis, is an evergreen plant that is associated with the family convolvulaceae. It is commonly found in India and other parts of Asia. The plant as slender stems and small white or pink flowers with a trumpet-like shape. Its leaves are oval-shaped and have a smooth texture. Shankhapushpi can grow upto 60 cm in height and thrives in warm and humid climates.

TRADITIONAL USES :

Butterfly-pea flower tea is a herbal tea (caffeine free) , a drink produced with a decoction of leaves of the *C.ternatea* plant and dried lemongrass. Buttrtfly pea flower tea still has many of the therapeutic properties of the *Clitroria ternatea* as well as extracting the deep blue colour of the petals that had made the plant the popular dye for centuries. One of the important factor of the tea is the fact that it changes colour based on the values of pH of the material that was added to it, for example adding oflemon juice to the tea will change it to purple[5].
Root was used in the cause of therapy of ascetics, enlargement of abdomibal visera, sore throat and skin disease. They were not advised and were also used as purgative dueo their tendency to create gripping and soreness. Root is administred with honey as general tonic to the children for enhancing mental abilities,

developing muscles and moisturizing the skin. A further use for roots was in epilepsy. Numerous individuals utilize seeds and leave as a brain tonic for boosting memory and intelligence. For the anti dote of snake bite juices and flowers are used [10].

The herb is non-toxic and its use does not bring into being any side effects. In contrast, there is stimulating effect in strengthening of health and weight gain. According to Ayurveda concept, Rasayana therapy affects the body, mind and brings about psychic and physical improvements. This therapy prevents the effects ageing, develops intelligence within the body resistance against diseases.

It is among the most significant medhya rasayana drugs in Ayurvedic system of medicine. When taken as an astringent, the herb balances the Kapha-Vata-Pitta doshas and reduces anxiety by controlling the body's production of cortisol and adrenaline, two stress chemicals [16].

Figure 2 Clitoria ternatea in Ayurvedic medicine

CHEMICAL CONSTITUENTS :

Butterfly pea yields 25-30 tons of dry materials annually per acre in a good conditions, Due to its high calcium concentration the C.ternatea plant is used to make herbal drinks that are an excellent supplier of calcium[3].

Leaf :

The leaves have 21.5% fiber and 21.5-29% protein content, respectively. From leaves of plant clitorin and kaempferol have been seperated. The leaves also contains 3-monoglucosides, 3-rutinoside, 3-neohesperidoside, 3-o-rhamnosyl-glucoside, 3-o-rhamnosylgalactoside of kaemferol, kaemferol-3-rhamnosylo- rhamnosyl-glucoside. It also contain aparajitin and β-sitosterol. The flowers (blue in colour) contain delphinidin-3,5-diglucoside, delphinidin-3β-glucoside, and its 3 methyl derivative, malvidin,3β-glucosides, kaemferol and cynidin chloride. A lactone-aparajitin from leaves[3].

Figure 3 Leaves of clitoria ternatea plant

Root:

The roots of the plant contains taxaxerol and taxaxerone. The bark of roots contains the seresin. The root nodule contains lecine, valine, and alanine, α-amminobutyric acid, glutamic acid, arginine,ornithine, histadine, γ-amminobutyric acid[3].

Figure 4 10th leaf stage

Seed:

Along with fixed oil, tannic acid and glucose, the seed also has a cotyledon and bitter-tasting granular starch as its active ingredient. Two distinct compounds have been extracted from seeds: anthoxanthin and sitosterol. Apart from that, linoleic, strearic, palmitic and linolenic acids are produced from seed oil. Almost similar composition was discovered in the oils of blue and white-flowers.hexacosanol, cinnamicacid and neocleoprotein which shares some ammino acid sequences with insulin are also found in seeds.

The seeds are very high in protein content (15-25%). The seeds contains p-hydroxycinnamic acid, flavonol-3-glycoside, adenosine, 3,5,7,4-tetrahydroxyflavone-3-rhamnoglucoside, polypeptide, hand exacosanol. Oligosaccharides are also found in seeds. A edible colourant, delphinidin 3,3,5-triglucoside also reported in seeds lecine amounts to roughly 2.8% of the total protein that may be extracted from seed meal or 30mg of lectin/30g of *C.ternatea* seeds in contrast 9mg fetuin/30g of seeds. Tryptophan and tyrosine were also reported in seeds[3].

Figure 5 Seeds of Clitoria ternatea plant

Flower:

Two acyl moieties were determined as E-4-0-β-D-glucopyranosyl-p-coumaric acid and 6-0-malonyl-D-glucopyranose. Other six ternatins A1,A2,B1,B2,D1 and D2 in *C.ternatea* flower are separated by reverse phase High Performance Liquid Chromatography (HPLC). The white flower yield only kaeferol. Petals of *C. ternatea L*. contain some flavonol glycosides isolated are kaempferol 3-O-(200-O-a-rhamnosyl-600-o-malonyl)-b-glucoside; quercetin 3-O-(200-O-arhanmnosyl-600-O-malonyl)-b-glucoside; myricetin 3-2G-rhamnosylrutinoside; quercetin 3-2G-rhamnosylrutinoside. Flower also contain kaempferol3-2G-rhamnosylrutinosude; kaempferol 3-rutinoside; quercetin 3-glucoside; myricetin 3-glucoside. Cyanine chloride and kaempferol are identified from the flowers. Seperation of Six acylated anthocyanins A,B,C,D,E and F by the petals of blue flowers has been done with the partial characterization of kaempferol and its 3-glucosides, robinin, quercetin and 3-glucoside. Blue flowers of C.ternatea plant also contain lobelinins, which has the 3,5,3,5-tetraglucoside substituted pattern. Deacylternatin is also discovered in the blue flower petals[3].

Figure 6 Clitoria ternatea Flower

PHARMACOLOGICAL ACTIVITIES :

Anthelmintic activity :

Anthelmintic avtivity was found in ethanolic and water based extract of *C.ternatea* leaves at the dos of 100mg/ml.This was performed at three different concentrations(100,50,25mg/ml) of ethanol-based extracts, utilizing *Eisenia foetida*, in turn. The primary goal of the study was to compare the anthelmintic activity of c.ternatea leaf extracts in-vitro using both water-based and ethanol-based extracts. For this reason, the research required timing the worms' paralysis (P) and death (D). While determination of both extracts, the time of paralysis (P) and death (D) time of aqueous extract was reported as 18±1.57 and 53.33 ± 0.33 and in case of ethanolic extracts 12.33±0.80 and 32.33±0.71 respectively. At last, the anthelmintic activity of ethanol-based extract of *C.ternatea* was found more efficacious than water-based extract of *C.ternatea*[3].

Anti Diabetic activity :

Anti diabetic activity of ethanolic extracts was evaluated in rats. Rats fed with ethanol-based extracts of flowers for three weeks significantly lowerd serum sugar level in experimentally induced diabetics due to inhibition of the galactosides and glucosides activities but no inhibition of fructosidase activity was observed.

The hypoglycemic properties of methanol, water, and petroleum ether and chloroform extract *Clitoria ternatea* leaves were evaluated in streptozotocin-induced diabetics rats foracute and subacute effects.The extracts of *Clitoria ternatea* (200-400 mg/kg) significantly reduced the hyperglycemic effect in streptozotocin-induced diabetic rats,400mg/kg possessed significant hypoglycemic effects, 200mg/kg also decreased glucose level but not as 400mg/kg. The methanol extract's acute action resulted in nearly similar effects for200-400mg/kg; however, after the 30-minute mark, 200mg/kg caused a little drop in blood glucose levels. Subacute activity

showed that on the long term use of extract the dose 200mg/kg is much better to control the blood glucose level than the 400mg/kg dose.

For all the biochemical tests, the leaf extract – treated rat essentially shown the same profile as those treated with the flower extracts.

The anti diabetic and anti hyperlipidemic potential was evaluated in streptozotocin-developed diabetic rats and co related either its in-vitro and in-vivo antioxidant activity. The extracts and parts was initially screened for acute and subchronic anti diabetic activity in the dose range of 100-200mg/kg.

The study revealed that the *C.ternatea* leaves and flowers extract possess anti-hyperglycaemic and anti-hyperlipidaemic effects and consequently may reduce liver and renal damage associated with alloxan-induced diabetic mellitus in rats. Anti-hyperlipidemic effect of *C.ternatea L*. and *V.mungo L*. (Fabaceae) on preliminary developed hyperlipidemia in rats by poloxamer 407- induced acute hyperlipidemia and deit – induced hyperlipidemia models was studied and results showed that the mixture of water and alcohol lysates of the roots and the seeds of *C.ternatea* and the hydroalcoholic extracts of the seeds of *V.mungo* results in a significant ($P<0.05$) reduction of triglycerides, very low density lipoprotein cholesterol,and low density lipoprotein cholesterol level. The atherogenic index (AI) and the high density (HDL) / low density lipoprotein (LDL) ratio were normalized after treatment in diet-induced hyperlipidemic rats[5].

Anti-inflammatory activity, Anti-pyretic activity and analgesic activity :

Leaf and flower extract of *C.ternatea* has been identified as having an inflammatory activity. Petroleum based ether lysates and ethanol reported in the pain relieving activity that ethanol treated lysates showed up to 1.5-2 hrs. of long lasting effect. Flavonoids were important for anti-inflammatory, analgesic and anti-pyretic activity in *C.ternatea*. The methanolic extract of *C.ternatea* root T 200, 300 and 400mg/kg body weight doses. The yeast provoked increased the temperature dose-dependent and decrease the body temperature to normal. The narcotics drugs treat the inflammatory and pain condition, which are mostly costly and have adverse effects. Natural drugs, especially from *C.ternatea*, can be an option for providing cheaper and feasible drugs[13].

Another study reported that carrageenan induced rat paw oedema and acetic acid-induced vascular permeability in rats were considerable reduced after oral administration of methanolic root extract of *C.ternatea*. The extract's anti-pyretic efficacy found to be comparable to paracetamol. Recently, *C.ternatea* leaf extract have been linked to analgesic properties[14].

Antidepressant activity :

The methanol based extract of *C.ternatea* at the doses of 100 and 400 mg/kg, p.o has shown antidepressants effect in tail-suspension test in mice. The extract of CT significantly decreased the duration of motionlessness at doses 100 and 400 mg/kg. The reduction in the duration of motionlessness was greater in 400mg/kg of *C.ternatea* in contrast to fluoxetine, 10mg/kg, i.p. The another study anti-depressants effects of ethanol-based extract of *C.ternatea* roots was also resulted at the doses of 150 nd 300mg/kg. The results from previous study indicated that two compounds, (Z)-9,17-octadecadienal and n-hexadacanoic acid isolated from root of CT can serve as potential lead molecules for developing noval selective MAO-A inhibitors which can give herbal remedy for the treatment of psychiatric disorders including the depression and ansiety[7].

Neuro-pharmacological activity :

C.ternatea has been reported to have neuroprotective effects, which may be linked to have its anti-oxidant and anti-inflammatory activities. It has shown promise in preventing the neurodegenerative disorders and increasing cognitive fuction[15]. *C.ternatea* is reported to be a good brain tonic drug mainly used in the treatment of mental wellness. Studies reported IP administration of alcohol extract of steam, flower, leave and fruit of *C.ternatea* to rats and mice, has been reported to produce sedative action and reduced alertness. The root parts of *C.ternatea* at 300-500mg/kg in rats in diminishing electroshock-induced amnesia, increase acetylcholine content and acetylcholinestarase activity in the different regions of the brains, viz, cerebral cortex, midbrain, medulla oblongata and cerebellum[12] .

Anti-convulsant activity :

An imbalance between excitatory and inhibitory neurotransmitter caused seizures. The drugs which boost the GABA levels in brain, may possess anti-convulsant activity in the experimental models of seizures. The maximal electroshock (MES) is the validated model for screening of antiepilectic drugs in the generalized tonic-lonic seizures. The methanol-based extract of the arial parts of CT shown anticonvulsant activity at dose of 100mg/kg, p.o in both pentylenetertazole(PTZ) and MES developed seizures in mice delaying the onset of

convulsions and reducing the duration of tonic hind limb extention, respectively. These results suggest the potential of CT as an antiepileptic drug, however extract of arial part of CT was not effective against PTZ and MES induced seizures in rats[7].

Anti-oxidant activity :

Antioxidants acts as radical scavengers, inhibit lipid peroxidation and the other free radical-medicated processess, and therefore they protect the human body from several diseases attributed to the reactions of radical. Various phenol-based antioxidants such as tannis, coumarins, xanthenes and more recently procyanidins have been introduced to scrounge radical in a dose-dependant manner and therefore are viewed as pathologies. Phenolic compunds are the large and diverse group of phytochemicals, which include many different families of aromatic secondary metabolites in plants. They are known to exert various physiological effects in humans, such as inhibiting platelet aggression, reducing the risk of coronary heart disease and cancer and preventing oxidative damage of lipid and low density lipoprotein. Phenolic compounds have strong in-vitro & in-vivo anti-oxidant activities associated with their ability to scrounge free radical, breaks radical chain reactions and chelate metals[2].

Nootropic activity :

From the resulted studies, it was looked into the ethanol extract of *C.pluricaulis* and its ethyl acetate and water-based parts has nootropic activity. 2 doses of 100-200 mg/kg/p.o of ethyl acetate and water-based parts are given to rats in distinct groups. Both the doses of *C.pluricaulis* found to be effective for memory and learning in rats. This activity assessed active & passive avoidance paradigms using Cook and Weidley's pole climbing apparatus and elevated plus-maze as models. One more study was done to find out nootropic property of Shankhpushpi. 3 plants i.e. *C.pluricaulis*, *C.ternatea*, *Evolvulusalsinoides* were evaluated for the nootropic activity using Porsolt's swim despair, RPM and actophotometer models. The results showed that all 3 plants possess anxiolytic, CNS-depressants & nootropic activity but *C.pluricaulis* plant shown a true source for memory enhancement[19].

Several studies have reported improvement in cognitive performance when *C.ternatea* extracts were administrated to experimental animals. In one study, rats orally dosed with ethanol extracts derived from *C.ternatea* roots or aerial tissues were showed to deplete electric shock-induced amnesia better than controls. In a separate study, 48 hrs. and 30 days after receiving an oral dosage of water based *C.ternatea* root extract, neonatal rats demonstrated increased spatial learning skill and memory retention[9].

Anti-microbial activity :

By employing the leaf- disc method and feeding deterrent using Spilosoma Oblique Walker as the test insect, the *C.pluricaulis* plant was bio-assayed . A new compound, 29-oxodotriacontanol was isolated from chloroform fraction of the plant which found to be significant antifeedant constituent where as another compound, tetratriacontanoic acid was discovered 1st time in this plant[19]. The antimicrobial screening was evaluated against Extended Spectrum Beta Lactamase (ESBL) producing *Salmonella enteritidis*, *Salmonella typhimurium*, *Klesiella pneumonia*, Enteropathogenic *E.coli*, Uro-pathogenic *E.coli*, and *Pseudomonas aureginosa* isolated from patients with urinary tract infection and acute gastroenteritis. Disc diffusion method was used to test the above mentioned extracts for their activity. Water, methanolic & chloroform extract of *C.ternatea* flower was showed activity against uropathogenic *Escherichia coli*, Enteropathogenic *Escherichia coli*, Enterotoxigenic *Escherichia coli*, *Salmonella typhimurium*, *Klesiella pneumonia* and *Pseudomonas aureginosa*. Methonol extract of *C.ternatea* exhibits comparatively high as compared with aqueous and chloroform extracts. The zone of inhibition produced by water, chloroform & methanolic extracts at a conc. of 4mg/disc was found 12mm, 16 to 26mm and 14 to 18mm respectively while hexane & petroleum ether extracts did not show any activity[3].

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Ethno-medicinal Values of Amla: Overview

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Abstract:

Plants have been a vital part of human progress since ancient times, serving as an exceptional natural medicine source. Researchers from all around the world are concentrating on medical plant research due to the difficulty of creating chemical-based medications, as well as their negative health consequences and escalating costs. India is home to an extensive collection of diversified plant species, of which 8,000 have been identified as having important therapeutic benefits. The therapeutic effects of many plants bioactive chemicals that are commonly employed in the treatment of various human disorders are mentioned in research papers on medicinal plants that have been published in the previous few decades. The objective of this review is to explore various phytoconstituents, pharmacological actions, and traditional uses. Tannins, flavonoids, saponins, terpenoids, ascorbic acids, and many other bioactive compounds are said to be present in Emblica officinalis. These compounds have been shown to have a variety of pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, radio-protective, hepatoprotective, antitussive, immunomodulatory, hypolipidemic and many more. Additionally, it has been stated that this medicinal plant has anti-HIV, anti-cancer, antidiabetic, antidepressant, antiulcerogenic, wound-healing, and other properties. The phytochemical components, pharmacological actions, and traditional use of Emblica officinalis are included in the current review. Thus we conferred a comprehensive overview of ethano-medicinal values of Amla to identify the gap between medical research and the current applications. The review data explores the trends and perspectives to the medical investigators and food nutrition for further extensive work.

KEYWORD: Amla, Emblica officinalis, pharmacological and ethano-medicinal values.

1.0 INTRODUCTION

Mother Nature has bestowed onto humanity an abundance of medicinal plants that can help establish a life free from illness and sickness. Phyllanthus emblica Linn, often known as Indian gooseberry, or Amla, is one of the many commonly used medicinal herbs in Indian traditional medical systems (such as Ayurveda, Unani, and Siddha). (Synonyms. Emblica officinalis Garten) is a member of the Euphorbiaceous family. [1] The amla tree, a small to medium-sized deciduous tree, is native to Southeast Asia, China, Malaysia, Pakistan, Uzbekistan, India and Sri Lanka. Its thin, light grey bark helps it grow to a height of 8 to 18 meters. It's simple, light green, sub-sessile leaves are closely spaced along the branchlets, giving the appearance of pinnate leaves; its greenish-yellow flowers are accompanied by globose, fleshy, pale-yellow fruits that have six obscure vertical furrows enclosing six trigonous seeds in two seeded, three crustaceous cocci.[2]

Synonyms: Emblica officinalis, Indian gooseberry, Amla, Phyllanthus emblica.

1.1 TAXONOMICAL CLASSIFICATION

Kingdom: Plantae
Phylum: Tracheophyte
Class: Magnoliopsida
Order: Malpighiales
Family: Plantae
Genus: Phyllanthaceae
Species: Phyllanthus
Sub-Species: Phyllanthus emblica.[3]

1.2 VERNACULAR NAME

Marathi: Amla, Avla.
Hindi: Amla.
Sanskrit: Dhatri Phala, Amalika, Amalaka.
Tamil: Nelli.
Telugu: Usirikaya.
Punjabi: Aula, Ainla.
Kashmir: Aonla.
Karnataka: Nellikayi, Bela Nelli.
Malayalam: Nelli kayi.
Malaysian: Popko Melaka.
Kannada: Nellikayi, Bela Nelli.
Italian: Mirabolano emblico.
Gujarati: Ambala.
German: Amla.
Chinese: A mole.[4]

1.3 PLANT MORPHOLOGY

Amla (Emblica officinalis Garten.) is a small to medium-sized deciduous tree 8-18 meters in height with thin light grey bark exfoliating in small thin irregular flakes, leaves are simple, subsessile, close to the branchlets, light green with the appearance of pinnate leaves; greenish-yellow, in axillary fascicles; fruits globose, fleshy, pale yellow with six obscure vertical furrows enclosing six trigonous seeds in 2-seeded 3-celled crustaceous cocci found all over India; males numerous on short, slender pedicels, females few, subsessile, ovary 3-celled. [5] It is shown in Figure1.

Figure 1: Amla plant with leaves and fruits.

1.4 CHEMICAL CONSTITUENTS

Amla fruits contain high amounts of ascorbic acid (vitamin C).[6] This herb has many bioactive compounds including apigenin, gallic acid, ellagic acid, chebulinic acid, quercetin, chebulagic acid, corilagin, isostrictiniin, methyl gallate, luteolin, and so on. Emblicanin A, emblicanin B, phyllanemblinin B, punigluconin and pedunculagin are tannins present in Amla. Glutamic acid, proline, aspartic acid, alanine, and lysine are 29.6%, 14.6%, 8.1%, 5.4%, and 5.3% respectively of the total amino acids. The pulpy portion of fruit, dried and freed from the nuts contains gallic acid 1.32%, tannin, gum 13.75%; albumin 13.08%; crude cellulose 17.08%, mineral matter 4.12%, and moisture 3.83%. Amla fruit ash contains chromium, 2.5 ppm; zinc 4 ppm; and copper, 3 ppm.[7]

The Figure 2 signifies various phytoconstitutents accessibility in Amla.

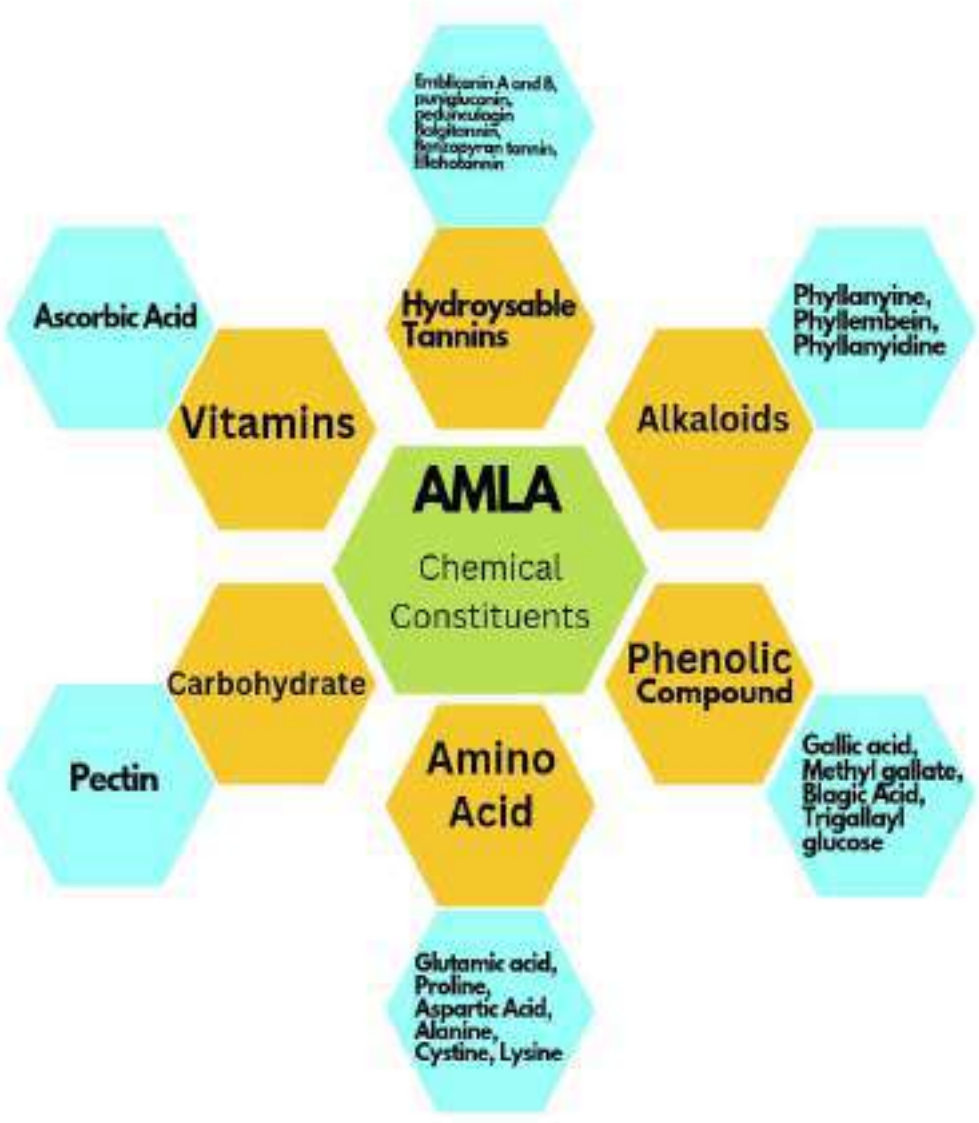

Figure 2: Phytoconstitutents of Amla.

Leaves: They contain gallic acid, chebulic acid, ellagic acid, chebulinic acid, chebulagic acid, malic acid, alkaloids phyllantine, and phyllantidine.[8]

Seeds: Phosphatides, a fixed oil, and a little amount of essential oil. The fixed oil (acid value 12.7; saponification value 185; iodine value 139.5; acetyl value 2.03; Un saponin- fiable matter 3.81%; sterol 2.70%; saturated fatty acid 7%. Contains linolenic acid (8.78%), and linoleic (44%). oleic (28.40%), steric (2.15%), palmitic (2.99%) and miristic acid (0.95%).[8]

Barks: contain leukodelphinidin, tannin, and proanthocyanidin.[8]

Roots: contain ellagic acid and lupeol.[8]

An overview of phytoconstituents isolated from specific parts of Amla is given in Figure 3.

Figure 3: Isolated Phytoconstituents from different parts of Amla.

1.5 PHARMACOLOGICAL ACTIVITIES

Nearly all components of Amla have therapeutic properties and are traditionally used to cure a variety of illnesses. Amla may possess antiviral, antibacterial, and antifungal properties, as per data collected from number of research papers. It is one of those old-fashioned plants that has been used traditionally for both medicinal and fruit purposes. It is amazingly effective as a natural antiaging drug. It is a very effective plant in the treatment of acidity and peptic ulcer.[9] The following are the pharmacological activities exerted by the Phyllanthus emblica.

1.5.1 Antifungal activity

The antifungal property of E. officinalis was reported against Aspergillus.[10] Fruit ethanol and acetone extracts showed moderate activity against Fusarium equiseti and Candida albicans where Griseofulvin was used as the standard antibiotic [11]. Plant methanolic extract of E. officinalis did not show antifungal activity against phytopathogenic fungi Aspergillus Niger F2723.[12]

1.5.2Antioxidant activity

Amla is rich in antioxidants such as gallic acid, ascorbic acid and phenolic compounds and thus helps the body's immune system and digestion. Antioxidant activity can be defined as a limitation or inhibition of nutrient oxidation by restraining oxidative chain reactions. Galic acid equivalent to total phenolic content from fruit and seed of E. officinalis has excellent antioxidant properties and plays an important role as free radical scavengers required in the maintenance of redox homeostasis responsible for diverse degenerative diseases. The methanolic seed extract of Emblica officinalis has promising free radical scavenging activity

of 1,1, Diphenyl-2-picryl-hydrazil (DPPH) in a concentration-dependent manner. Methanolic extract of fruit pulp also has antioxidant and free radical scavenging activity. [13-20]

1.5.3 Larvicidal and mosquitocidal activities

Larvicidal and pupicidal activities of methanol extract of E. officinalis against the malarial vector are observed where Anopheles stephensi showing a 98% mortality rate at 100 ppm. The ethanol and methanol extracts of E. officinalis also exerted 100% mortality (no hatchability) at 400 ppm and above and reported the larvicidal activity of Phyllanthus emblica ethyl acetate leaf extract. The study concluded that the ethyl acetate extract of P. emblica exhibited the maximum larvicidal activity (99.6%) with LC50 (lethal Concentration brings out 50% mortality) value of 78.89 ppm against the larvae of Aedes aegypti.[21-22]

1.5.4 Antidiabetics

The hypoglycaemic effects of herbal formulations made from extracts of Tinos Pora cordifolia, Trigonella foenum, and Emblica officinalis were assessed using the Oral Glucose Tolerance Test (OGTT) in rats with normal blood and rats that had been given Alloxan to induce diabetes. When various herbal combinations were used, there was a significant, marginal, and very little drop in blood glucose level.[23] A significant approach to managing diabetic problems would be to examine the medicinal advantages of natural ingredients which would incorporate people into their everyday lives.[24] The aqueous fruit extract of Phyllanthus emblica was evaluated on type-II diabetes, triglycerides (TG), and liver-specific enzyme, alanine transaminase (ALT). This study showed that in a dose of 200mg/kg body weight, the aqueous fruit extract can significantly reduce the blood glucose level in alloxan-induced diabetic rats.[25]

1.5.5 Cardio-protective activity

The long-term effects of oral administration of fresh, homogenous Amla fruit on antioxidant levels in the heart and ischemia-reperfusion injury (IRI) due to oxidative stress were examined in rats. Long-term treatment promotes cardiac adaptation by increasing natural antioxidants and securing the heart of rats against oxidative stress linked with IRIs.[26]

1.5.6 Anti ulcerogenic activity

The ethanolic extract of E. officinalis has been found highly effective in controlling the growth of H. pylori in-vitro with minimum inhibitory control ranging from 0.91 to 1.87 µg/ µl. The result concluded that the plant ethanolic extract is well retained with total phenolics, reducing power, flavonoids, and antioxidant properties which make amla a proper remedial use against H. pylori infection and gastric ulcer.[27]

1.5.7 Antipyretic and analgesic activity

The extracts of E. officinalis are strengthened by strong antipyretic and analgesic action. With just one dosage of ethanol extracts and aqueous extracts (500 mg/kg), brewer's yeast hyperthermia in rats has been decreased. Prominent inhibitory effects on acetic acid-induced writhing retort in mice were reduced by both extracts revealed in the analgesic test. Such symptoms may have been caused by the involvement of alkaloids, tannins, amino acids, phenolic compounds, or carbohydrates. [28]

1.5.8 Memory enhancing activity

Anwala churna may prove to be a useful remedy for the management of Alzheimer's disease on account of its multifarious beneficial effects such as memory-improving the property, cholesterol-lowering properties, and anticholinesterase activity.[29]

1.5.9 Hepato-protective activity

Ayurvedic traditions are said to have utilized amla fruits. As an edible and medicinal natural resource, Amla has been reported to possess hepatoprotective, antioxidsnt and anti-inflammatory activitiesand have an ameliorating effect on hepatic fibrosis. Phyllanthus emblica extract has been tested for hepatic rat damage due to ethanol. The extent of hepatic fibrosis caused by thioacetamide, and carbon tetrachloride was lessened by a hydroalcoholic (50%) extract of fruit E. officinalis (EO-50). Because of its antioxidant function, EO-50 effectively reverts profibrogenic events. EO-50 probed hepatoprotective role in

antituberculosis drug-induced hepatic injury. Due to the perceived character of antioxidant, membrane stabilizer, and inhibitory CYP2E1, the EO-50 has hepatic protection activity. [30-32]

1.5.10 Ophthalmic activity

A cataract is a clouding of the eye lens that reduces the amount of incoming light and results in deterioration of the vision. A combination of P. emblica and honey can improve eyesight. Opium juice is combined with Trifala and Opium poppy (which contains doda) to make medicinal tablets. These tablets are kept over closed eyes and bandaged. It helps soothe pain in the eyes. Research also supported benefits in various ophthalmic conditions such as conjunctivitis, postoperative cataract, acute dacryocystitis, xerosis, and conjunctival degenerative conditions.[33-34]

1.5.11 Role in cancer treatment

Ellagic acid, a potent antioxidant found in amla, has the ability to stop gene mutations and fix chromosomal defects. It inhibits the growth and spread of various cancers like breast, uterus, pancreas, stomach, and liver cancers.[35] Breast cancer is considered one of the most common cancers among females. Fats, lipoproteins, and lipid metabolism enzymes were major risk factors for breast cancer. Kalpaamruthaa (KA) is an improved preparation of Siddha which contains E. officinalis, honey, and Semecarpus Anacardium. As treated by KA and SA, the raised levels of phospholipids, free fatty acids triglycerides, total cholesterol, free cholesterol, and the replacement of ester cholesterol in blood, liver, and kidney in animals with cancer have reversed to almost normal rates. [36]

1.5.12 Snake venom neutralizer

The traditional application of Emblica officinalis Linn. an Indian medicinal herb. Root extract and its active compound (Phthalate in nature) against snake venom has been established in experimental animal models. The present study confirmed the phytomedicinal value of an Anti-snake venom compound present in the root of Emblica officinalis. [37]

1.5.13 Dyslipidaemia and cholesterol reduction activity

The efficacy of E. officinalis in treating hypercholesterolemia and atherosclerosis is well-established in animal experiments and human studies. The pharmacological and clinical studies have indicated that amla has potent antioxidant effects against several test systems such as superoxide radicals, lipid peroxide formation induction by Fe+++/ADP ascorbate system, hydroxyl radical scavenging action, and in systemic augmentation of antioxidant enzymes in the brain of laboratory animal. According to a recent rat research, flavonoids from E. officinalis effectively reduced lipid levels in serum and tissues and had a significant inhibitory effect on hepatic HMG CoA reductase activity. The effect of standardized amla extract on atherosclerosis and dyslipidaemia in animals is well-studied.[38] The efficacy of Amla was evaluated in patients with type II hyperlipidaemia and its hypolipidemic effects were compared with those of the commonly used HMG Co-A reductase inhibitor – simvastatin.[39]

1.5.14 Immunomodulatory activity

Reports suggest that Triphala can stimulate neutrophil functions in the immunized albino rats.[40] In albino mice treated with emblica, there was a significant dose-dependent increase in the following parameters: total leukocyte count, percentage lymphocyte distribution, respiratory burst activity of peritoneal macrophages, haemagglutination antibody titer, macrophage migration index, hypersensitivity reaction, serum globulin, and relative lymphoid organ weight. These findings suggest that emblica can stimulate both humoral and cell-mediated immunity in addition to macrophage phagocyte stimulation. [41]

1.5.15 Insecticidal activity

Important components of E. officinalis, saponins, have the ability to kill or cytotoxically affect certain insects. However, saponins that had shown insecticidal activity were collected from natural sources other than E. officinalis. But as saponins are bioactive compounds found in E. officinalis too, it is obvious that E. officinalis might have insecticidal activity and further evaluation can be conducted to get a more precise evaluation.[42]

1.5.16 Radioprotective activity

It has been reported that mice treated with Emblica officinalis extract before exposure to different doses of gamma radiation can reduce the severity of symptoms of radiation sickness and mortality.[43] Similarly delayed onset of mortality and reduction in the symptoms of radiation sickness in mice were seen in consecutively triphala-treated mice before irradiation when compared with the non-drug-treated irradiated controls.[44]

1.6 TRADITIONAL USES

Amla is used in several medical systems such as Ayurveda, Siddha, Unani, Tibetan, Sri Lankan, and Chinese medicine for a range of diseases. It is considered a Ras Ayana (rejuvenator) [45] and is used in delaying degenerative and senescence-related processes. In folk medicine, the fruits, are sour, astringent, bitter, acrid, sweet, and anodyne. Exert several beneficial effects include cooling, ophthalmic, carminative, digestive, stomachic, laxative, dyspepsia, aphrodisiac, rejuvenate, diuretic, antipyretic, and tonic. They are useful in vitiated conditions of tri dosha, diabetes, cough, asthma, bronchitis, cephalalgia, ophthalmopathy, dyspepsia, colic, flatulence, hyperacidity, peptic ulcer, erysipelas, skin diseases, leprosy, haematogenesis, inflammations, anemia, emaciation, hepatopathy, jaundice, diarrhea, dysentery, hemorrhages, leucorrhoea, menorrhagia, cardiac disorders, intermittent fevers and premature greying of hair (Hair tonic).[46] Moreover, antioxidant, anti-inflammatory, analgesic, antipyretic, and restorative qualities are claimed for amla, along with hepatic, cardiac, nephron, and neuroprotective benefits.[47] Furthermore, the active principles of amla were reviewed and considered as a peerless clinical intervention for infected wounds.[48]

Some traditional uses are shown in Figure.4.

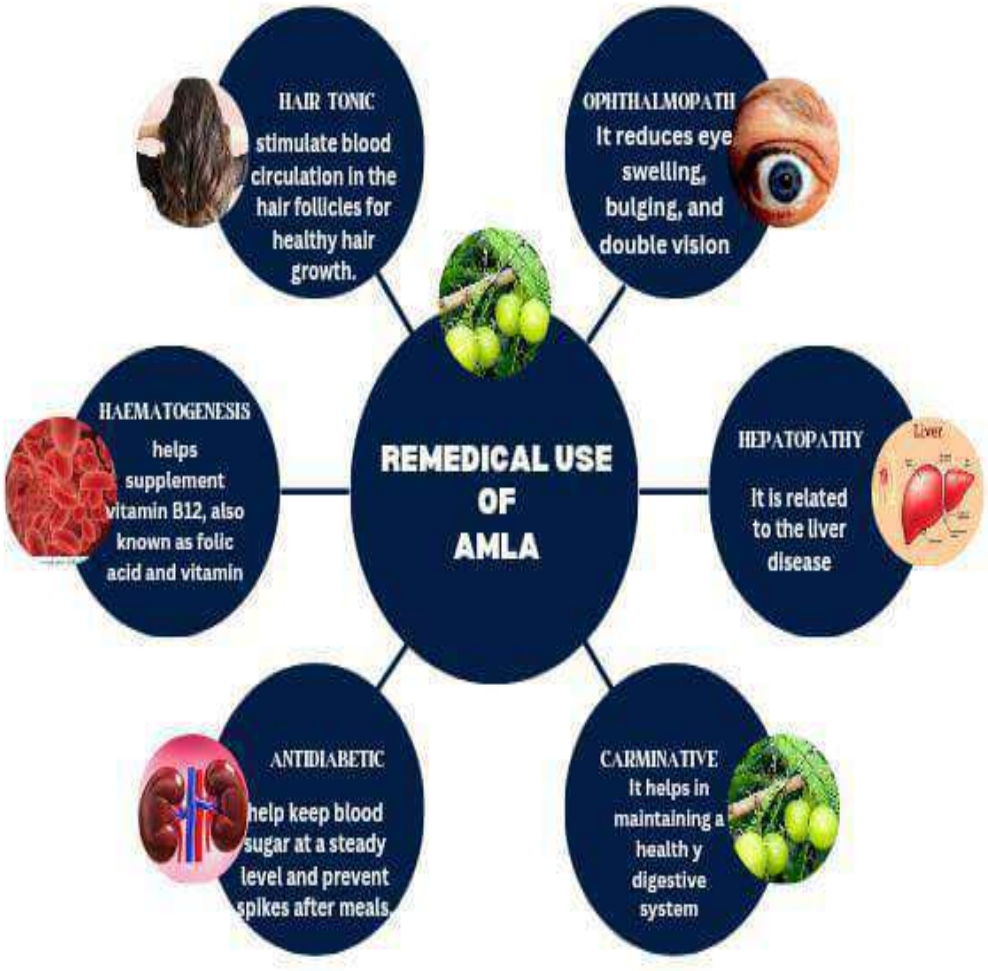

Figure.4. Therapeutic activities of solvent extract and compounds of Emblica officinalis.

1.7 CONCLUSION

Since ancient times, amla, also known as Indian gooseberry, has been used extensively in tribal, traditional, and Ayurvedic medicine. Most of the phytochemicals that are extracted from Amla, including tannins, flavonoids, terpenoids, and other polyphenolic compounds, have been the subject of several biological and biopharmaceutical studies over the past few decades. Amla phytochemicals have been shown to exhibit a variety of biological functions. These include ellagic acid, emblicanin A, emblicanin B, gallic acid, phyllantine, quercetin, phyllantidine, etc. These chemicals where to be found have different pharmacological activities such as antioxidant, antimicrobial, anti-inflammatory, antidiabetic, antitussive, anti, radioprotective, chemo preventive, and wound healing activities. According to the current study, many of Emblica Officinali's bioactive components are also often found in other therapeutic plants. Consequently, more analysis of undiscovered bioactive Amla components will be necessary to reveal ever-new bioactivities of this effective medicinal plant.

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A Mini Review: Nutritional and Pharmacological Importance of Psidium guajava

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ABSTRACT:

Increasing industrialization has leaded to many modification in lifestyle, which giving rise to the diseases which are reducing the quality of life so the scientific studies demonstrated that consumption of parts of the plants (fruit, seeds, leaves, roots) can be helpful to prevent risk factors of many diseases. *Psidium guajava* (P.G.) is one of them which is worldwide known for its nutritional and medicinal values. It is popularly known as "Guava". It possess a wide range of medicinal and traditional use for other ailments. Parts of *Psidium guajava* plant plays major role in development of various industrial and pharmaceutical products. The main aim of review is to highlight chemical components and their pharmacological effects which are present in different parts of *Psidium guajava* plant. It contains phytoconstituents like kaempferol, naringenin, rutin, epicatechin, catechin, gallic acid, isoflavonoids, flavonoids, phenolic compound. The pulp is rich in ascorbic acid and seed, skin, bark are rich in glycosides, carotenoids. The different extracts of skin, pulp, leaf, seed and fruits have activities to prevent cancer, regulating blood pressure, and treating diarrhea. The medicinal uses are validated by the scientific research work of P.G. The plant has been extensively studied in terms of pharmacological activities of its major components and the results show antifungal, antipyretic, antioxidant , antimicrobial, hypotensive, analgesic & anti-inflammatory effects. The review data supports to the investigators and food nutrition for further extensive work.

Keywords : *Psidium guajava*, Guava, Medicinal & Nutritional values

1.0 INTRODUCTION:

Psidium Guajava (P.G.) is part of family Myartaceae and Myrtie. It is a traditional medicinal plant and having wide history of its parts like bark and leaves are used as medicinal uses.[1] It has genera about 133 and 3,800 species of tropical shrubs and grows in all kind of soils. It is considered as 4th important fruit in terms of production and area after banana, mango and citrus. The origin of *Psidium guajava* found in New Mexico and America.[2] There are different purposes of production of *Psidium guajava* in different countries like Colombia , Mexico and Venezuela uses *Psidium guajava* in fresh beverages and candies etc. Brazil is the one of the top producer of *Psidium guajava* for juices, jams, frozen pulps etc.[3][4] In India it is produced in different states like Uttar Pradesh, Bihar, Madhya Pradesh, Maharashtra, Andhra Pradesh, Tamil Nadu, West Bengal, Assam, Orissa, Karnataka, Kerala, Rajasthan and many more states and with many varieties. But the medicinal uses of *Psidium guajava* are common in all countries according to their parts of plant leaves, pulps are used for respiration and gastrointestinal disorders, antispasmodic, anti-inflammatory and cough sedative antidiarrheal managements hypertension obesity in control of diabetes mellitus also anticancer where the seeds gives antimicrobial, gastrointestinal, antiallergic, carcinogenic pharmacological activities. *Psidium guajava* full of vitamins of which Vitamin C is very powerful in combating against oxidation and free

radicals while vitamin A gives the quality and health of eyesight, skin, teeth, bones and the mucus membranes. *Psidium guajava* is also of rich of dietary fibers and phenolic acid, dietary minerals, potassium, copper and manganese *Psidium guajava* is called the super fruit because it is said to contain four times more vitamin C than orange and three times more proteins and four times more fiber than pineapple.[5] It is also said to have more potassium than a banana. The leaves of P. G. are used as a black pigment in the textile industry. The ethanomedical uses which are produced by crushing leaves includes wound healing, soft tissue infections.[6]

1.1 Local Names:

Table 1 shows different names of *Psidium guajava* according to different regions in the world.

Table 1: Local Names of *Psidium guajava* [7]

Countries	Names
Arabic	Guwafah
Bengali	Piara
Brazil	Araca
Combodia	Trapaeksruk
Chinise	Fan shiliu
English	Apple P. guajava
French	Gouyave
Germany	Guavenbaum
India	Amarood; jamba
Portugese	Goiaba
Spanish	Guayaba
Thailand	Farang
Philippines	Bayabas

1.2 Taxonomical Classification:

The taxonomical classification of the *Psidium guajava* plant shown in Table 2.

Table 2: Taxonomical classification of *Psidium guajava*[8]

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Sub Class	Rosidae
Order	Myrtales
Family	Myrtaceae
Genus	Psidium
Species	Guajava

1.3 Morphology of *Psidium guajava*:

Psidium guajava grows in the form of shrub or small tree upto 1-6m tall in height. The stems of *Psidium guajava* have different colours according to their ages like older stems have reddish brown, newly revealed bark have greenish colour and younger stems have greenish in colour with hairy and quadrangular shapes. The leaves are present in opposite to each other along with stems and grows in oval shape with rounded or pointed tips with rounded bases.[9] Every leaf have a prominent central vein and around 10-20 pair of lateral veins. The flower grows on upper leaf forks. These flowers grow on hairy stalk (pubescent penduncle)1-2.5 cm long. Every flower consists of 4-5 green sepals (6-15 mm long) that are fused together at the base and four or five white large numbers of small white steamns (6-10mm long) and style (6-12 mm long) topped with stigma. The fruit of *Psidium guajava* is either rounded (globose) or egg shaped (pyriform) and during ripening turns from green to yellowish coloured as it matured (Figure 1). This *Psidium guajava* berries (2.5-10 cm long) are crowned with remains of persistent sepals (calyx lobes) and have juicy white or yellowish

coloured pulp containing numerous seeds.[9] The seeds are yellowish in colour and shape like a kidney. Seeds can be planted and wild trees are used for fruit which aids their spread.

Figure 1 : *Psidium guajava* fruit with leaves.

1.4 Various Species:

Psidium guajava is distributed in various species according to its different location. Guava belongs to genus Psidium and various species like Amplexicaule, Freidchsthalium, Incanescens, Radd, Galapageium, Montanum, Aracaraddi, Guajava , Robustum, Cinerium, Harrisianium, Rostratum, Dumetorum, Sartorianum, Firmum, Spathulatum, Sinetensii, Havanense.[10]

1.5 Nutritional Status:

Psidium guajava is full of nutrients and known as "Rich of Nutrient Booster" .The nutritional status of *Psidium guajava* shown in Table 4.

Table 4: Nutritional status of *Psidium guajava*[10-12]

Name	Content
Calories	77-86 g
Moisture	2.8-5.5g
Crude fiber	0.9-1.0g
Protein	0.1-0.5
Fat	0.43-0.7mg
Carbohydrates	9.1-17mg
Calcium	17.8-30mg
Phosphorus	0.30-0.70mg
Iron	200-400 I.U
Carotene	0.046mg
Thiamine	0.03-0.04mg
Riboflavin	0.6-1.068
Niacin	40 I.U
Vitamin B3	35 I.U
Vitamin C	125mg
Vitamin A	0.046mg

1.6 Chemical Constituents of *Psidium guajava* :

Psidium guajava fruit contains high amounts of chemical constituents. The chemical components are present in whole plant but differentiated according to their parts of the plant which are shown in Table 5

Table 5: Chemical Constituents of *Psidium guajava*

Sr. No.	Parts	Constituents
1	Fruit	Vitamin C , Vitamin A , Iron , Calcium , Manganese , Phosphoric , Oxalic and Malic acids, Saponin combined with Oelanolic acid.[13]
2	Leaves	Farnesene , Humulene , Selinene , Cardinene and Curcumene , Mallic acids ,Nerolidiol , Ursolic , Cartegolicandguayavolic Acids , Cineol , Triterpene, Oelanolic acid, Triterpenoids, falvinonen, Prenol , Cryptonine.[14]
3	Bark	Polyphenols , Resin and Crystals of calcium oxalate [15]
4	Root	Tannin , Leukocyanindins , Sterol , Gallic acid carbohydrates , Salts , Tannic acid.[16]
5	Seed	Glycosids, Carotenoids,Phenolic compounds [17-19]
6	Twigs	Calcium , Magnesium, Phosphorus , Potassium , Sodium , Fluoride , Copper, Iron, Zinc ,Manganese and Lead.[20]

1.7 Ethanomedical uses of *Psidium guajava* :

Psidium guajava shows the different pharmacological activities through the different parts of the plant which are shown in Figure 2, while Worldwide Ethanomedical uses of *Psidium Guajava* is shown in Figure 3.

Figure 2: Ethano-medicical uses of *Psidium guajava* [21-25]

Figure 3: Worldwide Ethano-medicical uses of *Psidium Guajava* [26]

1.8 Pharmacological Activities of *Psidium guajava*:

Scientific research's demonstrated that *Psidium guajava* shows promising pharmacological activities. The particular concentration of extract shows versatile pharmacological activities which are shown in Table 6.

Table 6: Pharmacological Activities of *Psidium guajava* [27-29]

Sr. No.	Pharmacological Effect	Extract	Concentrations
1	Hepato-protective activity	Water	250 and 500 mg/kg
2	Anti-diarrheal Activity	Water	50-400 mg/kg
			1 mg/kg
			10 mg/kg
3	Contractile effect	Water	0.25-2 mg/ ml
4	Anti-hypotensive effect	Water	50-800 mg/kg
5	Analgesic & anti-inflammatory Activity	Water	50-800 mg/kg
6	Anticancer activity	Acetone	250 µg/ml
		Water	1.5 mg/day
		Essential oil	0.019-4.962 mg/ml
7	Anti-hypertensive effect	Water and ethanol	0.5 g/kg body weight
			2.0 g/kg body weight
8	Antifungal activity	Hexane	50mg/ml
		Acetone	
		Methanol	
9	Anti-proliferative activity	Water	29.0 ± 0.4 µg/ml
10	Antipyretic activity	Water	200 mg/kg

11	Treatment of plaque	Methanol	2mg/ml, 4mg/ml
12	Spermato protective activity	Ethanol	250 mg/ kg/d and 500 mg/ kg/d
13	Spasmolytic effect	Methanol	
14	Immuno modulatory activity	-	55 µg/ ml
15	Anti-malarial activity	Aqueous	10-20 µg/ml
16	Treatment of cough	Water	2 and 5 g/kg
		Water	250 mg/kg
17	Anti-diabetic activity	Methanol	0.2-1.0 ml
		Water	10, 5. & 0.16 mg/ml
18	Antibacterial activity	75% Methanol	5 & 0.16 mg/ml
		Acetone	20.0 & 0.31 mg/ml
		Water	0.63 g/L
19	Antioxidant activity	65% Ethanol	0.47 g/L
		95% Methanol	0.58 g/L

2.0 CONCLUSION:

From the evolution of Ayurveda being *Psidium guajava* has a long history in traditional and medicinal uses. Nutritional benefits are consumed by raw fruit, fresh juices and or marketed juices. The multiple numbers of chemicals isolated from the plants such as quercetin, guaijaverin, flavonoids and galactose, specific lecithin which shows promising pharmacological activities like antifungal, antipyretic, antimicrobial, hypotensive, analgesic, anti-inflammatory effects. The review work emphasis on Nutritional values and Pharmacological activities of *Psidium guajava*. Hence the extra investigation and analysis should be done with pharmacokinetics and pharmacodynamics studies.

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All authors have read and agreed to the published version of the manuscript.

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A BRIEF REVIEW ON GREEN SYNTHESIS OF IRON OXIDE NANOPARTICLES –WITH FOCUS ON BIOMEDICAL APPLICATION

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ABSTRACT

Green synthesis of iron oxide nanoparticles pays an immense attention nowdays as they are safe, ecofriendly and less toxic . Conventional mehods of iron oxide nanoparticles synthesis had badly affect the environment .Hazardous chemicals has been used for their synthesis which produced toxicity and side effects .Green synthesis of iron oxide nanoparticles is the best option to overcome all this problem . Iron oxide nanoparticles can be synthesis from bacteria, fungi, algae and plants extract .Various plant parts such as root, stem,leaves, fruits and seed had been used which contain phytoconstituents .Some plant parts has naturally possess antimicrobial properties which help to treat microbial resistance. This review mainly focus on green synthesis methods of iron oxide nanoparticles ,their biomedical application such as antimicrobial properties,anticancer properties,wound healing and antioxidant properties.Characterization technique and stability of green synthesized iron oxide nanoparticles by UV-Vis spectroscopy, X-ray diffraction(XRD), Fourier transform infrared spectroscopy(FTIR), Transmission electron microscopy(TEM), Scanning electron microscopy(SCM) have been studied. The challenges and future prospects are also mentioned.The main focus is on biomedical application.

Keywords: Nanotechnology, Nanoparticles, Green Synthesis, Iron Oxide Nanoparticles, Biomedical applications.

Introduction

Nanotechnology

Nanotechnology is the technology concern with their ability to control or restructure the matter at molecular level in the size range of 1-100 nm.[1] Nanotechnology has great advancement in biomedicine.Antibiotics are generally used to treat bacterial infection, due to lack of pathogen detection method antibiotics are overuse and bacterial resistance develop cause various health issues.Nanotechnology provides a better option by using nanoparticles it overcome the resistance and also help in early detection of pathogen.[2].Nanotechnology helps to avoid the use of hazardous medication by modifying the structures which transport drug to the pathogen and also protects host body and cause less side effects.Antimicrobial and antiviral properties had demonstrated with physiocochemical properties in nanoparticles[3]. By changing the size and shapes at nanoscale nanotechnology incorporates synthesis ,design,characterization and application of materials,instrument and systems [4] .

Nanoparticles

Nanoparticles defined as the particles which size ranges from 10 to 1000nm[5]. Nanoparticles can be synthsized by chemical and physical method but this methods result in causing side effects ,use of chemicals which are harmful to environment so to avoid this consequences nanoparticles are synthesized by biological methods which are safe and ecofriendly. In this method by using plant extract ,fungi ,microorganism synthesis of nanoparticles is done.[6]

Iron oxide nanoparticles

Iron oxide nanoparticles in nanotechnology defined as the particles in terms of transport and properties it behaves as whole unit..These are chemical compounds which are composed of iron and oxygen.[7]. Leads to formation of 16 iron oxide phases among which maghemite,hematite,magnetite are most useful due to their polymorphism involves temperature-induced transition. They also possess magnetic,biochemical,intrinsic catalytic and other properties which helps them for biomedical application.[8]The ability of iron oxide nanoparticles to act at both cellular and molecular level leads to their application under in vivo and in vitro conditions for target drug delivery and cell therapy.[9].

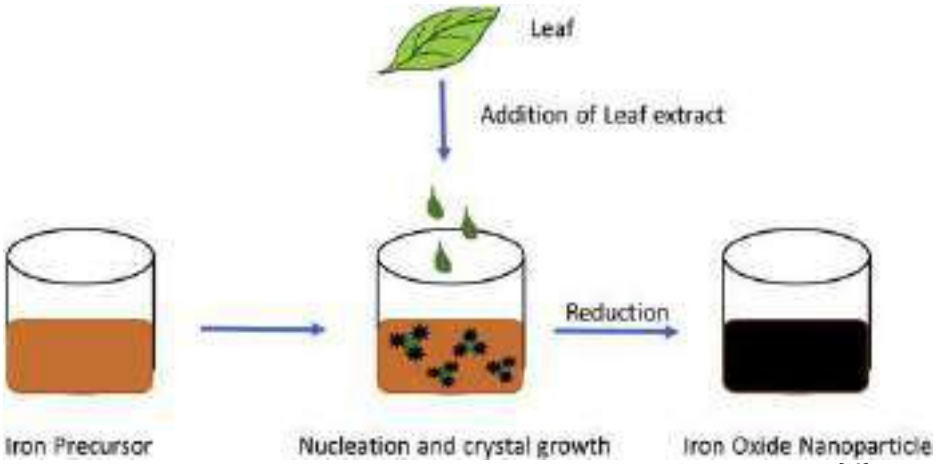

Figure 1:It include process of synthesis of iron oxide nanoparticles.[10]

Green Synthesis Method

Nanoparticles can be synthesized by various methods such as physical,chemical and biological method but physical and chemical methods may results in arising the toxicity and environment issues as physical method required large space and use of heat result in rising the temperature and in chemical method hazardous chemicals and reagents are used which causes toxicity .There was a need to find out the alternative method for nanoparticles synthesis and green nanotechnology was developed which is ecofriendly and safe.. Green nanotechnology is the technology where nanoparticles are synthesized from various biological routes such as bacteria ,fungi and plants[11] .The nanoparicles synthesized are ecofriendly and free from toxic chemicals and for synthesis of nanoparticles mainly three conditions are required that are selection of ecofriendly solvent, good reducing agent and last is harmless material for stabilization.Green synthesis can be carried out by using plant ,algae,bacteria and fungi.Various parts of plants such as leaves,stem,fruits,roots and seeds has been used for nanoparticles synthesis due to the phytoconstituent present in it which act as reducing agent.[12].

Green synthesis of iron oxide nanoparticles from plant Iris Kashmiriana has been reported to have antibacterial ,antioxidant and photocatalytic properties[13]. The extract obtained from plant Platanus orientalis has used for green synthesis of Iron oxide nanopartcles as it possess antioxidant,antifungal properties[14].Salvia officinalis shows best results for green synthesis of iron oxide nanoparticles with antimicrobial properties[15] . Vitex negundo plant extract has been used for synthesis of iron oxide nanoparticles possess anticancer and anti-inflammatory properties.[16]. Abutilon indicum and Mimosa pudica extract has been reported for green synthesis of iron oxide nanoparticles with additional properties such as anticancer and antibacterial [17] [18]

Table1:It summarizes the Plant source used in green synthesis of iron oxide nanoparticles, with their biologically active constituents.

Plant source	Bioactive compound	Reference
Iris kashmiriana	Quinones and triterpenoids	(25)
Platanus orientalis	Phenols, tannins and flavonoids	(26)
Salvia officinalis	Saponins tannins and alkaloids	(27)
Vitex negundo	Favonoids and terpenoids	(28)
Abutilon indicum	Alkaloids anfd flavonoids	(29)
Mimosa pudica	Mimosine	(30)

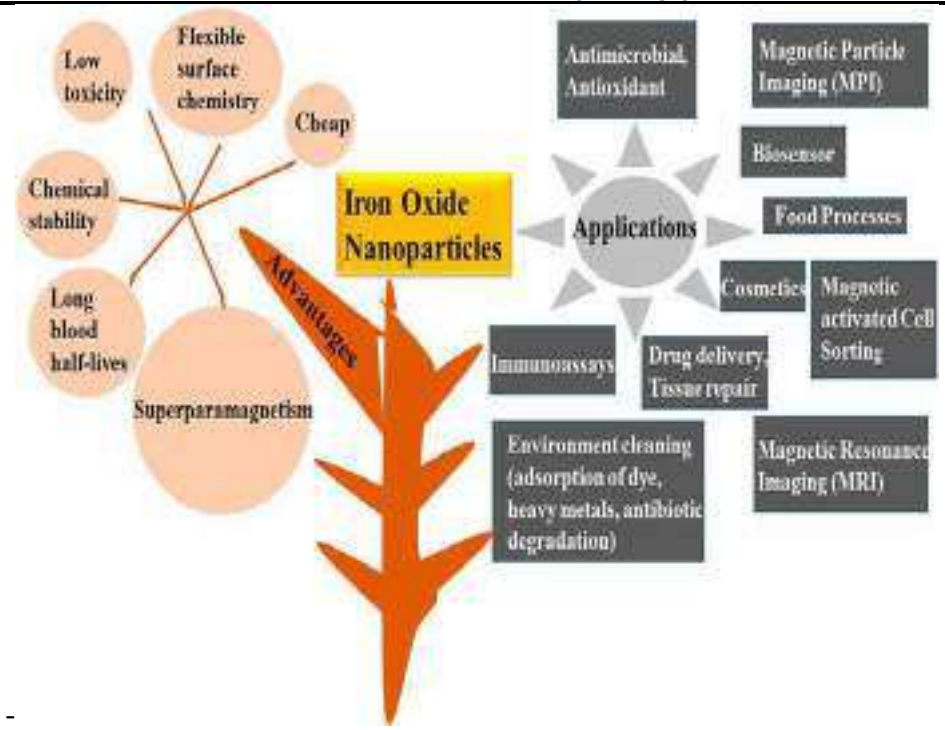

Figure 2: It summarizes the Advantages and Applications of Green synthesized Iron Oxide nanoparticles. [19]

Biomedical application of Iron oxide nanoparticles

Antimicrobial properties

Due to the presence of naturally occurring antimicrobial properties of many leaf extract they had used for green synthesis of iron oxide naoparticles.For example,Achyranthes aspera and Tamarix aphylla leaf extract are generally used as anti inflammatory agents.the size of nanoparticles is too small that it can easily penetrate the cell wall and inhibit the enzyamatic activity of bacteria.[20]Antimicrobial resistance is defined as microorganisms developed itself in such a way that it reduce the effect of antibiotics.Resistance can be result from mutation with subsequent generations inherit the resistance[21].Iris kashmiriana posess antibacterial activity[13]

IONPs shows unique antibacterial properties as they possess different physical and chemical properties for example their surface charge and ability to generate ROS. Due to differences in cell wall structure the antibacterial acitivity depends on bacterial strains. The gram positive bacteria possess thick peptidoglycan layer contain negative charge due to teichoic acid whereas gram negative bacteria have thin peptidoglycan layer and lipopolysaccharide layer with negative charge.thus IONPs interacts with negatively charge bacterial membrane results in depolarization and integrity of cell membrane gets disturbed. The structural differences in cell wall composition results in gram positive bacteria are more susceptible than gram negative bacteria to the IONPs[22].

Iron oxide nanoparticles also possess antifungal properties by the interaction of IONPs with the fungal cell which affect cell permeability and result in entry of nanoparticles into the fungal cell. Which results in oxidative stress on fungal cell leads to no cell development ultimately cell death occurs. The antifungal activity of IONP depends upon their chemical properties and physical composition such as size, charge at surface and solubility.[23]

Table 2: It contains the antimicrobial properties of iron oxide nanoparticles with the plant extract used and type of activity:

Plant	microorganism	activity	citation
Achyranthes aspera	Leaf extract	Anti-inflammatory activity	[24]
Sphagneticola trilobata	Staphalococcus aureus	Antibacterial activity	[25]
Lagenaria siceraria	Escherchia coli	Antibacterial activity	[26]
Capparis zeylanica	Pseudomonas aeroginosa,candida albicans	Antibacterial activity	[27]
Laurus nobilis	Aspergilus flavus , penicillium spinulosum	Antifungal activity	[28]

Anticancer properties

In recent few years ,drug targeting at cancerous site via IONPs had increased the research interest. All the conventional therapies used for treatment of cancer result in much more side effects and also result in killing of cancer cell as well as normal cell leads to suffer a lot to cancer patient .IONPs has mostly used for diagnosis as contrast agent in MRI and for the transfer of chemotherapeutic drugs to targeted site. IONP used as magnetic nanocarriers in cancer treatment .Superparamagnetic IONPs had successfully used to carry chemotherapeutic drugs such as doxorubicin in cancer treatment [29]. IONPs are used in cancer treatment as they provide sustained drug release at targeted site which leads to overcome the side effects of anticancer drugs. Nanoparticle based anticancer drug delivery can be achieved mainly by two mechanisms -first is by passive targeting via EPR and second is by active targeting via receptor targeted endocytosis[30]

The leaves of Mimosa pudica contain mimosine which shows anticancer properties .Mimosine can inhibit the proliferation of various lung and liver cells.(30). Punica granatum shows higher anticancer properties against human breast cancer ,colon cancer, prostate cancer ,thyroid cancer and cervical cancer.[31].

Table 3: It summarise the plant source and also its anticancer properties:

plant	activity	citation
Punica granatum	Anticancer agent acts against nasopharyngeal carcinoma (NPC) cells.	[32]
Chaetomium cupreum	Increase production of relative oxygen species (ROS) leads to cell death	[33]
Pimenta dioica	Toxic to DLD-1 human colon cancer cell but not affect the L929 (fibroblast) cell leads to antiproliferative effect	[34]
Turbinaria conoides	Growth of cell lines HeLa and DID1	[35]
Terminalia catappa	Show anticancer activity via killing to human cervical carcinoma cells	[36]

Wound healing properties

Due to their antibacterial and antioxidant properties along with a great effect on biofilms and drug resistance iron oxide nanoparticles are used in wound dressings.Iron oxide nanoparticles used in dressings as reinforcing materials which increases their effect as iron oxide nanoparticles shows broad spectrum antibacterial properties.IONPs are used in chronic dressings in diabetic patient as they inhibit the enzyme alpha –amylase thereby maintained blood sugar level to normal.[37]

Table 4:it includes the wound healing properties of plant used and description is also given:

Plant source	Wound healing activity	description	citation
Ficus carica	Antibacterial activity	mostEffective against bacteria and moulds	[38]
Trianthema portulastrum	Anti-inflammatory actvity	Reduce inflammation	[39]

Antioxidant properties

Antioxidants defined as those compunds which are able to prevent oxidation and by which free radicals are formed.[40] IONPs synthesized from coriander leaf extract shows antioxidant properties as coriander leaves are rich in natural antioxidants such as kaempherol,acacetin, P-coumaric acid trans feruic acid,and vanilic acid.[41].

Table 5: it contains plant source along with its antioxidant properties:

Plant source	activity	citation
Senna bicapsularis	Increased antioxidant property as rich in phytochemicalconstituents	[42]
Madhuca indica	Antioxidant properties with DPPH inhibition	[43]

Characterization of green synthesized iron oxide nanoparticles

Green synthesis of iron oxide nanoparticles is confirmed by varius characterization techniques such as UV –vis spectroscopy,fourier transform infrared spectroscopy(FTIR),transmission electron microscope (TEM),Scanning electron microscopy (SEM),X-ray diffraction (XRD). To overcome environmental impact the characterization of green synthesized iron oxide nanoparticles are done which include study of their shape ,size,phase structure,magnetic properties and their biocompatibility.Using UV spectrophotometer characterization is done by assessing absobance levels which assures synthesis of iron oxide nanoparticles with low toxicity.[44]

Table 6: it includes the various chacterization technique with brief description:

Technique	Information obtained	Reference
UV-vis spectroscopy	Determination of stability, size, aggregation and structure of nanoparticles.	[44]
FTIR	Functinal groups and characterization of precursors	[45]
TEM	morphological properties	[44]
SEM	morphological and size analysis	[44]
XRD	Crystalline structure of particles (angle position, width, and intensity)	[45]

Stability of Green-Synthesized Iron oxide

The stability of nanoparticles defined as stable when the particles are not precipitate visibly over a mentioned time period .Through the characterization of nanoparticles such as using scaterring technique help to maintained the stability of nanoparticles.[46] The stability of nanoparticles has major impact on biomedical and bioengineering applications. To enhance the stability of nanoparticles , the particles must have high magnetization, narrow particle size distribution and smaller particle size less than 100nm thereby it achieve uniform physico-chemical properties.[47] .During the synthesis and storage of nanoparticles, the stability of nanoparticle is essential parameter. For the implementation of the nanoparticle application, the particles must posses the following properties, such as magnetic saturation, stability, interactive functions at the surface and biocompatibility. Organic compounds used to increase surface of iron oxide nanoparticles during its preparation, to avoid the agglomeration between particles. .The aggregates cause instability in iron oxide nanoparticles and the reason behind of forming this aggregates are improper surface coating and hydrophobic interaction between nanoparticles.Furthermore to expand biological application of iron oxide nanoparticle biomolecules are used to increase its biocompatibility.[48]

Challenges and Future Aspects

Iron oxide nanoparticles (IONPs) have significant impact in biomedical applications, thus they face various challenges that must be studied for future advancements. [19]

The particle size and morphology, surface optimization, and maintain stability are the challenges for green synthesis of iron oxide nanoparticles. Future aspect should focus on enhancing biocompatibity to enhance biomedical applications.[49] Other challenges are to achieve uniformed size nanoparticles for narrow size distributionAnd other future aspects are functionalize this nanoparticles by coating it with biocompatible material to enhance its biomedicine application. [50]

Conclusion

Green synthesis of iron oxide nanoparticles is alternative method to chemical method as this method is safe, and ecofriendly. Green nanotechnology is the technology where nanoparticles are synthesized from various biological routes such as bacteria ,fungi and plants. Iron oxide nanoparticles has various biomedical application such as antimicrobial ,anticancer,antioxidant and in wound healing. Iron oxide nanoparticles have various biomedical applications due to their advanced properties such as eco-friendly nature, low toxicity, biocompatibility and supermagnestism. Various chacterization technique such as UV vis spectroscopy,X-ray diffraction,scanning electron microscope,Transmission electron microscope,and ,fourier transform infrared spectroscopy are used to reduce environmental impact by studying their size,shape,magnetic properties and phase structure. Stability is also important factor as it can affect the storage and quality of product. To inhance stability ,nanoparticles must have smaller particle size ,narrow particle size which help to maintain uniform

physico-chemical properties.The future challenge is to maintain the uniform size of nanoparticles and enhance their biomedical application.

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GREEN SYNTHESIS OF ZINC OXIDE NANO PARTICLES: AN EXPANED REVIEW WITH FOCUS ON BIOMEDICAL APPLICATIONS AND OPTIMIZATION TECHNIQUES

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ABSTRACT
Zinc oxide Nanoparticles i.e. Zinc Oxide Nanoparticles (ZnO NPs) have been in the limelight in recent years due to their unique properties and especially their biomedical applications. This review focuses on green synthesis of these zinc oxide nanoparticles highlighting the safer, nontoxic, harmless and eco-friendly nature of the method in contrast to conventional methods that often involve harmful chemicals. The threat of antimicrobial resistance has also been noted. This article discusses the recent developments in green synthesis of Zinc Oxide Nanoparticles (ZnO NPs), emphasising the biomedical applications including antimicrobial, anti-cancer, wound healing and antioxidant properties. The plant sources for the Zinc Oxide Nanoparticles (ZnO NPs) and their components are explored. The influence of biomolecules on synthesis as well as various characterization techniques and optimization techniques are thoroughly discussed. This paper also addresses the challenges and future prospects for scaling up the green synthesis for industrial production. The increasing role of Zinc Oxide Nanoparticles (ZnO NPs) in drug delivery, diagnostic imaging and tissue engineering are comprehensively examined as a transformative tool with potential to revolutionize the biomedical science.

KEYWORDS:
Green Synthesis, Zinc Oxide Nanoparticles (ZnO NPs) , plant extract, antioxidant properties, antimicrobial properties, nanotechnology

INTRODUCTION

The application of nanoparticles in biomedical field have been the centre of attraction in the recent years, particularly nanoparticulate metal oxides have garnered significant focus due to their extensive biomedical application. Zinc oxide nanoparticles (ZnO NPs) being one of the prominent nanoparticulate metal oxides has wide ranging utilization because of its distinct physicochemical properties [1]. The conventional methods for synthesis of nanoparticles such as chemical vapour deposition, spray pyrolysis and so on have high energy requirements, instability in unfriendly environment, hazardous chemicals, toxicity and bioaccumulation problems. To overcome these drawbacks green synthesis method is employed [2,3]. The green synthesised Zinc Oxide Nanoparticles (ZnO NPs) are proven to be eco-friendly as they apply green approach. The green synthesised Zinc Oxide Nanoparticles (ZnO NPs) are made by using different types herbal extracts for example the extracts of *Cayratia pedata*, [4] and other plants have been discussed in **table 1**. By using the herbal extract of plants like *Phlomis* the green synthesis of zinc oxide nanoparticle is possible and has been recognised as eco-friendly, energy saving and effective, results to be non-toxic and dodges the application of hazardous chemicals, making it eco-friendly which is highly unlikely in case of conventional methods that apply noxious and harmful substances and utilize huge amount of energy[5]. The activities like antibacterial, antidiabetic, antioxidant, antiparasitic, larvicidal, antimicrobial and potent photocatalysts for dye degradation are all the vital functions exhibited by green synthesised Zinc Oxide Nanoparticles which has been proven to be appropriate for biomedical and environmental applications [6]. This review focuses on the biomedical applications of Zinc Oxide Nanoparticles (ZnO NPs), the review puts light on their antimicrobial properties, anticancer properties, wound healing, and antioxidant properties. The review also focuses on optimization techniques of Zinc Oxide Nanoparticles (ZnO NPs). Furthermore, the review includes introduction of nanotechnology and characterization of the nanoparticles and their stability, the review also emphasizes the future prospects and challenges.

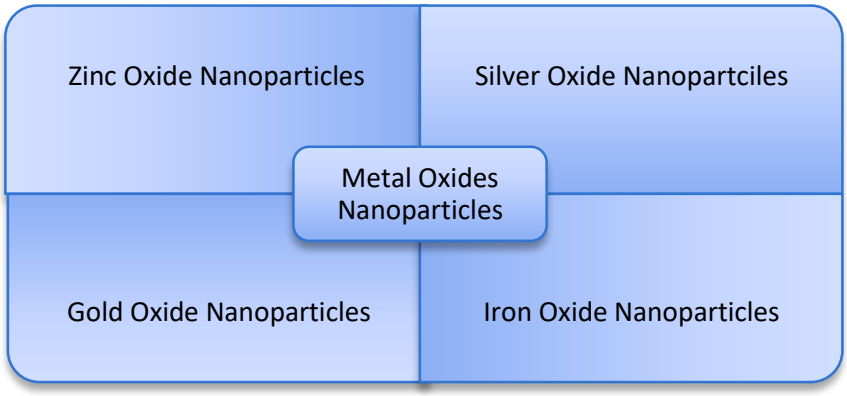
Nanotechnology

Nanotechnology has multiple usages in the betterment of the world and is one of the innovative routes for development in the sectors of technology which is related to the organization of the materials at nano meter scale (One billion smaller than meter). Further the nanotechnology is concerned with any technic which is scaled at nanoscale [7].

Human made nanoparticles typically range in less than 100 nm and show increased reactivity and large surface to volume ratio due to their miniature size. They have vast application as a contrast for medical imaging purpose or as vehicle in drug delivery.[8]

Nanotechnology in medications can enhance the bioavailability, bioactivity, efficacy, and achieve targeted drug delivery while reducing side effects, improving patient compliance and overcoming the drawbacks of traditional drug delivery [9].

The nanoparticles can be formed by changing the technique of fabrication and can be applied as vehicles used in drug delivery. Nanoparticulate drug delivery body capillary then conventional and do not cause embolism[10].
Many Inorganic nanoparticles such as metal oxides (zinc, aluminium, copper, gold, titanium and so on) are used in the biomedical industry for their effective antimicrobial properties.[8]
Different Metal Oxide Used in the Biomedical Applications. The Examples of Metal Oxides Are Given Below:
Figure no.1: Examples of Metal Oxides Used in Nanoparticle Synthesis (Figure referring to Various kinds of Metal Oxides used in the formulation of Nanoparticles)



Green Synthesis Methods
The outstanding green synthesis is a well-defined initiative made with the application of the natural sources such as herbs and the flora of microorganism which results in reducing the metal oxides like Zinc Oxide Nanoparticles (ZnO NPs). They are said to be causing nominal environmental hazard then chemical applied methods[11]. When compared to other "green" methods, plant extracts are considered to be the superior organic medium as they have a higher frequency rate of successful synthesis and have more stability, enhanced reduction speed of metal ions and are considered simple to scale up in contrast to microorganisms [12]. The green synthesis of the nanoparticles has been using the natural resources such as the crude extracts of herbs and plants. As the herbs and the environmental resources are applied they are obliging to the formation of nanoparticles more nontoxic and harmless[13]. Applications of the green synthesis in the last 10 years has got renowned, the nanotechnology has earned a greater success and application. It is reported that the green synthesized produced nanoparticles are has performed a substantial character in the diagnosis of various diseases and also has been used for clinical and hospital purposes[14].

Table 1: Plant Extracts Used for Green Synthesis of Nanoparticles of Zinc Oxide Nanoparticles (ZnO NPs)

Plant sources	Bioactive Compounds	References
Azadirachta indica	Flavonoids, vitamins, minerals, terpenoids, glycosides, alkaloids	Lema Yadeta Gemachua and Asnake Lealem Birhanub[15]
Vitex negundo	Flavonoids, terpenes, lignans, steroids, volatile oil	Singh et.al. [16]
Eucalyptus lanceolata	Phenols, flavonoids	Kumar et.al.[17]
Cassia fistula	Anthraquinones, flavonoids, flavon-3-ol derivatives, alkaloids, glycosides, tannins, saponin, terpenoids	Md. Asraf Ali[18]
Santalum album	Sandal wood oil, bargamotenes, sesquiterpenes hydrocarbons α-Santalol, α- andβ-Santalene	Kumar et.al.[19]

Biochemical Application of Zinc Oxide Nanoparticles (ZnO NPs)
1. Antimicrobial Properties
As the world is rapidly progressing towards the application of the Zinc Oxide Nanoparticles (ZnO NPs), these nanoparticles are seen to be demonstrating the antimicrobial activity against an infectious entity which have been proving an better antibiotic medicament substitutes for biomedical application as they are reported to possess exclusive mode of action and physiochemical parameters[20]
During literature review we have studies different articles which the possess the use of different plants extracts like, for an occurrence, it has been reported that using the green synthesis of Zinc Oxide Nanoparticles (ZnO NPs), with the leaves of *Salvia officinalis* leaves crude extract, reported to be possibly applicable in the antifungal activities and an effective photocatalytic derivative thus not explicitly for herbs[21]

During the literature review it is also noted that the green synthesis of zinc oxide nanoparticles (ZnO NPs) exhibited antimicrobial effects counter to E. coli, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans further signifying the possibility for antimicrobial application [22] The Zinc Oxide Nanoparticles (ZnO NPs) show evidence of antibacterial activity against the Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella, and Staphylococcus aureus, outstanding the efficiency and of the antibiotics such as penicillin, gentamycin, and tetracycline[23] Also the literature explains the mechanism that the antimicrobial activity of the Zinc Oxide Nanoparticles (ZnO NPs) occurs by damaging the bacterial cytoplasmic membranes and formation of reactive oxygen species and emission of Zn2+ ions, they are capable in destruction of Gram- negative and Gram-positive bacteria[24]

Table 2: Table summarizing the antimicrobial properties of Zinc oxide nanoparticles including microorganism and type of mechanism of action

Microorganism species	Antimicrobial Mechanism of zinc oxide nanoparticles	References
Escherichia coli, Bacillus subtilis	Zinc oxide disturb bacterial cell membrane because of nano size which results in cell death	**Jasni Mohamed Ismail et al. [25]**
Streptococcal strains	Zinc oxide shows Reduction in the viability of streptococcal oral strains further avoiding bacterial colonization on dental implants	**Petrini et al. [26]**
Pseudomonas aeruginosa	Disrupt the cytoplasmic membrane of the microorganism which result in damage to membrane, inhibition of protein synthesis and oxidative stress and the DNA replication	**Hakmin Lee[27]**

2. Anticancer properties

The Zinc Oxide Nanoparticles (ZnO NPs) are proven to showcase an outstanding approach in and as anticancer drug. The green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) are recognized to be non-hazardous to the natural sources and further propose to be eco-friendly method for the anticancer application as they are reported to have innate cytotoxicity activities proving them as an significant emerging new anticancer medications[28]. For an instance the research of Al-Ajmi et al. states the anticancer property of Zinc Oxide Nanoparticles (ZnO NPs) using various leaves extracts such as using the *Alstonia macrophylla* leaves extract has been proven to be cost effective, environmental and adaptive technique. It's have been noted that with different concentrations of zinc oxide nanoparticles was measured in human cancerous cells lines of MCF-7(breast cancer), hepG (liver cancer). It's is reported that, as there was increase in the concentration of the Zinc Oxide Nanoparticles (ZnO NPs) the cancer cell viability was proven to decrease after all the cytotoxicity assay was done .This has helped in understanding that by green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) there is a hope of developing anticancer drug using the Zinc Oxide Nanoparticles (ZnO NPs)[29].

The anticancer mechanism that is shown by the Zinc Oxide Nanoparticles (ZnO NPs) have also been noted in the review such as the Zinc Oxide Nanoparticles (ZnO NPs) persuade and bring apoptosis in Neuro 2a neuroblastoma cells through the intrinsic mitochondrial pathways, activating caspases 3 and 9 though dropping Bcl-2 and upregulating Bax protein[30].The anticancer mechanism in different type of cancer is given in **table no.3.** One of many such anticancer mechanism of Zinc Oxide Nanoparticles (ZnO NPs) was given by Shawki et al. as ZnO NPs also demonstrate the anticancer activity by augmenting the cell death in cancerous cells, predominantly when combined with tumor- treating fields, boosting deadliness without raising reactive oxygen species levels[31]. The anticancer mechanism of Zinc Oxide Nanoparticles (ZnO NPs) also possesses the following mechanism example that the Zinc Oxide Nanoparticles (ZnO NPs) revel substantial anticancer activity against HeLa cells by propagating apoptosis through the inhibition of β-catenin and enhancing p53, caspase-3 and caspase-9 levels[32].

Table 3: Table summarizing the anticancer properties of Zinc oxide nanoparticles including different type of cancer and of mechanism of action

Cancer Types	Anticancer Mechanism of zinc oxide nanoparticles	References
Human Breast Cancer	Zinc oxide nanoparticles inhibit the cancerous cell growth by up-regulating p53 expression and down regulation of the Bcl-2 which decreases the cell invasion in MCF-7 cells and increases the apoptosis	**Hoseinzadeh et al. [33]**
Lung Cancer	Zinc oxide nanoparticles give the controlled release of anticancer drug such as doxorubicin through pH-sensitive dissolution then generate hyperthermia under near IR-radiation thereby inhibit cancerous cells in lungs	**Cai et al. [34]**
Skin Cancer	Zinc oxide nanoparticles are proven to disrupt the mitochondrial membrane, activating the caspase cascades and persuading apoptosis in cancerous cells	**Anjum et al. [35]**
Prostate Cancer	Zinc oxide nanoparticles show apoptosis used and intraprostatic zinc ion injection is used to treat tumor, effective in prostatitis, benign hyperplasia, and early carcinoma	**Mostafa S. Fahim[36]**

3. Wound Healing applications

As the Zinc Oxide Nanoparticles (ZnO NPs) are seen and perceived to have the wound Heal activity because of their antimicrobial properties. In achieving the Wound Healing activity of Zinc Oxide Nanoparticles (ZnO NPs), many different herbal extracts are used such as, the studies have shown that with the green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) using the *Sea lavender* extracts, they have been proven effectives as in wound healing, antioxidant, antimicrobial activities as when they were estimated and characterized[37]

This green synthesis methods have been applicable in the mitigation of different disease and work as to show antifungal, wound healing, anti-inflammatory, anticancer properties and further more is of great uses.[38] The Wound Healing mechanism of Zinc Oxide Nanoparticles (ZnO NPs) have also discussed in literature review such as the Zinc Oxide Nanoparticles (ZnO NPs) improve the wound healing by modulating inflammation, antimicrobial efficiency, and proven to be mitigating biofilm development of key wound pathogens[39] One of various Wound Healing mechanism it is also been noted in the literature that the Zinc Oxide nanoparticles (ZnO NPs) enhance wound healing by endorsing the process of re-epithelization, cellular migration, collagen deposition and also angiogenesis as confirmed by improved healing quality in PLGA/SF nanofibrous membranes[40] In the literature review as the wound healing properties of Zinc Oxide Nanoparticles (ZnO NPs) have also been noted in animal burns, such as the wound healing by Zinc Oxide Nanoparticles (ZnO NPs) is enhanced by antioxidant enzyme activity and also rising microcirculation, as displayed in rat burn wound model hydrophilic nanocomposites[41] The Zinc Oxide Nanoparticles (ZnO NPs) when coated with different polymeric layer shows significant activity, this has been also covered in the literature review such as the zinc oxide nanoparticles when coated with Rhamnolipid shows remarkable wound healing activity that promote wound contraction and efficient tissue remodelling in wounds which possess infection this study was noted by 5th day of treatment by the researchers [42] The different investigational reports of wound healing mechanism are also have been made by the researchers this has also been noted in the review such as like by increasing antibacterial activity and endorsing wound healing properties of Zinc Oxide Nanoparticles (ZnO NPs) as demonstrated by the fast and hasty regeneration and amplified collagen-1α and cytokeratin-14 expression in the Zn-Eclp3 Hydrogel investigational report[43] In Different conditions like diabetes mellitus, the Zinc Oxide Nanoparticles (ZnO NPs) are proven to be useful like as Zinc Oxide Nanoparticles (ZnO NPs) present antibacterial properties and elevate the wound healing process in infectious wound of skin, it is then beneficial in diabetic conditions with is being taken care in nursing care in training of sports[44] The wound healing mechanism in different type of wounds are given in **table no.4** The comprehensive comparison in between nanoparticle and microparticle is also noted in our literature review such as when as the study for microparticles and nanoparticles are done it's have been proven that Zinc Oxide Nanoparticles (ZnO NPs) possess higher healing rate of 16.23% compared to microparticles. It is also has been reported that Zinc Oxide Nanoparticles (ZnO NPs) has 24.33% higher healing than the control group in burn wound models[45]

Table 4: Table summarizing the Wound Healing properties of Zinc oxide nanoparticles including different type of Wounds and of mechanism of action

Wound Types	Wound Healing Mechanism of zinc oxide nanoparticles	References
Stomach Ulcer	Zinc Oxide Nanoparticles shows antibacterial, anti-inflammatory properties that promotes wound healing and re-epithelialization	**Raguvaran et al.[46]**
Diabetic Foot Ulcer	The wound healing is achieved by enhancing re-epithelialization, collagen deposition and angiogenesis	**Khan et al.[47]**
Chronic wounds and Burns	Zinc oxide nanoparticles modulate inflammation and inhibit biofilm formation in wounds and burns	**Rayyif et al.[48]**
Surgical wounds	Zinc oxide nanoparticles and gold oxide nanoparticles when combined as core shell structure promotes fibroblast and keratinocyte migration and re-epilialization and heal surgical wounds	**Khan et al.[49]**

4. Anti-oxidant properties

Zinc oxide nano particles exhibit antioxidant properties by inducing oxidative stress which help in mitigation of various conditions like cancer, diabetes and infections[50]. The Zinc Oxide Nanoparticles (ZnO NPs) that are synthesized by application of plant extracts have been reported to be exhibiting more boosted antioxidant activity when as equated and compared to the traditional ways of chemically synthesized ZnO nanoparticles, as representing their latent possible potential as effective antioxidant agents which can be great use[51]

The application of various plants extracts and Zinc Oxide Nanoparticles (ZnO NPs) that exhibits Anti-oxidant properties are also has been discussed in our literature review as follows; As the Zinc Oxide Nanoparticles (ZnO NPs) possess the anti- oxidative properties the study have been shown that using plants extracts of *mulberry fruit* as a green reducing agent and zinc acetate as a precursor, the antioxidative properties of Zinc Oxide Nanoparticles (ZnO NPs) are achieved and noted[52] The study also made with using different herbs like *Syzygium cumini* (java plum) extract as reducing agent to the zinc oxide nanoparticles and identify the antioxidant properties[53] The Zinc Oxide Nanoparticles (ZnO NPs) enhance antioxidant activity in *Persicaria* hydropiper by boosting phenolics, flavonoids, activating antioxidative enzymes and also free proline thus lessening oxidative stress from lead exposure[54] The Zinc Oxide Nanoparticles (ZnO NPs) which are made and synthesised by the *Maranta arundinacea* root extracts

are proven to present the significant antioxidant activity which are Signifying their outstanding potential for medical applications and necessitating antioxidant properties[55] The Zinc Oxide Nanoparticles (ZnO NPs) shows antioxidant activity by increasing levels of antioxidant enzymes and dropping the oxidative damage, predominantly when united with *Green Tea extract* in contradictory to monosodium glutamate toxicity[56] Some of various mechanism of antioxidant properties of Zinc Oxide Nanoparticles (ZnO NPs) are also have been cover in our literature review such as the supplemental Zinc Oxide improves antioxidant activity in broilers by enhancing GSH-Px, T-AOC levels and CAT though forming reduction in free radical content, at optimal doses of 40 & 80 mg/kg[57] As the analysis done by Ismet Meydan et al.the Zinc Oxide Nanoparticles (ZnO NPs) shows antioxidant activity, with a DPPH radical quenching value of 79.871, this results in indication as effective antioxidants compared to positive controls BHA and BHT[58]

Table: 5 Table summarizing Anti-oxidant properties of Zinc oxide nanoparticles including different types protective mechanism of action including different types protective mechanism of action

Type of diseases	Anti-oxidant Mechanism of zinc oxide nanoparticles	References
Cardiovascular Diseases	Zinc oxide nanoparticles reduce oxidative stress by increasing glutathione levels and superoxide dismutase activity, lowering inflammatory markers	**Bashandy et al.**[59]
Urinary tract disease	Zinc oxide nanoparticles restore the redox status and decrease oxidative stress in diabetic nephropathy which leads to urinary diseases	**Abd El-Khalik et al.** [60]
Skin diseases	Zinc oxide nanoparticles reduce oxidative stress by triggering excessive reactive oxygen species formation which can lead to cell apoptosis and reduce inflammation	**Murali et al.**[61]

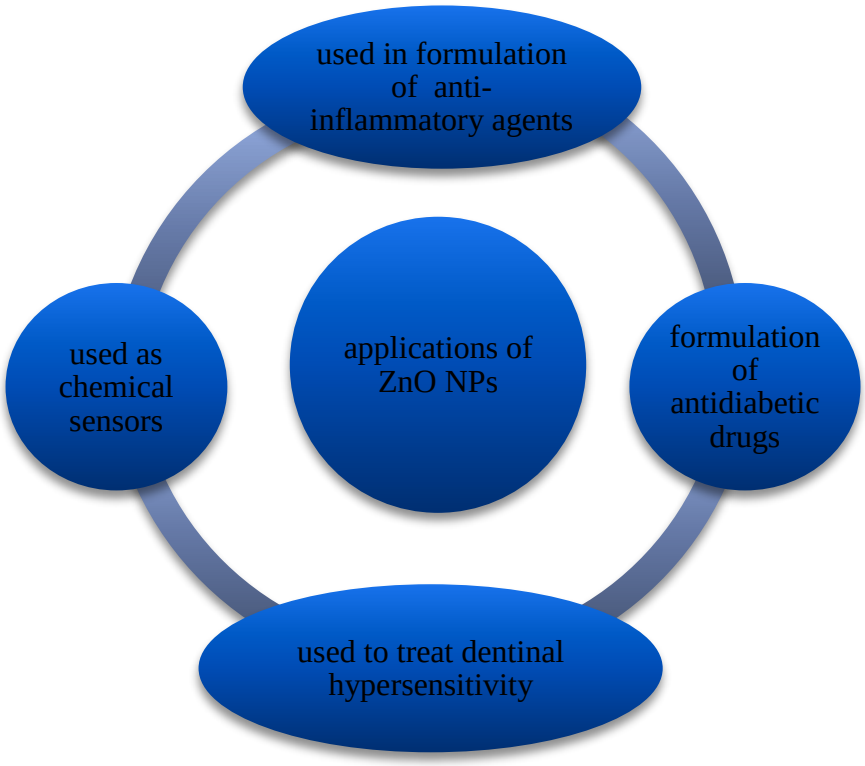


Figure no. 2: Applications of Zinc Oxide Nanoparticles (ZnO NPs) (Figure referring to different types of applications which are performed by the Zinc Oxide Nanoparticles (ZnO NPs) in association with different diseases and areas)

Characterization of Green- Synthesized Zinc Oxide Nanoparticles (ZnO NPs)

The most amazing and successful green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) can be characterized by using these techniques such as **scanning electron microscopy (SEM), Energy Dispersive X-ray analysis (EDX), Fourier transform infrared spectroscopy (FT-IR),X-ray diffraction(XRD), and UV-Vis spectroscopy**[62]

Table 6: Characterization Techniques for Zinc Oxide Nanoparticles (ZnO NPs)

Technique	Information Obtained	Reference
UV-Vis Spectroscopy	optical properties of nanosized particles and Absorption spectra	**Talam et al. [63]**
SEM	Homogeneity and agglomeration	**Hammadi et al. [64]**
XRD	Zinc oxide forms as ZnO and has hexagonal structure	**Arora et al. [65]**
TEM	Particle size of zinc oxide nanostructure	**RL et al. [66]**
FTIR	Indicate purity of zinc oxide	**AL- Asady et al. [67]**

These characterization techniques as mentioned above are of great importance for determining the size, shape, and the factors of Zinc Oxide Nanoparticles (ZnO NPs), they certify their efficacy, potency and suitability for multiple industrial usages[68]

After performing the above characterization techniques and confirming the synthesized product was zinc oxide nanoparticles, Jayachandran et al. immobilized the glucose oxidase enzyme on the synthesized zinc oxide nanoparticles and noted that the green synthesized zinc oxide nanoparticles gave 60% of relative activity for enzyme immobilization and it is 88.2 % of the native zinc oxide activity [69].

Optimization of green synthesized Zinc Oxide Nanoparticles (ZnO NPs)

The Optimization of green synthesized Zinc Oxide Nanoparticles (ZnO NPs) are covered in our literature review such as **Quality By Design i.e. QBD** helps in comprehending critical quality attributes(CQAs) such as particle size ,stability, and drug entrapment, as they are crucial for Zinc Oxide Nanoparticles (ZnO NPs) used in the novel drug delivery system[70]

It has been shown in the study that for determining optimal conditions for Zinc Oxide Nanoparticles (ZnO NPs) synthesis, nanoparticle loading, initials concentration, pH, and reaction time the **I-optimal Method** is used as optimization process[71]

The optimization process for Zinc Oxide Nanoparticles (ZnO NPs) uses **Taguchi Method** in order to classify and improve synthesis parameter, which advance the photocatalytic degradation effectiveness of toxins like Methylene blue[72]

The study shows that effective optimization of Zinc Oxide Nanoparticles (ZnO NPs) through the technique like **Microwave-assisted synthesis** by the application of plant extract of *Pistia Stratiotes*, further getting the size in range of 35nm and advantageous antibacterial and anticancer activity[73]

Table 7: Table summarizing Optimization Techniques of green synthesized Zinc Oxide Nanoparticles (ZnO NPs)

Optimization techniques	Optimized Outcomes	References
Taguchi Methodology	pH, concentration, voltage and conductivity parameters	**Anand et al. [74]**
ANOVA (Analysis of Variance)	Evident the relationship between the variables of model and the average size of nanoparticles	**Al-Kordy et al. [75]**
Design of Experiment (DOE)	Used in identifying and controlling variables involved in scaling-up process of nanocarriers in large scale production	**Marcela Tavares Luiz[76]**

The optimization process for Zinc Oxide Nanoparticles (ZnO NPs) can be done by involving different plant extracts such as;

The study presented that by optimization of Zinc Oxide Nanoparticles (ZnO NPs) which by involving the extracts of *Calendula officinalis* leaf have been fixed through spectroscopic methodologies, that to increase their structural stability and functional properties[77]

The study has been done that optimization of Zinc Oxide Nanoparticles (ZnO NPs) can be made by fluctuating the synthesis temperature in between 70°C and 80°C and by application of herbal extracts of *Onion Peel* extract, that results in crystalline particles sized in between 21.4 and 38.1nm[78]

Software use: Minitab for design of experiment (DOE)

Stability of Green Synthesized Zinc Oxide Nanoparticles (ZnO NPs)

The stability is the degree of being stable, the stability is a vital aspect of the Zinc Oxide Nanoparticles (ZnO NPs). The stabilizing agents of the Salvia Officinalis leaves are reported to be proven to increase the stability of the bio-fabricated Zinc Oxide Nanoparticles (ZnO NPs) which results in the avoiding of agglomeration during the Zinc Oxide Nanoparticles (ZnO NPs) administration[21]

The green synthesised Zinc Oxide Nanoparticles (ZnO NPs) i.e. the zinc oxide which are prepared by the green methods reveals lower thermal stability. The thermal stability is lesser compared to those Zinc Oxide Nanoparticles (ZnO NPs) Which are made by using chemical methods, specified by DTG and TGA analyses[79]

Zinc Oxide Nanoparticles (ZnO NPs) while in green synthesis have essential factor of stability, the stability of the Zinc Oxide Nanoparticles (ZnO NPs) in green synthesis can be boosted by application of microorganisms, biomolecules, natural extracts while being in the synthesis procedure as they act as reducing agents and increase stability[80]

Challenges and Future Prospects

In spite of all the vital advancement there are still many challenges to be faced in the green synthesis of Zinc Oxide Nanoparticles (ZnO NPs).

The changeability in nanoparticle's shape and size, the stability matters all this can be a challenge and there is always a necessity for an widespread research to scale up the industrial production when using the nanoparticles and to evaluate and recognize the pharmacokinetic, pharmacodynamic and bioavailability in the mankind[81]

Moreover, challenges can include change in the extract used, its composition, the scale up of the synthesis, nature of biodegradation and also effect on environment. The limitation can be proficiency of dye degradation and the efficacy of the nanoparticle in antimicrobial activity under different conditions[82]

The most prominent challenge is above mentioned i.e. scaling up of the synthesis for functioning in industrial scale this is a barrier and a problem because sustaining the efficacy and the quality at industrial scale is very difficult[83]

The future prospects of the green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) are promising as they possess multiple functions and they are eco-friendly in nature and their production methods. The future prospects may include boosting the usage in drugs, increasing application in nanotechnology, influence their biocompatibility, antimicrobial, antibacterial properties and developing workable production methodologies for large scale industrial production[84]

The promising future aspect of Zinc Oxide Nanoparticles (ZnO NPs) may also consist of heightened use in the photocatalysis and antibacterial agents[85]

CONCLUSION

The green synthesis of Zinc Oxide Nanoparticles (ZnO NPs) demonstrates a favourable approach to production of nanoparticles showcasing an eco-friendly, safe and sustainable alternative to the conventional methods. By utilizing the plant extracts and other natural resources like algae, and microorganism, the environmental impact is significantly reduced and also with the introduction of bioactive compounds that improve stability and biocompatibility enhance the therapeutic potential of the Zinc Oxide Nanoparticles (ZnO NPs). The aforementioned applications in the antimicrobial therapy, cancer treatment, anti-oxidant therapy, wound healing, drug formulation and drug delivery highlight the versatile nature of the ZnO NPs in biomedical field. The optimization techniques were also have been discussed in the review.

Future research should focus on the most prominent challenge i.e. developing workable production methodologies for scaling the production to large scale industrial level.

Further exploration of enhancing stability and efficacy of nanoparticles in antimicrobial activity, and deeper understanding of biological interaction is necessary.

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In Press, Corrected Proof What's this?

Short review

Nanosuspensions: Enhancing drug bioavailability through nanonization

Nanosuspensions : améliorer la biodisponibilité des médicaments par la nanonisation

Rohit Chavhan ✉

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Highlights

- Nanosuspensions revolutionize drug delivery: nanosuspensions represent a cutting-edge dosage form with the potential to transform drug delivery by enhancing the bioavailability of poorly soluble medications.
- Critical role of particle size reduction: nanonization techniques play a pivotal role in reducing particle size, thereby overcoming challenges associated with low solubility in both aqueous and organic environments.
- Versatility in administration routes: nanosuspensions offer versatility in administration routes, spanning parenteral, peroral, ocular, and pulmonary pathways, making them suitable for various dosage forms.

- Diverse preparation techniques: various preparation techniques such as high-pressure homogenization, media milling, and precipitation contribute to the expanding repertoire of nanosuspension formulation methods, each offering unique advantages and limitations.
- Focus on targeted drug delivery: ongoing research aims to further nanosuspensions' application in site-specific drug delivery, indicating their potential for tailored therapeutic strategies.
- Importance of formulation and stabilization: careful formulation and stabilization using polymers and surfactants are essential to ensure the efficacy and safety of nanosuspensions.
- Comprehensive overview: the article provides a comprehensive overview of nanosuspensions, covering their benefits, drawbacks, characterization, patents, marketed products, and intended uses, serving as a valuable resource for future research endeavors in pharmaceutical sciences.

Summary

Introduction

Nanosuspensions have emerged as a promising avenue in pharmaceutical innovation, particularly for enhancing the bioavailability of poorly soluble medications. This article explores the transformative potential of nanosuspensions, emphasizing the critical role of particle size reduction through nanonization techniques. With conventional approaches often falling short in addressing the bioavailability challenges of hydrophobic drugs, nanosuspensions offer multifaceted applications and distinctive advantages in drug delivery.

Methods

The study delves into various nanosuspension preparation techniques, including high-pressure homogenization, media milling, emulsification-solvent evaporation, precipitation, and supercritical fluid processes. Each method brings unique advantages and limitations, contributing to the expanding repertoire of nanosuspension formulation methods. The article emphasizes the necessity for meticulous planning, evaluation, and ongoing research across different drugs to optimize their use effectively.

Results

Nanosuspensions exhibit versatility in administration routes, spanning parenteral, peroral, ocular, and pulmonary pathways, making them applicable across diverse dosage forms.

Current efforts are directed towards furthering their application in site-specific medication administration, indicating their potential in tailored therapeutic strategies. Nanosuspensions offer a promising solution for enhancing drug solubility and bioavailability, addressing the persistent challenge of poor solubility in pharmaceutical compounds.

Discussion

The significance of careful formulation and stabilization using polymers and surfactants is underscored, ensuring the efficacy and safety of nanosuspensions. By discussing the benefits, drawbacks, and nuances of each preparation technique, the article aims to simplify future research endeavors in the field of nanosuspensions. Additionally, a comprehensive overview of nanosuspensions, including their preparation methods, benefits, characterization, patents, marketed products, and intended uses, sheds light on this evolving domain in pharmaceutical sciences.

Conclusion

Nanosuspensions represent a promising approach for overcoming bioavailability challenges associated with poorly soluble medications. The article highlights their transformative potential in pharmaceutical innovation, emphasizing the importance of continued research and optimization to harness their benefits effectively. Nanosuspensions offer a viable solution for enhancing drug solubility and bioavailability, with implications for improving therapeutic outcomes in various medical conditions.

Introduction

Surfactants and polymers stabilise submicron colloidal dispersions of pharmaceutical active ingredient particles in a liquid phase, with a size less than 1 μm, and no matrix material. These are known as nanosuspensions. Solid lipid nanoparticles are lipid carriers of medications, while nanoparticles are polymeric colloidal carriers of pharmaceuticals [1]. This is how nanosuspensions vary from both types of nanoparticles. A growing number of recently created medications have low solubility; often, these medications have poor solubility in both organic and aqueous environments, making conventional methods of addressing such solubility variables ineffective and leading to issues with bioavailability [2]. To get around these issues, making medication nanoparticles, or nanosuspensions, is a different and potentially effective strategy. Because of their many uses and distinctive benefits, nanosuspensions have become a viable method for the effective administration of hydrophobic medications. Because of their specific qualities, nanosuspensions may now be used in a wide range of dosage forms, including ones that need specialised delivery methods like mucoadhesive hydrogels. This technology's main benefits are its simplicity and broad application to most medications. Making a nanosuspension is easy and works with any medication that is insoluble in water [3]. Wet mills, high-pressure homogenizers, melt emulsification, emulsion solvent evaporation, and supercritical fluid processes are used to

create nanosuspensions. It is possible to administer nanosuspensions orally, parenterally, pulmonaryly, or intraocularly. Utilising nanosuspensions in mucoadhesive hydrogels and ocular inserts allows for tailored medication delivery as well. At the moment, efforts are focused on expanding their use in medication administration that is site-specific. The distribution of nanosuspensions via parenteral, peroral, ocular, and pulmonary routes has advanced quickly [4], [5].

The pharmaceutical industry is always looking for innovative methods to achieve a sufficient oral bioavailability since the majority of biological characteristics that show non-clinical oestrogens are poorly soluble in water. The pharmaceutical industry's efforts to develop new formulations are hindered by the growing number of poorly water-soluble natural compounds (NCEs) that show therapeutic activity. This is because lead compounds in drug formulations with poor permeability and solubility have a low turnout rate for the development of new molecular entities. Recently, the development of new and innovative drug delivery methods using nanoscale systems –drugs smaller than 1 μm in size– has progressed quickly [6], [7]. These systems' primary feature is their quick rate of dissolution, which improves bioavailability after oral delivery. Reviewing nanosuspensions as a new and exciting option for the formulation of poorly soluble medications is the goal of this paper.

Section snippets

Rapid onset of action

Parenteral administration delivers drugs directly into the bloodstream or specific tissues, resulting in a swift therapeutic effect. This is particularly beneficial for emergency treatments, where rapid drug action is crucial, such as in acute pain management or life-threatening infections. …

High bioavailability

Since the drug bypasses the gastrointestinal tract and first-pass metabolism, almost the entire dose reaches systemic circulation, ensuring maximum efficacy. This is especially important for drugs with poor …

Convenience

Oral administration is the most preferred route due to its ease of use and non-invasiveness. Patients can self-administer oral medications without the need for healthcare professionals, making it highly convenient and increasing adherence to treatment regimens. …

Versatility

Nanosuspensions can be incorporated into various oral dosage forms, including tablets, capsules, and liquid formulations, allowing for flexibility in formulation design. This versatility enables the tailoring of dosage forms to meet …

Localized delivery

Ocular nanosuspensions provide targeted drug delivery to the eye, minimizing systemic exposure and reducing the risk of systemic side effects. This is crucial for treating eye conditions where high local concentrations of the drug are needed, such as in glaucoma or uveitis. …

Enhanced penetration

The small particle size of nanosuspensions facilitates better penetration through the ocular barriers, such as the cornea and conjunctiva, leading to improved drug efficacy and therapeutic outcomes. This can be particularly …

Direct lung delivery

Pulmonary administration allows direct delivery of drugs to the lungs, making it ideal for treating respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary infections. This targeted approach results in high local drug concentrations and rapid therapeutic effects. …

Rapid absorption

The extensive surface area of the alveoli and the thin epithelial barrier facilitate rapid drug absorption into the bloodstream, making the pulmonary route suitable for both local and systemic …

Non-invasive

Dermal application is non-invasive and can be self-administered, enhancing patient compliance. It avoids the pain and potential complications associated with injections, making it more acceptable to patients. …

Localized treatment

Nanosuspensions allow for localized drug delivery to the skin, reducing systemic exposure and side effects. This is particularly useful for treating skin conditions where high local drug concentrations are required, such as in psoriasis or localized infections. …

Skin penetration

Achieving adequate penetration …

Targeted therapy

Site-specific delivery allows for the direct administration of drugs to the intended site of action, enhancing therapeutic efficacy. This targeted approach minimizes systemic exposure and reduces the risk of off-target effects, making it particularly valuable for treating localized diseases such as tumors or infections. …

Reduced side effects

By concentrating the drug at the site of action, systemic side effects are minimized. This improves the safety profile of potent drugs, such as chemotherapeutic agents, which can …

Definition

When a pharmaceutical is administered orally, topically, parenterally, or through the lungs, it is described as a “very finely dispersed solid drug particles in an aqueous vehicle, stabilised by surfactants, with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability”. The suspended particle has a diameter of less than 1 μm, or between 0.1 and 1000 nm. With an average particle size spanning between 200 and 600 nm, the solid particles in …

Differentiating nanosuspensions

Nanosuspensions represent a remarkable departure from conventional drug delivery systems like solid lipid nanoparticles and polymeric nanoparticles. They are a distinct form of drug delivery characterized by submicron-sized solid drug particles dispersed within an aqueous medium. These particles are skillfully stabilized by surfactants, forming a stable colloidal dispersion without the presence of any matrix material. This unique composition allows nanosuspensions to overcome some of the …

Rising need due to poor solubility

The emergence of nanosuspensions as a crucial pharmaceutical innovation is rooted in the prevailing challenge of poor solubility encountered by a significant number of newly developed medications. A considerable portion of these medications exhibits low solubility in both aqueous and organic environments. Conventional drug formulation techniques often fall short in effectively addressing this inherent issue, resulting in compromised bioavailability and efficacy of these drugs. This growing need …

Nanosuspensions as a solution

Nanosuspensions offer a compelling solution to the hurdles posed by the low solubility of medications. Their effectiveness lies in their simplicity and their adaptability across a wide spectrum of medications, particularly those categorized as hydrophobic drugs. These suspensions serve as a versatile platform that accommodates various drugs with different solubility profiles, offering a viable method for enhancing their bioavailability. By breaking down drugs into submicron-sized particles and …

Enhanced drug solubility

The primary objective of nanosuspensions is to address the challenge of low solubility by reducing drug particle size to a submicron scale. This reduction significantly increases the surface area of the drug particles, leading to improved solubility in both aqueous and organic environments. …

Improved bioavailability

By increasing drug solubility, nanosuspensions play a crucial role in enhancing the drug's bioavailability. The submicron-sized particles dissolve more rapidly, resulting in a higher concentration gradient …

Oral bioavailability challenges

Pharmacokinetic analyses of medications falling under Biopharmaceutics Classification System (BCS) class-II reveal a common challenge–low oral bioavailability. This issue primarily stems from the low water solubility of these medications, hampering their efficient absorption and utilization within the body [21]. …

Novel techniques exploration

The limitations in bioavailability associated with BCS class-II drugs have spurred a quest for innovative strategies to overcome this challenge. Nanosuspensions emerge as a promising …

Nanosuspensions and dissolution rates

Nanosuspensions play a pivotal role in enhancing the dissolution rates of medications. By reducing the particle size of drugs to submicron levels, nanosuspensions significantly increase the surface area available for dissolution upon administration. This, in turn, accelerates the rate at which the drug dissolves [23]. …

Concentration gradient improvement

The heightened dissolution rate achieved through nanosuspensions leads to a more significant concentration gradient between the drug in the gastrointestinal lumen and its presence …

Prevalence of solubility issues

Over 40% of medications encounter solubility challenges, posing significant hurdles in their effective formulation and delivery. Among these, BCS class-II medications are particularly notable for their low solubility in both organic and aqueous mediums [25]. …

Complexity of class-II medications

Class-II drugs, characterized by their low solubility and high permeability, present a unique challenge due to their ability to dissolve only at a slow rate in the gastrointestinal tract. This limits their absorption and subsequently impacts …

Tailored approach for class-II medications

Nanosuspensions present a tailored approach to address the solubility challenges specifically encountered by BCS class-II medications. By reducing drug particle size to the nanoscale, these suspensions offer a viable solution to improve solubility and subsequently enhance bioavailability [26], [27]. …

Comprehensive examination of solubility enhancement mechanisms in nanosuspensions

Nanosuspensions have emerged as a promising strategy for enhancing the solubility and bioavailability of poorly soluble drugs. Understanding the underlying mechanisms, including the application of fundamental equations such as the Noyes-Whitney and Nernst-Brunner equations, is essential for elucidating the solubility enhancement process. Let's delve deeper into these mechanisms and explore the effects of key parameters on solubility enhancement in nanosuspensions. …

Noyes-Whitney equation: enhancing dissolution rate

The Noyes-Whitney equation describes the rate of dissolution of a solid particle in a solvent and highlights the critical role of particle size in enhancing dissolution kinetics. It is expressed as:$$dM/dt = A \cdot D \cdot (Cs - C/h)$$

Where:

- dM/dt represents the rate of dissolution; …
- *A* is the surface area of the solid particle; …
- *D* is the diffusion coefficient of the solute in the solvent; …
- *Cs* is the concentration of the solute at the surface of the solid particle; …
- *C* is the concentration of the solute in the bulk solvent; …
- *h* …

…

Particle size (surface area)

According to the Noyes-Whitney equation, the dissolution rate is directly proportional to the surface area of the solid particle. By reducing particle size to the nanoscale, nanosuspensions significantly increase the available surface area for dissolution, leading to enhanced dissolution rates and faster onset of action. …

Diffusion coefficient

The diffusion coefficient reflects the mobility of the solute molecules within the solvent. In nanosuspensions, the reduced particle size results in a larger interface between …

Nernst-Brunner equation: electrostatic stabilization

The Nernst-Brunner equation describes the electrostatic stabilization mechanism employed in nanosuspensions, particularly in the presence of stabilizing agents such as surfactants or polymers. It is expressed as:$$V = k \cdot T \cdot e/\mu \cdot \ln(Cs/C)$$

Where:

- *V* is the zeta potential; …
- μ is the electrokinetic potential; …
- *k* is Boltzmann's constant; …

- *T* is the temperature; …
- *e* is the elementary charge; …
- *Cs* is the concentration of the solute at the surface of the solid particle; …
- *C* is the concentration of the solute in the bulk solvent. …

…

Zeta potential (electrokinetic potential)

The zeta potential reflects the surface charge of the nanoparticles and plays a crucial role in electrostatic stabilization. By increasing the zeta potential through the adsorption of stabilizing agents, nanosuspensions can prevent particle aggregation and maintain colloidal stability, thereby enhancing solubility and dispersion. …

Concentration gradient

The concentration gradient of charged species influences the distribution of ions around the nanoparticles, affecting the magnitude of the zeta potential. …

Top-down approach

This method involves reducing particle size from larger particles to nanoscale dimensions. Techniques like high-pressure homogenization and media milling fall under this category. Here, the process begins with larger particles that are subsequently broken down into smaller particles, ultimately achieving nanosuspensions [31], [32]. …

Bottom-up approach

In contrast, the bottom-up method assembles nanoparticles from molecular components. Techniques such as precipitation, emulsification-solvent evaporation, and …

High-pressure homogenization

This technique involves applying high pressure to force drug particles through small gaps, reducing their size. It is advantageous due to its scalability and ability to produce stable nanosuspensions. However, it may require multiple cycles for optimal particle size reduction [32]. …

Media milling

Using milling media, this method applies high-energy forces to break down drug particles into smaller sizes. While it is effective in achieving small particle sizes, it can be time-consuming and might result in some …

Particle size control

Each technique offers varying control over particle size, allowing for tailored nanosuspensions. …

Stability and scalability

Some methods provide stable nanosuspensions suitable for scaling up production. …

Ease of production

Certain techniques are simpler and more straightforward in their application. …

Particle size distribution

Some methods might result in a broader particle size distribution, affecting uniformity. …

Production time

Certain techniques can be time-consuming, impacting efficiency and scalability. …

Stability challenges

Some processes might require additional stabilizers or surfactants to maintain …

Process explanation

High-pressure homogenization is a mechanical process used to reduce particle size through intense forces generated by forcing drug particles through small gaps at high pressure. This action subjects the particles to cavitation, shear stress, and collisions, effectively breaking them down into smaller sizes. However, this process often necessitates the creation of a suspension before the actual homogenization step. The suspension ensures the uniform dispersion of drug particles before subjecting …

Bottom-up process technology

The bottom-up approach involves synthesizing nanoparticles from molecular or atomic levels. This method includes various sophisticated techniques, each designed to ensure precise

control over particle size and distribution. …

Top-down process technology

The top-down approach involves breaking down larger particles into nanosized particles. This method includes several techniques, each employing different mechanisms to achieve the desired particle size reduction. …

High-pressure homogenization in detail

High-pressure homogenization is one of the most popular methods for producing nanosuspensions. This technique involves several detailed steps and considerations to achieve the desired nanoparticle size and stability. …

Impact

Higher pressure typically results in smaller particle sizes. It is crucial to optimize the pressure settings for each drug to maximize efficiency and achieve the desired nanoparticle size. Different drugs may require different pressures to achieve optimal results. Excessive pressure can lead to the degradation of sensitive drugs, so the process must be carefully monitored. …

Considerations

The type of homogenizer, the design of the homogenization gap, and the cooling system are important factors to consider. …

Simplicity in synthesis

High-pressure homogenization is suitable for synthesizing nanosuspensions of drugs poorly soluble in both organic and aqueous environments, making it a versatile method for various formulations. The process is straightforward and can be easily implemented in pharmaceutical manufacturing. …

Scalability

The method allows for easy scale-up with minimal batch-to-batch variation, ensuring consistent product quality. High-pressure homogenizers are available in various capacities, from laboratory-scale to …

Comprehensive examination of drawbacks and techniques in nanosuspension preparation

Nanosuspensions, hailed for their potential in improving drug delivery for poorly soluble medications, undergo meticulous preparation processes. Understanding the intricacies of these methods, along with their associated challenges and advantages, is crucial for optimizing nanosuspension formulations. Let's embark on a detailed exploration of the drawbacks encountered during nanosuspension preparation and the nuanced techniques employed to overcome these obstacles. …

Discussion

The emergence of nanosuspensions as a pivotal innovation in pharmaceutical sciences represents a significant leap forward in addressing the long-standing challenge of poor solubility encountered by a multitude of medications. The comprehensive exploration of various preparation techniques underscores the versatility and complexity of formulating these submicron dispersions. Each technique offers unique advantages while contending with limitations that necessitate careful consideration in the …

Conclusion

The comprehensive exploration of nanosuspensions and their preparation techniques not only addresses the challenges posed by poor solubility but also underscores their potential in reshaping the landscape of pharmaceutical formulations. This research sets the stage for further advancements and applications, propelling nano-suspensions into a pivotal role in modern drug delivery systems. …

Disclosure of interest

The author declares that he has no competing interest. …

Ethical statement

As the author of the article titled “Advancements in nanosuspensions: revolutionizing drug. delivery through nanonization for enhanced bioavailability”, I, Dr. Rohit Chavhan, affirm the following ethical considerations: …

Originality and integrity

The content of this article is original and has not been published previously in any other publication. All information, data, and findings presented in the article are authentic and accurately represent the research conducted. …

Plagiarism

I attest that the content of this article is free from any form of plagiarism. All sources, including publications, articles, and references, have been appropriately cited and acknowledged in accordance with academic and ethical standards. …

Authorship

I declare that I am the sole author of this article and have not enlisted the assistance of any ghostwriters or unauthorized individuals in its preparation. All contributions from co-authors, if applicable, have been duly acknowledged. …

Ethical approval

If applicable, I confirm that ethical approval was obtained from the relevant institutional review board or ethics committee for any research involving human participants, animals, or sensitive data. All research procedures were conducted in accordance with ethical guidelines and regulations. …

Informed consent

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Data availability

I am committed to transparency and openness in research. Any datasets or supplementary materials associated with this article will be made available upon request to facilitate further research and verification of findings. …

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I acknowledge the contributions of individuals, organizations, or funding agencies that supported or contributed to the research presented in this article. Their support is duly recognized and appreciated.

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A COMPREHENSIVE REVIEW OF POLYHERBAL NIOSOMAL CREAM FOR ANTI-AGING AND SKIN REGENERATION: A SYNERGISTIC APPROACH

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ABSTRACT

Skin aging is a complex biological process characterized by exposure to intrinsic and extrinsic factors that lead to damage to the skin, resulting in wrinkles, dryness, and changes in the pigmentation of the skin. This is the major problem in today's world, which leads to an increase in demand for an effective solution. As the demand for effective anti-aging solutions increased, the focus shifted toward novel herbal treatments, including the use of herbal medicines, as they are very effective and have less side effects on skin as compared to allopathic medicines. This review highlights the study of the potential of polyherbal niosomal creams in improving skin repair, rejuvenation, and protection against aging factors that cause aging; the individual profiles of common herbs used in skincare; studying their roles in anti-aging and skin regeneration; and comparing traditional herbal creams with niosomal formulations. The advantages of using niosomes for targeted delivery and improved efficacy are demonstrated. This comprehensive review provides valuable insights into the future potential of polyherbal niosomal creams as a synergistic approach to combating skin aging and promoting youthful skin.

KEYWORDS: Niosome, Synergistic, Polyherbal, Anti-Aging, Skin regeneration, etc.

1. INTRODUCTION

Skin aging is a complex biological process in every living thing. The skin, which is exposed to environmental oxidative material, leads to skin degeneration. Aging can occur due to environmental factors, namely sunlight, humidity temperature, cigarette smoke, and air pollution.[1] Aging means the thinning, sagging, appearance of age spots, and dryness of skin. Anti-aging products are therefore in high demand due to the growing desire to look or at least stay young. Free radicals are extremely reactive oxygen molecules that interact with collagen molecules to cause a loss of tone and elasticity in the skin, which is the first sign of aging.[2] Aging leads to progressive deterioration of skin structure and function which leads to wrinkles, dryness, reduced elasticity, and pigmentation changes. Skin regeneration after aging is the process by which aged or damaged skin attempts to restore its youthful properties. In the recent advances, various therapies have emerged to promote skin rejuvenation. A complex strategy involving biological processes such as stem cell activation, collagen synthesis, and extracellular matrix remodeling is required to regenerate skin after skin aging.[3] Recent advances in treatments range from topical solutions to advanced therapies like polyherbal antiaging creams and laser treatments.[4] In this review we highlight the potential of combining herbal extracts with niosomal technology to enhance skin repair, rejuvenation, and protection against aging.

1.1. Brief explanation of skin aging process (intrinsic and extrinsic factors)

The skin aging is influenced by two factors based on the cause of aging, namely intrinsic (internal) and extrinsic (external). These factors contribute to both functional and visual changes in the skin over time, leading to signs suchas wrinkles, sagging, and loss of elasticity. The major changes occur in the form of reduced skin barrier function, slowed epidemic cell turnover, and reduced vascularity in the skin layer, so the skin looks atrophic.[1]

1.1.1. Intrinsic factors

1) **Genetic predisposition**: the aging is largely dependent on the individual genetics. The rate at which collagen and elastin degrade and the capacity for cellular repair are influenced by the genetic factor of the individual person, it also depends on the gender of the individual.[5]
2) **Hormonal imbalance**: Hormonal imbalances, specifically decrease in testosterone in males lead to changes in the skin of males. Estrogen or other hormones in females during menopause, accelerate the breakdown of collagen and elastin which are essential proteins

in skin leading to thinning, dryness and wrinkling of the skin.[6]

3) **Reduced Cellular Turnover**: due to decrease in skin turnover, As we age, the ability of skin to regenerate reduces. There is a decrease in the production of collagen and elastin, while the breakdown of this protein increases. This results in thinner and more fragile skin.[7]
4) **Decreased Moisture Retention**: as we age, the ability of skin to retain moisture decreases due to a reduction in natural moisturizing factors, lipids, and hyaluronic acid. This leads to dry, rough skin.[8–10]

1.1.2. Extrinsic factors

1) **Ultraviolet (UV) Radiation**: UV exposure is the most significant cause of extrinsic aging. Exposure to UV-B leads to damage to DNA and causes oxidative stress, leading to the degradation of collagen and elastin fibers. This leads in the formation of wrinkles, pigmentation, and leathery texture, known as photoaging.[9]
2) **Pollution**: Environmental pollutants, particularly in urban areas, can cause oxidative stress in the skin by generating free radicals. Pollutants like particulate matter, ozone, and smoke degrade the skin barrier, leading to inflammation, pigmentation, and accelerated aging.[11]
3) **Smoking**: Tobacco smoke contains thousands of chemicals that promote oxidative stress, leading to premature wrinkling, loss of elasticity, and reduced skin repair capacity. Smoking also decreases blood flow, impairing the delivery of oxygen and nutrients to the skin.[12]
4) **Diet and Lifestyle**: Poor nutrition, particularly diets lacking in antioxidants, can hasten skin aging. Antioxidants neutralize free radicals that contribute to skin damage, and a diet rich in fruits and vegetables can help slow this process. Additionally, lack of sleep, chronic stress, and excessive alcohol consumption can also negatively impact skin health.[13]

1.2. Importance of skin regeneration in anti-aging treatments

Skin regeneration is the crucial process for maintaining skin health and reversing the signs of aging. The ability of skin to repair reduces with age, leading to damage to the skin from various factors like sunlight, humidity, etc. In the antiaging treatment, skin regeneration plays a vital role as it enhances the restoration of skin and reduces the damage by enhancing cellular turnover, collagen synthesis, and the overall repair mechanisms. Skin regeneration

also helps to restore the skin rejuvenation, improve texture, and reduce the visible signs of aging.[4,14]

1.3. Importance of Herbal Remedies in Skincare

Herbal plants have been used in skincare products for centuries because they constitute natural ingredients that do not have side effects as shown by synthetic compounds, and they are able to check skin damage and aging. That's why herbal cosmetics have gained immense popularity among the populations in recent years. The inclusion of herbal extracts in cosmetics can minimize skin damage due to oxidative stress, and thus aging process gets delayed. Herbal products improve various functions of skin by boosting collagen growth and thus eradicating harmful effects of free radicals, maintaining the structure of keratin, and keeping skin healthy.[15]

2. Common Herbs Used in Skincare

There are varieties of herbs, which is used in the skincare in the traditional system of medicine Here's a detailed overview of the Biological classification and chemical constituents, and their physiological actions on the skin:

Table no 1: Individual profile of common herbs used in skin care.

Sr no	Plant	Image	Biological classification	Chemical constituent and Skin benefits	Reference
1	Aloe vera		Kingdom: Plantae Subdivision: Angiosperms Class: Monocots Order: Asparagales Family: Asphodelaceae Scientific name: Aloe barbadensis miller	Chemical constituents: Vitamins (A, C, E), enzymes (Brady kinase carboxypeptidase), amino acids, salicylic acid, cholesterol, campesterol, β-sisosterol, and lupeol, etc. Skin benefits: Increases collagen synthesis, Moisturizing, soothing, anti-inflammatory, wound healing, and anti-aging properties.	[16]
2	Turmeric		Kingdom: Plantae Subdivision: Angiosperms Class: Monocots Order: Zingiberates Family: Zingiberacear Scientific name: Curcurma longa	Chemical constituents: Curcumin, Polyphenol, Turmerone, Curcumol, antioxidants, Arturmerone, etc. Skin benefits: Anti-inflammatory, antioxidant, reduces acne, brightens skin, and combats	[17,18]

				hyperpigmentation.	
3	Green Tea		Kingdom: Plantae Subdivision: Angiosperms Class: Eudicots Order: Ericales Family: Theaceae Scientific name: Camelia sinensis	Chemical constituents: epigallocatechin-3-gallate, catechin, epicatechin, tannins, flavonoids, etc. Skin benefits: Antioxidant, anti-inflammatory, anti-aging, reduces acne, and skin regeneration.	[19]
4	Neem		Kingdom: Plantae Subdivision: Angiosperms Class: Dicots Order: Sapindales Family: Maliaceae Scientific name: Azadirachita indica	Chemical constituents: Nimbidin, nimbin, quercetin, fatty acids, etc. Skin benefits: Antibacterial, antifungal, treats acne, reduces dark spots, and promotes wound healing.	[20]
5	Ginkgo		Kingdom: Plantae Subdivision: Gymnosperm Class: Ginkgopsida Order: Ginkgoales Family: Ginkgoaceare Scientific name: Ginkgo biloba	Chemical constituents: Ginkgolides, Bilobalide, Proanthocyanidins, Bilobalide, Carotenoids, etc. Skin benefits: Antioxidant, reduces scars, anti-inflammatory, skin regeneration, Wound healing.	[15,21]
6	Amla		Kingdom: Plantae Subdivision: Angiosperms Class: Dicots Order: Geranials Family: Euphorbiaceae Scientific name: Emblica ofiicinalis	Chemical constituents: Vitamin C, Gallic Acid, Ellagic Acid, Phyllembelic Acid, Emblicanin A and B, etc. Skin benefits: Anti-aging, Antioxidant, prevent, anti-inflammatory, wound healing.	[22]
7	Lavender		Kingdom: Plantae Subdivision: Angiosperms Class: Eudicotcots Order: Lamiales Family: Lamiaceae Scientific name: Lavandula augustifolia	Chemical constituents: Linalool, linalyl acetate, terpenoids, etc. Skin benefits: Antibacterial, soothing, promotes skin healing, and helps with acne and irritation.	[23]
8	Tulsi		Kingdom: Plantae Subdivision: Angiosperms Class: Dicots Order: Lamiales Family: Lamiaceae Scientific name: Ocimum sanctum	Chemical constituents: Rosemaric acid, gallic acid,eugenol, ursolic acid, Caryophyllene, apigenin, etc. Skin benefits: Antioxidant, anti-inflammatory, anti-acne, antiaging.	[24]

3. NIOSOMES IN DRUG DELIVERY

3.1. Introduction to Niosomes

Niosomes are non-ionic surfactant vesicles with a bilayer structure. They increase the shelf life of the drug and have the ability to deliver the drug at target site in controlled or sustained manner, which enhances the bioavailability of the drug. Non-ionic surfactants are used due to their ability to enhance the solubility and bioavailability of the poorly water soluble drugs .Mainly, the drugs of BCS class II and Class IV have low solubility and permeability can be given by this method.[25] This system is used to increase both permeability and fluidity of the biological membrane, so drug like podophyllotoxins, etopsides, and methotrexate show enhanced bioavailability by transdermal route via niosomes.[26,27]

3.2. Structure of Niosomes

Niosomes are made up of non-ionic surfactant vesicles with a bilayer structure. Hydrophilic heads face away from aqueous solutions, while hydrophobic heads face towards organic solutions.[28] The niosome vesicles can be divided into 2 types based on the number of layers that are unilamellar vesicles and multilamellar vesicles. Multilamellar vesicle consist of more than one layer. Niosome can be into 3 types based on size and number of layers. Small unilamellar vesicles (SUV) have particle sizes ranging from approximately 10 to 100 nm, large unilamellar vesicles (LUV) range from 100 to 3000 nm, and multi-lamellar vesicles (MLV) are larger than 5 µm.[29]

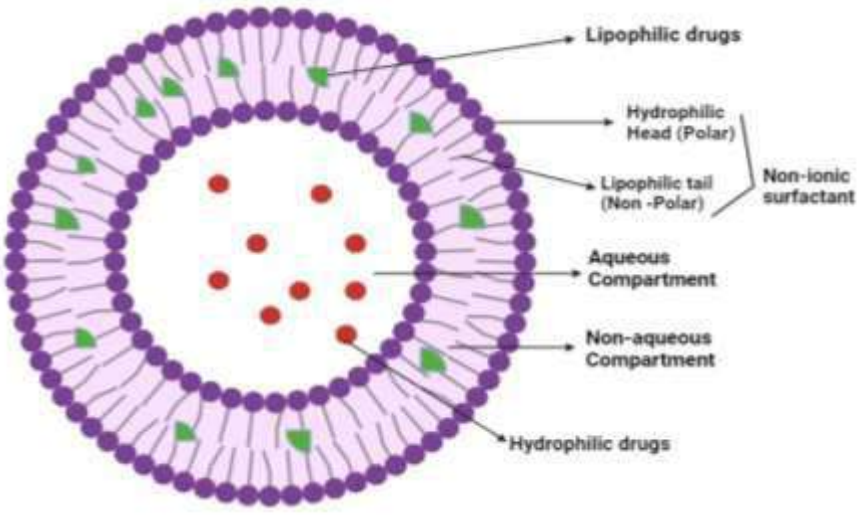


Figure 1: Structure of Niosome.

3.3. Components of Niosomes

The efficacy of a drug delivery system strictly dependent on its components. The basic

component of niosomes include non-ionic surfactant, cholesterol and charged molecules.[27]

3.3.1. Non-ionic surfactant

Non-ionic surfactants are the basic component of niosomes. Non-ionic surfactants are amphiphilic molecules that have distinct chemical structures, one of which is hydrophilic head and hydrophobic tail. Which, upon hydration form lamellar microscopic and nanoscopic vesicles.[30] Non-ionic surfactants are preferred due to their less irritation power, possessing high interfacial activity, and ability to form stable formulations. Which upon hydration form a bilayer and hence entrap both hydrophilic and hydrophobic drugs. They are stable, compatible and nontoxic; they also function as a solubilizer, wetting agent, and permeability enhancer which makes them to use in the formulation of noisome. The HLB value describes balance between the hydrophilic and lipophilic portion of non-ionic surfactant. The HLB range is from 0 to 20 for non-ionic surfactant. But the surfactant with HLB between 4 and 8 is preferred because of their vesical forming ability.[31]

Table no 2: Non-ionic surfactant used in noisome along with examples.

Non-Ionic surfactant	Examples
Alkyl Ethers **1.Alkyl glycerol ethers** **2.Polyoxyethylene glycol alkyl ethers**	 Hexadecyl diglycol ether(C16G2) Brij 30, Brij 52, Brij 72, Brij 78
Alkyl esters **1.Sorbitan fatty acid esters (Spans)** **2.Polyethylene sorbitan fatty acids (Tween)**	Span 20, Span 40, Span 60, Span 80 , Span65 Tween 20, Tween 40, Tween 60, Tween 80 , Tween 65, Tween85
Alkyl amides **1.Glycosides** **2.Alkyl polyglycosides**	 C-glycoside derivatives surfactant (BRM-BG) Octyl-decyl polyglycoside (OrCG110)
Fatty alcohol o fatty acids **1.Fatty alcohols** **2.Fatty acids**	 Steryl alcohol,cetyl alcohol ,myristyl alcohol Steric acid ,palmitic acid ,myristic acid

3.3.2. Cholesterol

Cholesterol is a steroidal derivative that is mainly used in the formulation of niosomes. It may not show any role in the formulation of bilayer[32], but In the bilayer structure of niosomes, cholesterol forms hydrogen bonds with the hydrophilic head of a surfactant. Cholesterol content of niosomes thereby influences the structures of niosomes and physical properties such as entrapment efficiency, long term stability, release of payload, and biostability.[31] Cholesterol improves the rigidity of vesicles, and stabilizes niosomes, decreases the permeability of vesicles for entrapped molecules thus inhibiting leakage. Drug entrapment

efficiency plays an important role in niosomal formulations and it can be altered by varying the content of cholesterol.[27]

3.3.3. Charged molecules

Charged molecules improves the stability of noisome by preventing vesicles aggregation by increasing surface charge density. Dicetyl phosphate (DCP) and phosphatidic acid are the commonly used negatively charged molecules for niosome preparation, and similarly, stearylamine (STR), and stearyl pyridinium chloride are well-known positively charged molecules used in niosomal preparations.[33] Normally, the charged molecule is added in niosomal formulation in an amount of 2.5–5 mol%. However, increasing the amount of charged molecules can inhibit niosome formation.[31] It forms the zeta potential, which is necessary for electrostatic stabilization.[29]

3.4. Method of preparation of Niosomes

3.4.1. Hand shaking (Thin film hydration techniques)

In the hand shaking method, non-ionic surfactant is dissolved in a volatile organic solvent such as diethyl ether or chloroform with cholesterol in a rotatory evaporator, then the organic solvent evaporates and the thin film of the solid mixture is deposited on the wall of the flask.[26] Then the film is rehydrated with an aqueous phase containing drug at room temperature with agitation. Multilamellar vesicles are formed by this method.[31]

3.4.2. Transmembrane pH gradient

Surfactant and cholesterol are dissolved in volatile organic solvent. The solvent is then evaporated, and a thin film is formed on the round bottom flask using a rotatory evaporator. Then the film is hydrated with citric acid (pH 3.0 or 4.0) by vertex mixing. Then sonicated three times and then the aqueous solution containing drug is added to the niosomal suspension. Then the pH of the sample is raised to 7.0 with phosphate buffer. This mixture is then heated at 60°C for 10 minutes to produce multilamellar vesicles.[31,34]

3.4.3. Reverse phase evaporation technique

Surfactant and cholesterol are dissolved in the mixture of ether and chloroform. The aqueous phase containing drug is added and then sonicated at 4-5°C. The clear gel is formed after sonication and then a small amount of phosphate buffer saline (PBS) is added. The organic phase is evaporated at 40°C under low pressure. The obtained viscous niosomal suspension was then diluted with PBS and heated in the water bath at 60°C for 10 min to yield large

unilamellar vesicles.[31]

3.4.4. Ether injection method

The ether injection method is based on the rate of injection of a solution of surfactant in diethyl ether through a 14-gauge needle. The aqueous solution containing the drug is maintained at 60°C, then the organic phase is added, if the speed of injection is slow (0.25 ml/min) into aqueous phase then there is the formation of large unilamellar vesicles, if the speed of injection is fast into aqueous phase then there is the formation of small unilamellar vesicles. The only disadvantage of this method is that a small amount of ether is frequently present in the vesicle suspension, which is difficult to remove.[31,35]

3.4.5. Sonication

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in the scintillation vial. then the mixture is homogenized using a sonicator at 60°C for 3 minutes. The small unilamellar vesicles are formed with uniform size.[31]

3.4.6. The bubble method

Surfactant and cholesterol are added into the three necked flask .niosomal components are dispersed at 70∘C, and then this dispersion is mixed with homogenizer for 15 seconds, and immediately afterwards it is bubbles using nitrogen gas to yield large unilamellar vesicles.[29]

4. SYNERGISTIC EFFECTS OF POLYHERBAL FORMULATIONS

4.1. Concept of synergy in herbal medicine

The concept of synergy in herbal medicine is rooted in the traditional system of medicine, that combining multiple herbs can enhance the therapeutic effect, leading to the effect that are greater than the sum of the individual action of the drugs. the interaction between various bioactive compounds, which may lead to improved efficacy, reduced toxicity, or broader therapeutic coverage.[36] The use of more than one plant extract to treat disease or disorder is called polyherbism. This concept was since the Ayurveda was effective in ayurvedic products for mankind are developed with the numbers of natural sources in a single formulation by getting synergism, which resulted in a better therapeutic effect than a single herb. The pharmacokinetic parameters like absorption, distribution, metabolism, and elimination will ease the drug to be effective and active metabolite with similar pharmacodynamics targeted by diverse mechanism of action will present in synergism effect.[37]

4.2. How combining multiple herbs leads to enhanced therapeutic effects

Synergism occur when mixture of two or more drugs produce greater action than expected which is greater than the sum of their individual effect of the drug. Synergy in polyherbal formulations enhance the therapeutic effect by several mechanisms:

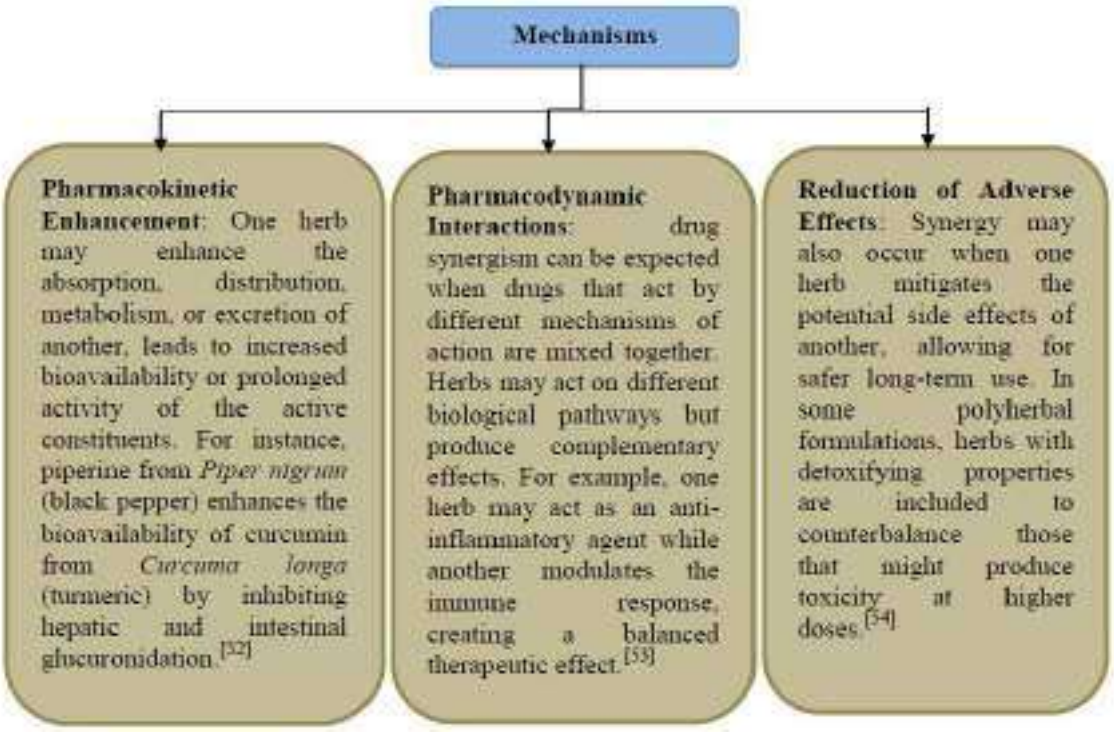


Figure no. 2: Mechanisms of Synergism.

4.3. Examples of Synergistic Polyherbal Formulations

Products	Composition of polyherbal formulation	Description and use	Reference
Triphala	Emblica officinalis (Amla), Terminalia bellirica, and Terminalia chebula	It is a classical ayurvedic formulation composed of three fruits. Triphala is known for its antioxidant, digestive, and anti-inflammatory properties. which synergistically work to enhance the gastrointestinal health.	[38,39]
Amruthotharam kashayam	Terminalia chebula (fruit), Tinospora cordifolia (stem), and Zingiber officinale (rhizome)	It is an ayurvedic formulation, which is also known for its synergistic effect in the treatment of fever, digestion, and other health issues like infections.	[40]
Jati kalpa ghrita	Jasminum officinale, Azadirachta indica, Stereospermum suaveolens, Hemidesmus indicus, Pongamia pinnata, Vetiveria zizanioides,	It is an ayurvedic formulation which is gives synergistic effect in the treatment of diabetic, chronic wounds, fistula, fissure, eczema, and burn management.	[41]

	Glycyrrhiza glabra, etc		
Bihat ashwagandha Ghrita	Ashwagandha, sarpi (goghrta), ksira (godugdha), chagamamsa, kakoli, honey.	It is an ayurvedic formulation. It is used in the treatment of wrinkling on skin, in aging, in graying of hairs, infertility, fever.	[42]
Agastya Haritaki Rasayana	Aegle marmelos Linn, Oroxylum indicum, Gmelina arborea, Stereospermum suaveolens, Premna mucronta, Desmodium gangeticum, Solanum indicum linn, Solanum surattense, Tribulus terrestis Linn.	It is an ayurvedic formulation known for its antioxidant, antimutagenic, anticarcinogenic, antiaging, antibacterial, antiviral, antifungal, antidiabetic, cardioprotective, antiulcer, and wound healing properties.	[43]
Polyherbal formulation	Ageratum conyzoides, Culcasia scandens, and Mitracarpus villosus	It is a polyherbal formulation. it shows the Antimicrobial activity, wound healing, antiaging properties.	[44]
Poly herbal cream	Malva Sylvestris, and Solanum nigrum	It is a polyherbal formulation it shows Antimicrobial activity and wound healing properties.	[45]

5. POLYHERBAL NIOSOMAL CREAM FORMULATION

The polyherbal niosomal cream is the cream that consists of multiple herbs that show synergistic effect, and that are encapsulated in the vesicular structure, which is made up of niosomes, and this structure is made into a cream formulation. The formulation of polyherbal niosomal creams involves several steps which are as follows:

5.1. Selection of herbs and active compounds

The selection of herbs is the crucial process in the formulation of polyherbal cream. The herbs which are compatible with each other and show the synergistic effect in the cream or enhance the action of cream are selected. The extraction of this plant is done in which separation of medicinally active portions of the plant using selective solvents through standard procedures given in the traditional system.[46]

5.2. Preparation of Niosomes

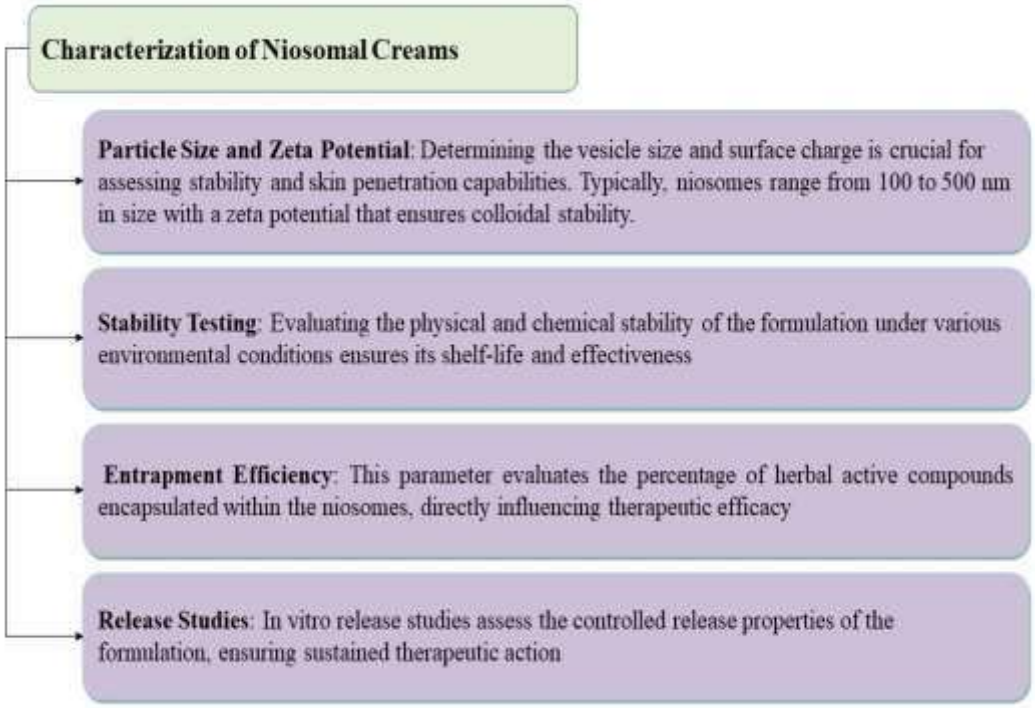
The next step of this formulation is the encapsulation of the extract in the niosomes. Niosomes are typically prepared using the thin-film hydration method or ether injection method. Where the drug is encapsulated, the non-ionic surfactants like Span 60 or Tween 80 are dissolved with cholesterol, followed by hydration and sonication to form niosomal vesicles.[47]

5.3. Incorporation into Cream Base

This is the final step in which the prepared niosomal vesicles are incorporated in the suitable base, often containing emulsifier, stabilizer, and preservative. The cream is prepared by the standard method to ensure consistency and shelf life of the formulation.[48]

5.4. Characterization of Niosomal Creams

Characterization of niosomal cream is essential to ensure the efficacy and stability if polyherbal niosomal cream. The characterization is as follows:



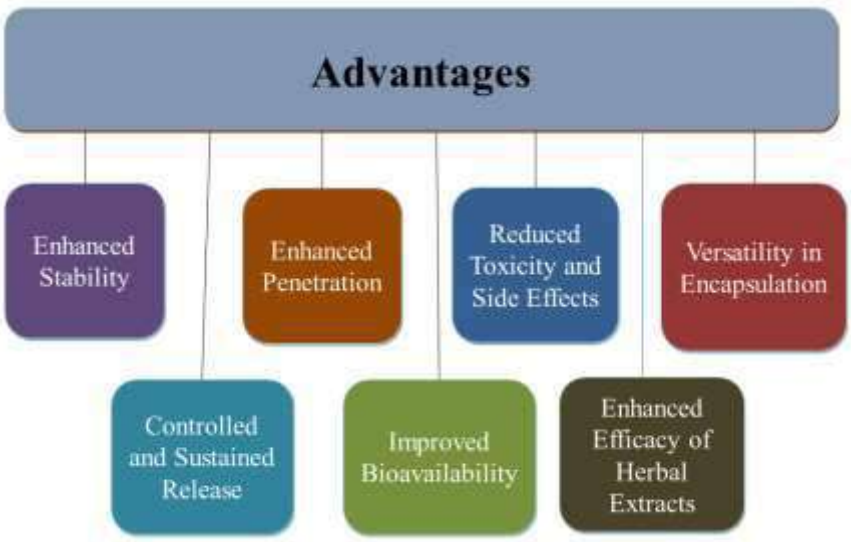


Figure no 3: Advantages of Niosomal creams.

5.5. Overview of Polyherbal Ingredients Used in Anti-aging and Skin Regeneration

Sr No	Ingredients	Description and use	REFERENCE
1	Aloe Vera (Aloe barbadensis Mill.), Neem (Azadirachta indica), Turmeric (Curcuma longa Linn.), Mint (Mentha piperata Linn.).	The polyherbal face cream which is prepared by using ethanolic extract of Aloe Vera gel, Neem, Turmeric, and Mint showing multipurpose effect such as whitening, anti-aging, antioxidant, antimicrobial effect.	[46]
2	Moringa oleifera, Ocimum sanctum.	the extract of moringa oleifera, and Ocimum sanctum are formulated using traditional knowledge. Which has synergistic effect and possess antiaging, antioxidant, antimicrobial, anti-inflammatory, antibacterial properties.	[49]
3	Moringa oleifera, Juglans regia, Vitis vinifera, Camellia sinensis, Punia granatum, and rosa grandiflora.	It provides excellent antioxidant, Anticollagenase activity, antiaging property, and shows skin rejuvenating effects. It also reduce fine lines, wrinkles, and also increase the collagen synthesis.	[2]
4	Turmeric (Curcuma domestica Val.), tamarind (Tamarindus indica L.), and mineral oil.	This formulation shows synergistic activity and used for its Anti-acne activity, anti-aging, skin regeneration property and beautifying property.	[50]
5	Lawsonia inermis, Ficus carica, Carica papaya and Pisidium guajava.	This formulation is used for its antimicrobial, antioxidant, anti-inflammatory, antidermatitic, wound healing, and in the treatment psoriasis.	[51]
6	Cucumber, Aloe Vera, Coconut oil.	It gives cooling effect, detoxes the whole skin and provide nourishment to skin. It act as a anti-dark spot, anti-aging, and provide hydration to the skin.	[10]

6. Traditional Herbal Creams vs. Niosomal Creams

Aspects	Traditional Herbal creams	Niosomal Creams
Definition	Topical formulation in which Herbal extract is dispersed in cream base, which comprising od oils, waters, emulsifiers, and other excipients.	Topical formulation in which herbal extracts are encapsulated within noisome which is incorporated in suitable base containing excipients.
Stability	High chances of degradation from environmental factors like light, heat and oxidation, which can reduce the efficacy of active compound overtime.	Enhanced stability as niosomes protect herbal extracts from degradation, extending shelf life and maintaining potency.
Bioavailability	Limited by the cream's ability to deliver active ingredients through the skin barrier, often resulting in	Improved bioavailability due to the encapsulation of herbal extracts in niosomes, which enhance penetration

	lower absorption and efficacy.	and absorption through the skin.
Controlled Release	Typically provides immediate release of active ingredients, which may lead to rapid depletion and the need for frequent reapplication.	Provides controlled and sustained release of herbal extracts, maintaining therapeutic levels over extended periods and reducing the frequency of application.
Compatibility with Multiple Ingredients	Potential for ingredient interactions within the cream base, which may affect the stability and efficacy of herbal extracts.	Niosomes can encapsulate multiple herbal extracts simultaneously, preserving their synergistic interactions and ensuring compatibility.
Shelf Life	Shorter shelf life due to the instability of certain herbal extracts and potential for microbial growth if preservatives are inadequate.	Longer shelf life as niosomes enhance the stability of encapsulated herbal extracts and can incorporate effective preservatives within the vesicles.

7. Challenges and Future Perspectives

Polyherbal niosomal creams offer a synergistic and novel application for anti-aging and skin regeneration by enhancing the drug delivery, stability, and efficacy of multiple herbal extracts. But there are some challenges, such as formulation complexity, encapsulation efficiency, and stable consistency. Advancements in nanotechnology, growing consumer demand for natural skincare products, and increased research into novel herbal combinations offer opportunities in the current world to make formulations like this. Future studies should focus on improving encapsulation technologies, and conducting detailed clinical studies to speed up the development and market acceptance of these innovative polyherbal niosomal formulations.

8. CONCLUSION

Polyherbal niosomal cream holds significant effect as a novel drug delivery system for antiaging and skin regeneration formulations, offering enhanced bioavailability and synergistic effect of the multiple herbal extracts. The niosomal creams have many challenges like formulation complexity, encapsulation efficiency, clinical validation, and rigrous regulatory approval. In the current scenario, the advancement in nanotechnology and rising demand for natural skin care products in the world, polyherbal niosomal cream, have a strong foundation for the future. Further research in the novel herbal combination is essential for establishing the safety and efficacy. Polyherbal niosomal cream is seen as very effective as it enhances the drug delivery and therapeutic use of herbal extracts makes the drug very effective. Niosomal formulations have the potential to revolutionize the skincare market.

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A CONCISE REVIEW ON SUSTAINED RELEASE DOSAGE FORM

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Abstract:

During past few years many conventional dosage forms are rapidly being replaced by novel controlled release drug delivery system in which sustained release drug delivery system has gaining more popularity because of its excellent advantages over conventional one such as, reduction in dosing frequency, reduced fluctuation in circulating drug levels, more uniform effect, maximum utilization of drug, improved bioavailability, increased patient compliance, etc. Sustained release system is considered as a wiser approach for the drug with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. Sustained release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. Sustained release drug delivery system provides better therapeutic advantages over traditional drug delivery system. The basic rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of the drug in such a way that utility is maximized, side-effects are reduced and cure of the disease is achieved. The present article is a brief review on various formulation approaches for Sustained release drug delivery system.

Keywords: - Sustained release drug delivery system, Dose frequency, Biological half-life, Physicochemical properties of drug.

Introduction:

Sustained release, prolonged release, sustained action, controlled release, depot release, extended release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug[1].The aim of designing sustained release dosage form is to reduce the dosing frequency or to increase overall effectiveness of the drug by targeting it at the site of action, by providing uniform drug delivery or reducing required dose. It is an ideal drug delivery system because it provides single dose administration and it delivers the active.

Terminology[2]:

Sustained Release drug delivery system: Any of the dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged period of time, after administration of a single dose. In case of injectable dosage forms it may vary from days to months.

Controlled release drug delivery system:

Controlled drug delivery is that type of system which release the medicaments from the dosage form at a predetermined specified rate for locally or systemically for a specified period of time.

Modified Release Dosage Forms:

According to USP these are those are dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or conveniences objectives not offered by conventional dosage forms.

Repeat Action Dosage Forms:

An individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

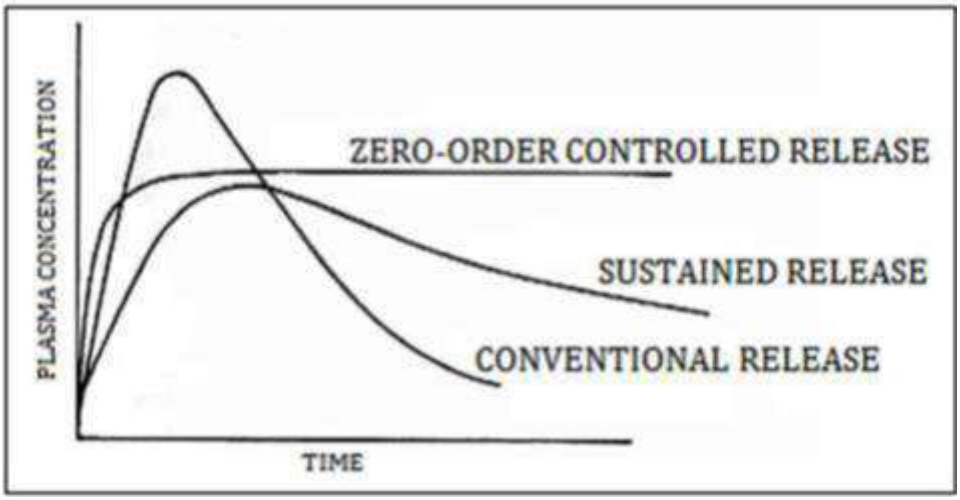


Fig. No. 1: Ideal Plasma Concentration Curves for Conventional release, Zero Order Release, Sustained Release Drug Delivery System.

Rationale: -

1. Formulation of SRDDS minimizes dosing frequency and sustained release provides availability of drug at site of action throughout the treatment to improve clinical efficiency of a drug molecule.
2. To reduce cost of treatment by reducing number of dosage requirement.
3. To minimize toxicity due to overdose which is often in conventional dosage form.
4. To enhance the activity duration of a drug possessing short half-life.
5. Uniform drug response achieved by using different combination of doses and dosage interval.
6. Frequent administration of dose produces side effect.

Limitations of conventional dosage forms[3]:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur.

Advantages[4][5]:-

i) **Patient compliance**: Lack of compliance is mainly observed with chronic disease which required long term treatment, as success of drug therapy depends on the patient ability to comply with the drug treatment. Patient compliance is affected by a various factor, like knowledge of disease process, patient faith in treatment, and understanding of patient related to a strict treatment schedule. Also the complication of therapeutic regimens, the cost of therapy and local or systemic side effect of the dosage form. This problem can be resolved to some extent by administering sustained release drug delivery system.

ii) **Reduced 'see-saw' fluctuation:** Drug concentration in the systemic circulation and tissue compartments show ‘see saw’ pattern frequently when the drug administration in conventional dosage form. The magnitudes of these fluctuations mainly depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' pattern is more prominent just in case of drugs with biological half-life less than four hours, since recommended dosing intervals are rarely less than four hours. A well designed sustained release drug delivery system can widely reduce the frequency of drug dosing and also maintain in a steady drug concentration in blood circulation and target tissue cells.

iii) **Total dose reduction**: To treat a diseased condition less amount of total drug is used in Sustained release drug delivery systems. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv) **Improvement of deficiency in treatment:** Optimal therapy of a disease requires an effective transfer of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable,

toxicological and immunological effects in non-target tissue. A sustained release dosage form leads to better management of the acute or chronic disease condition.

v) **Economy**: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over a prolong period of time may be less.

Disadvantages of Sustained Release System [4]:

i) **Inhibition of prompt termination of therapy**

Administration of sustained release medication does not permit the prompt termination of therapy such as might be encountered if significant adverse effects are noted, cannot be accommodated.

ii) **Dosage form design**

The formulation has less scope for flexibility in adjusting dosage regimens. This is fixed by the dosage form design.

iii) **Patient variation**

Sustained release formulations are specially designed for the normal population i.e. on the basis of average biologic half-lives of drug. If the disease condition is severe and responsible for the drug disposition or any adverse condition, then extra care should be taken.

iv) **Economic factors**

Sustained release dosage forms are specially designed system that's why it may require involvement of costlier processes and equipments in manufacturing. So economic factor should be considered prior to manufacture this type of system.

v) **Dose dumping**

Dose dumping is the condition in which quantity of drug release increases and causes dumping of drug which may leads to toxicity. This problem can be solved by using accurate choice of method for potent drugs.

vi) **Poor In-Vivo and In-Vitro correlations**

In sustained release dosage form, the rate of drug release is purposely reduced to achieve drug release possibly over a large region of gastrointestinal tract. Therefore 'Absorption window' becomes important and may give rise to poor drug absorption in-vivo in spite of outstanding in-vitro release characteristics.

vii) **Limited choice of selecting desired dose in the unit**

In conventional dosage forms, dose adjustments are much simpler e.g. tablets can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured[6,7,8]

Criteria to be met to incorporate the drug in sustained release dosage form[3]

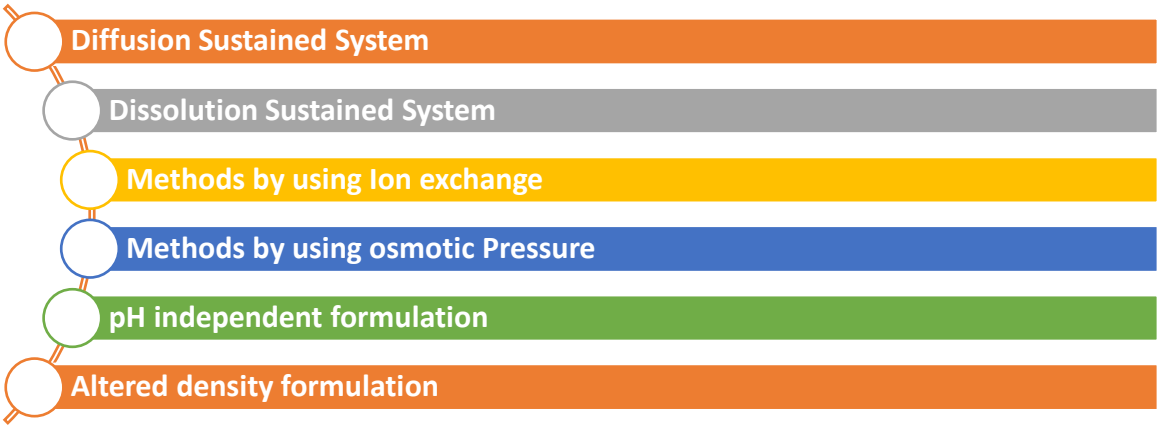
Table: Physicochemical parameter for drug selection

Sr. No.	Parameters	Description
1.	Molecular size	< 1000 Daltons
2.	Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General absorbability from all GI segments	Release should not be influenced by pH and enzyme

Table: Pharmacokinetic parameter for drug selection

Sr. No.	Parameters	Description
1.	Elimination half-life	Between 2 to 8 hrs
2.	Absolute bioavailability	Should be 75% or more
3.	Absorption rate constant (Ka)	Must be higher than release rate
4.	Apparent volume of distribution(Vd)	Larger Vd and MEC, larger will be the required dose
5.	Total clearance	Not dependent on dose
6	Elimination rate constant	Required for design
7.	Therapeutic concentration(Css)	The lower CSS and smaller Vd,the less amount of drug required
8.	Toxic concentration	Apart the value of MTC and MEC safer the dosage form

Formulation Strategies for oral SRDDS[2]:



Classification of Sustained Release System

The controlled release system for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

Depending upon the manner of drug release three systems are classified as follows:

1. Continuous Release systems

2. Delayed transit and controlled release systems

3. Delayed release system

Continuous release system

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

The various system under this category are as follow:

A. Diffusion controlled release system

B. Dissolution controlled release system

C. Dissolution and diffusion controlled release system

D. Ion exchange resin drug complexes

E. pH -independent formulation

F. Osmotic pressure controlled systems

A) Diffusion controlled sustained release system[9,10,11]: Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount/area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx

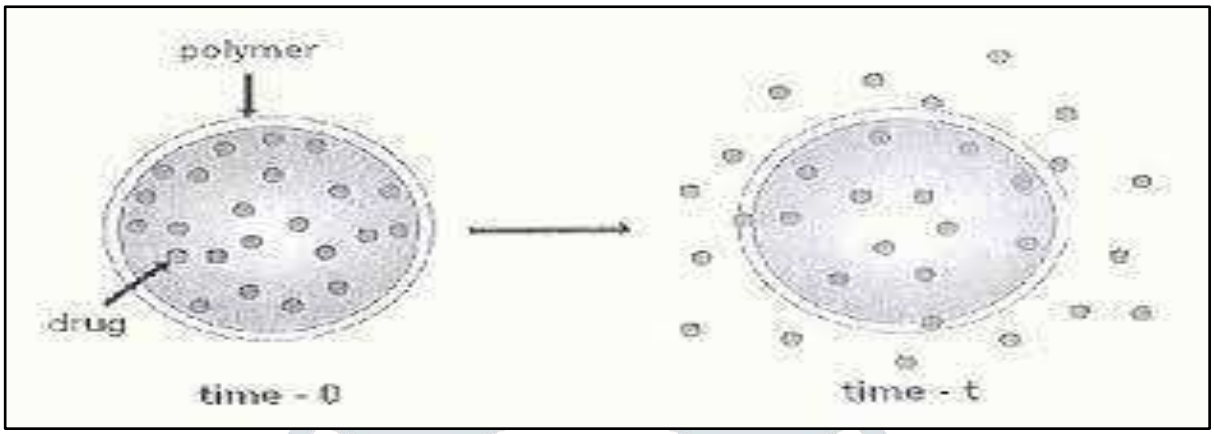
D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance 'x' In common form, when a water insoluble membrane surrounds a core of drug, it must diffuse through the membrane, the drug release rate dm/dt is given by,

dm/dt= ADK. C/L

Where, A = Area K = Partition coefficient of drug between the membrane and drug core. L= Diffusion path length (i.e. thickness of the coat in ideal case). C = Concentration difference across the membrane

i) Diffusion reservoir system: A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are: Zero order drug release is possible. The release rate is dependent on the type of polymer. High molecular weight compounds are difficult to deliver through the device.

Figure 1: Diagrammatic representation of Diffusion Type Reservoir System



ii] Diffusion Matrix type: It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are: Zero order release cannot be obtained. Easy to produce than reservoir devices. High molecular weight compounds are delivered through the device. ii] Diffusion Matrix type: A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system.

Q = D/T [2A–Cs] Cst ½.

Where, Q = weight in gms of drug released per unit area of surface at time t. D = Diffusion coefficient of drug in the release medium. ε= porosity of the matrix. Cs = solubility of drug in release medium. T = Tortuosity of the matrix. A = concentration of drug in the tablet, gm/ ml.

The release rate can be given by following equation:-

Release rate = AD/ L = [C1-C2]

Where, A = Area D = Diffusion coefficient C1 = Drug concentration in the core C2 = Drug concentration in the surrounding medium L = Diffusion path length

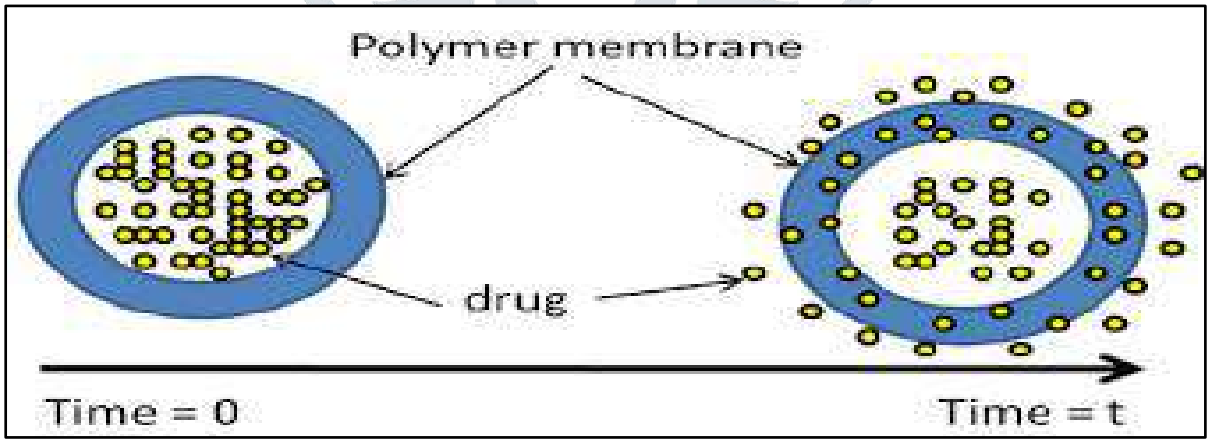


Figure 2: Diagrammatic representation of diffusion sustained drug release: matrix system.

B) Dissolution sustained systems[12]: A drug which having a slow dissolution rate this drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation. These systems are generally employed in the manufacturing of enteric coated dosage forms. Protection of stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine.

a) Soluble reservoir system: In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats.

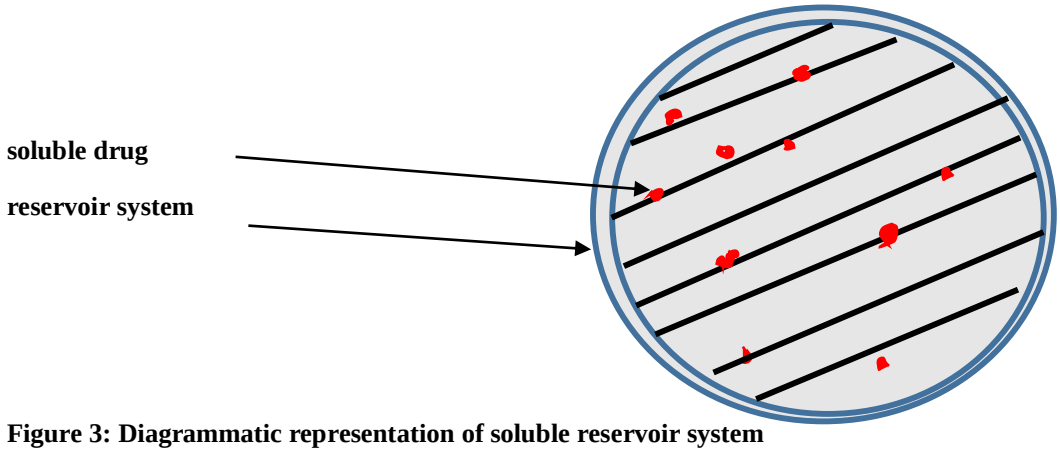


Figure 3: Diagrammatic representation of soluble reservoir system

b) Soluble matrix system: It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Figure 4: Diagrammatic representation of soluble matrix system.

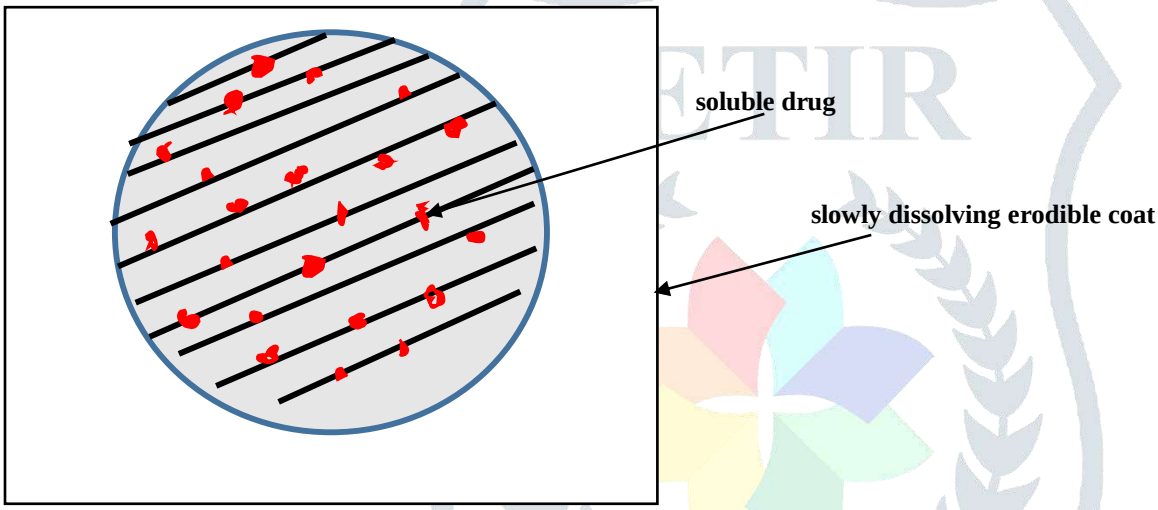


Figure 4: Diagrammatic representation of Soluble reservoir system

C. Ion exchange resin drug complexes [13]

Ion exchange resins are water insoluble, cross-linked polymers that contain acidic or basic functional groups and have the ability to exchange counter –ions within aqueous solutions surrounding them. IER have received considerable attention from pharmaceutical scientists because of their versatile properties as a drug delivery vehicle. During past few years, pharmaceutical research found that IER can be equally contributed in controlled release, transdermal, nasal, topical, and taste masking.

Drug, molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of the free drug molecules out of the resins as shown below,

Ion exchange based delivery system represent better approach for a drug that is highly susceptible to degradation by enzymatic process.

Ion exchange resin which are divided into types:

a) Cation exchange resin:

b) Anion exchange resin:

Cationic exchange resin: Contains acidic functional group generally they contain polysteryne polymer with either phenolic carboxylic phenolic group.

Anion exchange resin: Involved basic functional group capable for extracting anions from acidic solution. Ion exchange resin are used to sustain the effect of drug based on concept that negatively or positively charge drug moiety combine with appropriate resin producing insoluble poly salts resonates.

The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na+ and Cl- present in gastrointestinal tract. Resin+ – Drug– + Cl– ---------- > >> resin+ Cl– + Drug– where x- is Cl- conversely Resin– – Drug+ + Na+ ---------- > >> resin– Na+ + Drug Water insoluble cross linked polymer compounds are used for this system.[14,15]

Table: Common Ion Exchange Resins.[16]

Type	Exchange species	Polymers Backbone	Commercial Resins
Strong Cation Exchange Resins	$-SO_3H^+$	Polystyrene –DVB	INDION® 244,254, 404. TULSION® 344. AMBERLITE® IR120. Dowex 50. ZEOLITE.
Weak Cation Exchange Resin	COOH	Methacrylic Acid-DVB	AMBERLITE IRC 50.
Strong Anion Exchange Resins	N^+R_3	Polystyrene- DVB	DOWEX®-1 AMBERLITE® IR400.
Weak Anion Exchange Resins	N^+R_2	Polystyrene -DVB	DOWEX®2. Amberlite IR 4B.

These are some type of resins:

Resin type Chemical constituent Strong acidic cationic exchanger Sulfonic acid group attached to astyrene and divinyl benzene copolymer. Weak acidic cationic exchanger Carboxylic acid group linked to an acrylic acid and divinyl benzene copolymer. Strong basic anion exchanger. Quarternary ammonium groups attach to astyrene and divinyl benzene copolymer. Weak basic anion exchanger Polyalkylamine copolymer group linked to a styrene and divinyl benzene copolymer.

D) Altered density formulations [17,18]

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4g/cm3. In low density approach, the globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product. This system is generally used when, the single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension is required.

E) pH– Independent formulations: [19,20]

We know that most of the drugs are either weak acids or weak bases. The release from Sustained release formulations is directly or indirectly pH dependent. However; buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation to help to maintain a constant pH thereby rendering pH independent drug release. A buffered formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby providing a constant rate of drug release.

FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN

Two factors involved in oral sustained-release dosage form design.

A. Biological Factors

B. Physicochemical Factors

A. Biological Factors[3]

1. Biological half life : The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general,

drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples. [3,21,22,23]

2) Absorption: The goal of forming a SR product is to control the release rate of drug is much slower than the rate of absorption. If we presume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the extreme half-life for absorption should be in the region of 3-4 hours; otherwise, the dosage form will pass out of the probable absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. So, it accepts that the absorption of drug should occur at a relatively uniform rate over the entire length of small intestine. If a drug is absorbed by active transport or transport is restricted to a specific region of intestine, SR preparation may be disadvantageous to absorption.

3) Metabolism: Decrease bioavailability from slow releasing dosage form shown by Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slow releasing dosage form. a drug which having poor water solubility can be formulated in Sustain release dosage form. For this, various techniques which are available for enhancing the solubility of the drug after the enhancing the solubility Sustain Release formulation is possible. But during this crystallization of the drug is possible when the drug is entering into the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

4) Distribution: The rate of elimination of drug is mainly depends upon the apparent volume of distribution. So drugs with high apparent volume of distribution, influence the rate of elimination of the drug, this drugs are considered to be a poor candidate for oral SR drug delivery system. E.g. Chloroquine.

5) Protein Binding: To achieve pharmacological response unbound drug concentration is important rather than bound drug concentration and all drug bound to some extent to plasma and or tissue proteins. Protein binding of drug which shows a main role in its therapeutic effect in spite of the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

6) Molecular size and diffusivity: In several sustained release systems Drug must diffuse through a rate controlling membranes or matrix. Ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a role of its molecular size. An important influence upon the value of the diffusivity. 'D' in polymers is the molecular size for molecular weight of the diffusing species.

7) Margin of safety: Safety of drug generally depends upon the therapeutic index, Larger the value of therapeutic index of a drug safer is the drug. Drugs having less therapeutic index are generally poor candidates for oral SR drug delivery system. [24-27]

8) Absorption window[24]: Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. These candidates are also not suitable for SRDDS.

9) Plasma concentration response relationship: Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system.

10) Concentration dependency on transfer of drug: Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics.

Physicochemical factor: [14]

a) Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form.

b) Ionization, pka and aqueous solubility: Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Low soluble compounds (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

c) Partition Coefficient: To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds

with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes is mainly depending on the partitioning characteristics of the drug.

d) Stability: The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.[24,25,28,29].

Conclusion:

It is concluded that sustained release dosage form is one of the most productive dosage form. It helps in increasing patient compliance and also improves efficiency in treatment. Sustained release dosage form is advisable in many conditions like Drugs with shorter half life, taste masking etc. Certain criteria like molecular size, aqueous solubility must be met to incorporate the drug in sustained release dosage form. Controlled/Sustained release dosage form undergo certain mechanisms for medicament release. Some pharmacokinetic and pharmacodynamic parameter should be taken under consideration before formulating a drug into sustained release dosage from.

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THE REVIEW ON FORMULATION AND EVALUATION OF HERBAL FACE PACK OF SOME HERBAL INGREDIENTS

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ABSTRACT

The goal of this project is to create and assess formulations using natural ingredients in varying concentrations for a cosmetic herbal face pack for glowing skin. Such as charcoal, gram flour, neem leaves, sandalwood, aloe vera, banana pulp and rose water. The was evaluated based on various parameters such as organoleptic properties and physicochemical parameters and stability along with irritancy and microbial load test. Nowadays, human skin is becoming more prone to faster aging, atopic dermatitis, acne, and many other skin problems that arise mainly due to increased pollution, allergies, microbes, etc. Acne and dull skin are common problems that occur in various people. Because natural medicines are thought to be safer and have less adverse effects than synthetic ones, they are more widely accepted. Growing demand for herbal preparations on the world market. The aim of this work is to compile and evaluate an herbal face pack for acne and dull skin. Herbal face packs are primarily used to reduce dark circles, acne, and scars by boosting blood flow, preserving, and renewing skin, and clearing debris from pores. So, in this work we have created a package that can be easily made from readily available raw materials. All the benefits of the face mask have been proven and further optimization studies of its various parameters are needed to find out its useful benefits for human beings.

Keyword: Skin care, Natural ingredients, Herbal face packs, Preparation, Standardization, Evaluation.

I. INTRODUCTION

Herbal face packs are used to stimulate sense and increases blood flow, rejuvenate muscles on face and help retain skin elasticity and remove dirt from skin pores. The ingredients of the formula contain many important vitamins that are necessary for the health and radiance of the skin. Using natural face packs is simple. They allow blood to flow freely through the veins in the face, making the skin look more alive. An effective herbal face pack should provide the skin with essential nutrients that can be placed externally on the face as a loose powder. To supply the necessary nutrients, it should penetrate deep into the subcutaneous tissue. Every skin type has different needs when it comes to face packs. Several types of packaging are currently offered for oily, normal, and dry conditions. People have known for centuries that plants can provide many of the basic requirements for beautiful and healthy skin. Products called cosmetics are intended to enhance, clean, and promote a beautiful appearance. Most of the human body, the skin on the face, serves as a mirror reflecting its overall health. An adequate diet that contains carbohydrates, lipids and amino acids is essential for

maintaining fair, shiny, and healthy skin. When women lived in ancient times, they were especially aware of their skin type and took good care of it. People today still use natural remedies, especially in hilly and rural areas, such as neem, aloe vera, Tulsi, orange peel and rose extracts for cosmetic purposes.(1)

Global trends now include the use of herbal products and the subsequent adoption of more natural fashion. Organic foods, herbal medicines and other natural products are popular among consumers. Cosmetic victimization is very popular and generates a lot of interest. The reason behind this whole incident is that herbal products have fewer side effects. Herbal cosmetics are those that contain a bioactive ingredient or drug. The plant ingredients influence the biological processes of the skin and supply it with the nutrition it needs for health. The English word "cosmetic" comes from the Greek "kosm tikos" which means having the power, order, or ability to adorn. In the course of human history, a continuous history of the invention of cosmetics was created. In 3000 BC, man used colour as a decorative element to attract the prey he wanted to hunt. In addition, he used colours to decorate his body, to frighten opponents (whether human or animal), and to defend against attacks from rivals. The history of cosmetics begins with hunting, warfare, religion, gullibility, and then moved into medicine.

Herbal wraps or masks are used on the face to promote blood flow, stimulate muscles, maintain skin elasticity, and unclog pores. Herbal cosmetics are non-toxic, less likely to cause adverse reactions, and are made with ingredients that have been proven to work overtime. Cosmetics are products designed to improve desirable properties, clean, and beautify the skin and hair. Nowadays, skin care is not common. Since individuals have used cosmetics to preserve and beautify their skin throughout history, we can only assume that it is a basic human need. Although cosmetic products have changed, the basic concept of using cosmetics to promote the qualities of good health has not changed.(2)

- Advantages:
- Natural products. herbal cosmetics are derived from natural compounds.
- Safe and effective use. Compared to other cosmetic products flooded on the market, natural cosmetics are the safest and at the same time effective.
- Suitable for all skin types.
- Not tested on animals.
- No side effects.
- Wide selection. (3)

Benefits of Herbal Face Pack:

- Herbal pack provides skin with vital nutrients.
- Depending on the herbal components used, it helps to lessen scars, marks, acne, and pimples.
- Face packs often eliminate skin's dead cells.
- The skin is soothed and relaxed by these face masks.
- They assist in quickly restoring the skin's lost luster and sheen.
- Regular application of natural face masks improves the texture and tone of the skin and gives it a glow.
- The appropriate usage of face packs can successfully counteract the negative effects of pollution and severe weather.
- They aid in preventing skin aging too soon.
- The use of natural face packs can help to successfully control the formation of wrinkles, fine lines, and skin sagging. (4)

Charcoal

Charcoal is an organic carbon compound. Plant and animal items can be partially burned to make charcoal. Charcoal is widely used in outdoor cooking. Typically, the process of making charcoal involves burning plant materials such as cellulose, peat, wood, and bones. It is a highly porous microcrystalline structure. To save energy during the brick-forming process, charcoal and clay are combined. In cosmetics, activated charcoal has gained popularity. Burning wood, coconut shells, peat, and olive pits in a low-oxygen atmosphere creates pores and increases the powder's surface area many times, up to roughly three thousand square meters per gram. The charcoal absorbs and remove impurities from face treat acne, reduce skin pores size, and treat skin conditions.

Skin care is crucial to our well-being because skin is a delicate and protective layer of the human body that is exposed to both damaging UV radiation and pollution from the environment. Because the skin on the face is thinner and more delicate than the skin on the rest of the body, it requires even more attention and care from us. Activated charcoal is therefore only meant to be applied to the face as a cream, lotion, face mask, face cleanser, or peel-off mask for cosmetic purposes. Not only can a suitable face cleanser protect our skin from hazardous bacteria and harmful pollutants, but it may also increase our confidence. Africa consumes over half of the world's charcoal due to low conversion efficiency caused by outdated production methods. According to the FAO's dry weight conversion efficiency of 23%, 100 million tons of wood are cut down each year to produce charcoal. This research primarily focuses on African charcoal systems because of the significant and quickly growing share of charcoal consumption in Africa. It is challenging to quantify the production and consumption of coal in emerging nations. Using constant charcoal consumption per capita parameters for every nation, the FAO estimates the production of charcoal. These parameters remain constant over the 1981–1992 period depicted, meaning that the population growth is solely responsible for the variations in coal output. (5)

A portion of the populace in the nation may be dependent on charcoal fuel, and rates of charcoal consumption may vary from those reported by the FAO. Even in nations where laws govern charcoal. Government estimates are erroneous due to the manufacturing of illegal charcoal, which is taxed. In Rwanda, Karenzi (1994) discovered that the amount of charcoal used, as determined by field surveys, was far higher than the most recent energy data released by the government's Ministry of Public works, Water and Energy (MINITRAPE). He discovered that Rwanda consumes 9.1 GJ of charcoal annually as opposed to MINITRAPE's estimate of 1.2 GJ. Through the utilization of special contracts, official harvest levels in Senegal are frequently surpassed, potentially increasing overall charcoal production by 30–100% [Ribot, 1993]. These illustrations highlight the requirement for collection of data. Charcoal's adsorbent qualities were first noted in the 1700s, and the first clinical use of the material happened in the early 1800s. Its application as a detox component stems from these adsorptive qualities. The 2014 Goop newsletter from Gwyneth Paltrow suggested charcoal-in fused Lemonade gained attention for its health benefits after being named one of the best juice cleanses of the year. The modern age most associates charcoal with teeth whitening and skin blemish removal. As a result of this growing admiration, activated charcoal surpassed all other cosmetic and beauty product sales records in terms of marketing. This also paved the way for the widespread commercial manufacture of charcoal, which is now used in face cleansers, carbonated face masks, and pore strips in addition to everyday soaps and hand washes. An amazing accomplishment for a skincare ingredient as new as activated charcoal, the International Nomenclature of Cosmetic Ingredients (INCI) listed 148 skincare products using charcoal powder as an ingredient in 2015. Within four years, the numbers were already five times higher than that of 2015. (6)

History:

The Charcoal has been used since 3750 B.C., when the Egyptians utilized it extensively to cure a variety of intestinal issues, including diarrhea, bloating, and constipation, in addition to masking the smells of mining. More emphasis is now focused on using activated charcoal as soon as possible. Patients who have consumed a potentially dangerous amount of a poison (which is known to be adsorbed to charcoal) up to 60 minutes prior should be evaluated for using activated charcoal (Position statement 1997). In the meanwhile, some writers contend that administering activated charcoal within two hours of an overdose would make sense. Nevertheless, despite sporadic studies suggesting improved removal of specific toxins, there is no proof that activated charcoal truly enhances therapeutic result. Furthermore, there is a dearth of evidence to support the efficacy of charcoal used in repeated doses.

Charcoal was originally used to cure poisoning victims over 150 years ago. Even though activated charcoal is now almost universally accepted, the focus on treating poisoned patients with gastric emptying first has obscured the significance of activated charcoal. We go over how activated charcoal is currently used and new research that indicates it could be the only treatment that works best for a variety of poisonings. Enterohepatic loop disruption and 'back diffusion' are two new theories about the mechanisms of action. Clinical evidence supports activated charcoal's novel and proactive function in treating poisoned and overdosed individuals.

Preparation of active charcoal:

Any carbon-rich materials (from plants, animals, or minerals) can easily be converted into activated carbon by utilizing a combination of chemical and techniques for gas activation), wood, charcoal, nut shells, fruit pits, brown and bituminous coals, lignite, peat, bone, and paper mill waste (lignin) are the most often used raw materials in the production of activated carbon. Synthetic polymers like PVC are also utilized in this process. For adsorption, activated carbon derived from hard wood is preferred over charcoal derived from soft wood, like pinewood, which is prone to instability and crumbling. Some have claimed that apricot pits and coconut shells yield the highest grades of AC. Are often manufactured using the following two fundamental methods: (i) The physical or gas activation approach, and (ii) Chemical activation: The technique of activation chosen also depends on the starting material and the desired consistency of the powdered or granular carbon, depending on whether it is low or high density.

The gas activation method Involves 'first' carbonizing a raw material with less than 25% moisture at 400–500 C to remove most of the volatile matter. The carbon is then exposed to oxidizing gases, typically carbon dioxide or steam, at 800-1000 C or with air at room temperature, to achieve selective oxidation. Typically, a first carbonization of the source material occurs before the oxidation. Wood begins to pyrolysis at a temperature of about 225 C. (7)(8)(9)

Fiaure

Utilization

The Egyptians utilized it as well during the mummification process. In addition, the Greeks and Romans of antiquity employed it to preserve their dental hygiene. The civilizations residing in and around the Indus valley began using charcoal powder to purify their water around 400 B.C.

Even though activated charcoal has been around for ages, it wasn't until the 1700s that its adsorbent properties were first identified in science. Lowitz, a scientist, noticed that charcoal could successfully remove colour from other materials. Furthermore, in 1830, Tourey, a French pharmacist, demonstrated the adsorptive properties of charcoal with remarkable bravery by ingesting a significant amount of charcoal and a lethal dose of strychnine, highly poisonous, colourless insecticide used to kill birds and rodents. Notably, Tourey remained remarkably unaffected by his risky action.

Later in 1834, powdered charcoal was used by American physician Hort to heal a patient who had been poisoned by mercury dichloride. (10)

Uses:

Cosmetic preparations for skin-lightening creams contain activated charcoal, which can absorb fat, dark spots, and pollutants that stick to our skin.15 additionally; it's frequently found in soaps, pore strips, carbonated face masks, and facial cleansers. Numerous pharmaceutical and cosmetic companies assert that their products, which contain charcoal, can aid in the treatment of adult acne, wounds, minor infections, seborrheic dermatitis, and itchy scalps. Additionally, some dermatologists think that since activated charcoal forms strong bonds with poisons and eventually flushes them out of the body, if it can successfully perform gastric lavage in patients who have consumed poisons in the past, it can also use this mechanism to bind with dead skin and bacteria that attract sebum on when skin has been exposed to toxins in the environment, it can also employ this technique to bind with dead skin and germs that attract sebum, leaving behind clear, healthy skin

that can be rinsed off. Its antifungal and antibacterial qualities can also be used to treat skin disorders including eczema and psoriasis. Furthermore, it efficiently eliminates filth and dandruff from the scalp, which makes it a beneficial supplement to shampoos. Moreover, a number of mouthwashes and dental pastes that contain charcoal also make the claim that they can whiten teeth, which seems to be related to the abrasive nature of the charcoal, which helps to remove stains.(11)

Physical Properties of Charcoal

- Charcoal is amorphous in nature.
- The charcoal powder is black colour.
- Carbon makes up the porous, black substance known as charcoal.
- It is a low-density compound.
- Charcoal shows low mechanical strength properties.
- Carbon charcoal's structure reveals a vast surface area.
- Charcoal acts as a good absorbent. It readily absorbs moisture.
- Charcoal is more easily contaminated when it comes into accidental touch with dust and soil due to its high porosity and surface area. Therefore, it requires precautions while storing.

Chemical Properties of Charcoal

- Charcoal is a low ash compound. Charcoal has this quality, which makes it a valuable product.
- It is a highly combustible compound.
- It reacts strongly with carbon dioxide.
- Charcoal is not easily absorbed in the gastrointestinal (GI) tract.
- Charcoal is not metabolized in the body. Charcoal is a high surface area compound.
- Therefore, it absorbs chemicals in the stomach. The chemicals are captured by charcoal, which then removes them from the body before they can enter the bloodstream.

Types of Charcoal

Activated charcoal is a fine, black powder that is produced by combining coal, bone char, coconut shells, peat, and petroleum coke. High temperatures cause the activation of charcoal. By decreasing the pore size during the heating procedure used to create activated charcoal, the surface area is increased. Comparatively speaking, this type of charcoal has more pores than the others. Activated charcoal is used to absorb poisons and other toxic compounds into the intestines. It is hence in charge of preventing absorption. Charcoal has a negative charge, which attracts negatively charged positive molecules. As a result, it facilitates the removal of these particles.

Wood Charcoal Plant wood is heated to a high temperature to produce a carbon compound known as wood charcoal. It is a chemical with low weight. Wood charcoal has a black colour. Charcoal is solid amorphous state in nature.

BBQ Charcoal Sawdust is compressed at high pressure and temperature without the use of binders or additives to create BBQ charcoal. In the Middle East, Taiwan, Korea, and Greece, this kind of charcoal is preferred. It has a hexagon-shaped intersection at the centre where a hole is present. Barbecue charcoal is mostly used for barbecues because it burns for longer than four hours and produces no smoke, ash, or odours.

Activated charcoal in the form of coconut shell charcoal is produced by using coconut shells. So called coconut charcoal that has been activated. There are medical uses for this kind of charcoal. Soft tissue and skin infections are treated with it. It exhibits antimicrobial properties. Coconut coal is another name for this type of charcoal.

Activated Bamboo Charcoal This type of bamboo is produced when it goes through a pyrolysis reaction without oxygen. There are two kind of bamboo charcoal: raw bamboo charcoal and bamboo BBQ (briquette) charcoal.

Use of Charcoal in restaurants, food is heated, cooked, and flavour-infused with charcoal. Several dangerous poisons can be eliminated by using charcoal as an absorbent. It is used to treat overdoses and poisonings in emergency medical situations.

Benefits of charcoal face pack:

- Emergency toxin removal

- Detoxifies the Skin
- Remove cleanses oil.
- Reduces acne
- Reduces skin irritations.
- Prevents premature ageing.
- Smoothen skin.
- Reduce inflammation. (12)(13)

Gram flour:

This is a pulse flour produce from ground chickpea (also known as Bengal gram or garbanzo). Staple diet in the cuisine from the Indian subcontinent, this flour can be manufacture either from Raw or roasted chickpeas. The raw variety is slightly bitter, while the roasted variety is more Flavourful. Gram flour, also referred to as started, has been utilized. Widely known for its properties to enhance attractiveness since ancient times. It helps to clean and sluff the skin, acting primarily as a tonic for it. All that gram flour is made of is ground chickpea flour. It has several benefits for both skin and hair. It is applied to lessen skin tanning and oiliness, making it an effective anti-pimple agent. Because it lightens the skin tone, it is utilized as a direct agent for fairness. A 24-hour natural fermentation was carried out on a blend of finger millet and horse gram flour in various ratios (2:1, 3:1, 4:1, and 5:1). Biochemical study revealed that at 16 hours, there was a significant increase in titratable acidity (0.168–1.046%), soluble proteins (1.1-fold), free amino acids (2.6-fold), and a fair decline in pH (6.6–4.2) and starch content (25.52%). Throughout the fermentation process, the amount of lactic acid bacteria predominated in the yeast counts, and total soluble and reducing sugars decreased concurrently. During a 16-hour fermentation, the overall amount of essential amino acids grew by 1.1 times, with protein comprising 48.68% of essential amino acids relative to total amino acids. Between 5.87 to 6.73 g of lysine are present per 100 g of total amino acids. (14)

Figure 2 Gram

Gram flour is high in oleic and linoleic acids, two nutritionally significant unsaturated fatty acids, according to a study conducted in India. It is also an excellent source of beta-carotene, niacin, folate, and riboflavin, among other vitamins. Additionally, the flour may include some antinutritional ingredients that boiling will remove. Overall, the flour is produced using a significant pulse crop that offers several advantages. Gram flour contains zinc, which helps combat infections that lead to acne. Moreover, the fibre keeps blood sugar levels stable. Your hormones may be stressed by unbalanced blood sugar levels, which can lead to breakouts or pimples. That can be avoided with gram flour. Are you curious about using besan to remove tans? Now combine 1 teaspoon each of lemon juice, yogurt, and besan with 4 teaspoons. Mix with a small teaspoon of salt to create a smooth paste. After applying the mask to your entire face and neck, let it dry. Use cool water to rinse. This is a process you can repeat every day before taking a bath.(15)

It evens out skin tone and is a natural exfoliator. It brightens and thoroughly cleanses your skin. Zinc, which is present in gram flour, fights dark spots, minimizes blemishes, and delays the onset of ageing. Furthermore, it regulates the production of sebum and relieves irritated skin.

Besan is an extremely useful substance that is frequently seen in Indian kitchens and works incredibly well for skin issues. Whatever the issue with your skin, besan will nearly always help you deal with it. Beautifying your skin tone, eliminating hyperpigmentation and sun tan, and enhancing your complexion besan does it all.
Benefits of gram flour:

- Exfoliates our skin.
- Eliminates dirt.
- Pollutants
- Remove dead skin cells.
- Excellent exfoliating
- Lightening effects (16)(17)

Neem leaves:
Neem might have potential antimicrobial properties; it may be helpful for various skin problems and diseases such as acne, eczema, and other skin conditions. Psoriasis symptoms Treat by neem oil.
Neem leaves have long been used to treat a variety of epidermal dysfunctions, including acne, psoriasis, and eczema. Antioxidant-rich neem supports a stronger immune response in the tissues of the afflicted skin area. Bioactive substances with antibacterial, antifungal, and anticancer properties are also present. In this work, neem leaf extract was utilized to make herbal neem soap, which is intended to treat skin conditions. The study's chosen physical and chemical parameters' results indicate that the soap's moisture content was 4.02% and its pH value was 10.60, 57.40% total fatty matter, and 0.44% free caustic alkali. The findings suggest that herbal neem soap is safe for use on human skin and may be an effective treatment for skin issues.(18)

By highlighting the most recent research on neem extracts, we hope to shed light on a few key areas, including their significance as antioxidants and their potential to reduce the risk of cancer and diabetes. Prior to that, we will provide a quick summary of a few of the most significant bioactive compounds that are commonly present in many extracts. Despite this, we will continue to refer to other compounds throughout our work because it is reasonable that starting materials and extraction techniques vary widely. Additionally, we stress that a large portion of the work being done now is experimental, and as such, a section on the toxicity consequences is included. It is important to always take these impacts into account and to encourage more research to create better goods for human usage. Lastly, we talk about a section on neem as medical use. The neem tree, which is mostly grown in southern Asia and Africa, has long been associated with healing traditions. It is noteworthy to add that several elements of the Neem tree, such as the leaves, bark, fruit, flowers, oil, and gum, are linked to the previously described medical folklore for the treatment of certain medical ailments like diabetes, cancer, hypertension, and heart diseases. These extracts' potential effects can undoubtedly be attributed to cellular and molecular mechanisms. These mechanisms include the ability to modulate different signaling pathways, detoxification, DNA repair, cell cycle alteration, immune surveillance, autophagy and programmed cell death mitigation, immune surveillance, anti-inflammatory, anti-angiogenic, and anti-metastatic activities, and free radical scavenging.

Benefits of Neem for Skin Remove Pimples and Acne

It tightens the pore and assists in removing excessive sebum from the skin. Additionally, it relieves any skin irritation and itching caused by acne. Thus, applying neem oil for pimples might help get rid of zits. Frequent application would also aid in lowering skin redness and inflammation on the face. The use of need face packs for pigmentation regulates the skin's synthesis of melanin. Helps to remove or protect sunburn. It also lessens the visibility of black patches and scars.

Preparation of neem leaf extract:

As previously mentioned, 50 grams of powdered neem leaf was combined with 500 millilitre of distilled water and allowed to boil for approximately half an hour to create the aqueous leaf extract. Whatman No.1 filter paper was used to filter the boiling solution, yielding clear aqueous leaf extract. Until it was needed again, the extract was kept at 4°C. The assay was conducted in less than a day after the addition of 1 mm AgNO3 powder to 100 ml of distilled water.

Benefits of neem leaves:

- Moisturizes the skin.
- Soothes inflamed and irritated skin.
- Fight multiple signs of premature aging. Tackles blackheads and whiteheads.
- Treats uneven skin tone.
- Fights acne and pimples.
- Protects against environmental damage.(19)(20)

Sandal wood:

A class of woods from trees in the genus Santalum is known as sandalwood.

Native to the Malay Archipelago, northern Australia, and the tropical belt of peninsular India, sandalwood is a valuable commodity. The main areas of distribution include the Indonesian islands of Timor and Sumba as well as the drier tropical parts of India. The genus's taxonomy and nomenclature are based on the historical and widespread use of this species. In terms of etymology, it ultimately comes from Sanskrit Chandana (čandana), derived from the Latin candere, to shine or glow, and candrah, "shining, glowing," meaning "wood for burning incense." In the fourteenth or fifteenth century, it made its way into English via Late Greek, Medieval Latin, and Old French. The Malay Archipelago, northern Australia, and the tropical zone of peninsular India are the native home of sandalwood. The Indonesian islands of Timor and Sumba as well as the drier tropical parts of India are the primary distribution areas.

Infection, inflammation, and hyperplasia are the hallmarks of many skin disorders and illnesses. We need long-term topical therapy solutions that are both safe and effective. Conventional botanical remedies are being investigated as possible novel active components in dermatology. These remedies are frequently complex mixtures with various modes of action. The essential oil extracted from the sandal wood tree is called sandalwood album oil (SAO), or East Indian sandalwood oil (EISO). It has been shown to have biological action as an anti-inflammatory, anti-microbial, and anti-proliferative agent. Clinical research on the treatment of common warts, psoriasis, acne, and eczema has demonstrated the potential of sandalwood album oil. Sandalwood album oil of medicinal quality has recently been available, and its good safety profile, convenience of topical application, and assistance broader use as the basis of novel therapies in dermatology.

Benefits of sandal wood:

- Anti-inflammatory
- Antimicrobial
- Ant proliferative or inhibits undesirable cell growth Antiviral.
- Antiseptic
- Fever-reducing
- Scabies inhibiting (21,22)

Figure 4 Sandal Wood

Aloe- vera:

This perennial evergreen grows wild in desert, tropical, and semi-tropical conditions worldwide. It is indigenous to the Arabian Peninsula. Mostly used as a topical therapy for centuries, it is cultivated for commercial purposes. When grown indoors in a pot, the species looks good and is useful for decoration.

The polysaccharide gels an acemannan, which has numerous medicinal uses, is found in considerable quantities in aloe vera leaves. Aloin, a poison, is found in the skin. Typically, just the gel is used in aloe vera products. Numerous items, such as skin lotions, cosmetics, ointments, and gels for minor burns and abrasions on the skin, include the acemannan found in aloe vera because the reactions caused by oral intake of aloe vera extracts are yet unclear, they can be harmful. Pregnant women are particularly at risk because it can cause allergic reactions in certain individuals, even when given topically. However, some people may experience allergic reactions to topical use.

Two components of Aloe vera are used in the production of commercial products: the clear gel and the yellow latex. Topical treatments for skin ailments such burns, wounds, frostbite, rashes, psoriasis, cold sores, or dry skin are commonly made with aloe gel. Aloe latex can be taken on its own or combined with other substances to make a product that is consumed to relieve constipation.

History:

For millennia, aloe vera has been utilized medicinally in several countries, including Greece, Egypt, India, Mexico, Japan, and China. Nefertiti and Cleopatra, the queens of Egypt, incorporated it into their daily beauty regimens. It was used to cure soldiers' wounds by Christopher Columbus and Alexander the Great. John Good Yew's translation from the A.D. has the earliest known mention of Aloe vera in English in 1655 of 'Dioscorides' Medical treatise De Material Medica.2 By the early 1800s, Aloe vera was in use as a laxative in the United States, but in the mid-1930s, When it was effectively utilized to treat severe and chronic radiation dermatitis, it marked a turning point.(23)

Action:

Mucopolysaccharides provide a moisturizing and anti-aging impact by assisting the skin in retaining moisture. The production of collagen and elastin fibres by aloe promotes fibroblast, which makes the skin less wrinkled and more elastic. Additionally, by binding the superficially peeling epidermal cells together, it has cohesive effects that soften the skin. Zinc works as an astringent to constrict pores, while amino acids also soften tough skin cells. Aloe vera gel gloves have also been tested for their moisturizing properties in the treatment of dry skin brought on by industrial exposure; in these cases, the skin integrity, fine wrinkle appearance, and erythema were all improved.21 it has an anti-acne effect as well.

The fibroblast's growth factor receptors are contacted by the mannose-rich polysaccharide glucomannan and the growth hormone gibberellin, which stimulates the fibroblast's activity and proliferation. This, in turn, greatly boosts collagen synthesis following topical and oral Aloe vera treatment. Aloe gel improved the amount of collagen in the wound while also altering its composition to include more type III collagen and strengthening its cross-linking. As a result, it quickened the healing process and raised the scar tissue's breaking strength. There have been reports of enhanced hyaluronic acid and dermatan sulfate production in the granulation tissue of a healed wound after oral or topical therapy.(24)

Aloe vera frequently moisturizes skin cells and relieves facial discomfort.This gel is safe to use on the face and hair, and it would also offer quicker relief from irritation and inflammation. If chemicals like SLS and parabens were absent, it would be even better. The production of collagen and elastin fibres by aloe promotes fibroblast, which makes the skin less wrinkled and more elastic. Additionally, by binding the superficially peeling epidermal cells together, it has cohesive effects that soften the skin. Aloin, a well-known and organic depigmenting chemical, is found in aloe vera. This substance efficiently lightens skin, gets rid of dead skin cells, and removes skin flaws like dark spots and patches. Aloe vera can therefore help lighten your skin tone, so the answer is yes. With time, age-related symptoms including fine lines, wrinkles, and drooping skin around the eyes and neck become more noticeable. Try applying some aloe vera gel for comfort. It brings back the moisture balance and brightness of the skin. By restoring skin suppleness and healing damaged skin cells, it not only minimizes the appearance of fine lines and wrinkles on the face but also slows down the skin's natural aging process.

Benefits of aloe Vera

- Efficacy in treating burns or wound.
- Help in treat psoriasis, acne, and rashes, among other skin conditions.(25)(26)

Banana:

A banana is a long, edible fruit that belongs to the genus Musa. It is technically a berry. However, it is produced by several huge, herbaceous blooming plants. Dessert bananas are referred to as 'plantains' in some nations, whereas cooking bananas are termed "bananas." A rind that can be green, yellow, red, purple, or brown when ripe, covers the soft flesh that is high in starch. It is often elongated and curved. When the plant reaches its summit, the fruits climb upward in clusters. *Musa acuminata and Musa balbisiana* are two wild species that are the source of nearly all edible seedless (parthenocarp) bananas grown today. Depending on their genetic makeup, the most common cultivated bananas are known by their scientific names, *Musa acuminata, Musa balbisiana,* and *Musa* × *paradisiaca* for the hybrid *Musa acuminata* × *M. balbisiana. Musa sapientum,* the hybrid's previous scientific name, is no longer in use. However, there are certain alleged advantages of bananas that go beyond simply consuming them. Banana masks are becoming more and more well-liked as do-it-yourself treatments for a range of dermatological problems, from hair to skin care. Because of its high silica content and nutritious composition, banana face masks are supposed to help with skin problems. These advantages haven't, however, been thoroughly investigated in clinical settings.(27)

A serving of bananas provides a respectable 13% of the recommended daily intake of manganese. Despite being crucial to the formation of collagen, manganese is a trace mineral that is often overlooked in skin care products. In particular, proline, an amino acid necessary for the creation of collagen, is produced only with manganese. The protein called collagen keeps skintight and strong. Manganese, therefore, may help with anti-aging and healing properties of a banana face mask. Magnesium is last but most definitely not least. Magnesium has anti-inflammatory properties and may be used to treat acne when administered topically. Excess sebum and germs clogging pores cause blemishes, which are then followed by enema and irritation.

Inflamed pimples may be soothed by a banana face mask, hastening their healing process. For this reason, applying a banana face mask to treat acne is frequently advised.

Figure 6 Banana Pulp

Banana face masks benefits:
Nutrients found in bananas may benefit skin health in certain cases.
These include: 1. Potassium 2. Vitamin B-6 3. Vitamin C 4. Traces of vitamin A (28)(29)
Rose water:
To make rose-flavoured water, rose petals are soaked in water. It is the hydrosol fraction of the rose petal distillate, which is a leftover after rose oil is extracted for use in fragrances. Throughout Eurasia, rose water is also utilized for religious purposes, as a component of several cosmetic and medicinal products, and to flavour food.
Methods of rose water preparation
Simmering

- Fill your saucepan or pot with the cleaned rose petals.
- Add distilled water to just over the petals. Avoid diluting your rose water by adding excessive amounts of water.
- Place the pot on the gas stove on average heat condition.
- After placing a lid on the pot, simmer it for thirty to forty-five,
- Simmer until the petals lose their colour.
- Wait until rose water and be cool.
- Filter the water into a spray bottle.
- Refrigerate and use for up to a mon.

Distilling

- In the centre of a wide saucepan, place a small bowl that can withstand heat.
- Fill the pot with the cleaned petals, being cautious not to let them lodge beneath the bowl.
- Add distilled water in pot until the petals are barely submerged.
- Turn the pot's lid upside down, then add the ice.
- Bring to a boil.
- Continue adding ice cubes as needed.
- Simmer for thirty to forty-five minutes on low heat.
- Using tongs, carefully remove the cover to examine the colour of the petals. Once they've lost their colour, you're done!
- Allow the rose water to cool completely.
- After the rose water has cooled, pour it into a spray bottle.

- Refrigerate and use for up to 6 months.(30,31)

Figure 7 Rose Water

The rosewater was used at banqueting tables across medieval Europe to wash hands. Typically, scent ingredients include rose water. Rose water can also be found in cosmetics like toners, face washes, and cold creams. During the winter months, especially, some people use rose water sprayed directly on their faces as a moisturizing and scent. Additionally, Indian weddings frequently sprinkle it on guests to greet them. It should come as no surprise that rose water may lighten skin redness and improve complexion, it has been used as a cosmetic for hundreds of years. Reduced acne could be aided by the antimicrobial qualities. Skin redness can be lessened by the anti-inflammatory characteristics. Puppy Chow and a Reliable Source.

Benefits of rose water:

- Cleanses and Brightens Skin.
- Soothes irritated skin.
- Balances natural oils.
- Decongests skin pores.
- Moisturizes skin. (32)

Evaluation Parameter:

- Organoleptic Evaluation: It speaks about judging the herbal face pack based on its appearance, texture, colour, and so on. Based on the methodology, the formulation's exterior characteristics were investigated.
- Physicochemical Evaluation: The determination of physicochemical characteristics encompassed the assessment of extractive value, ash value, pH, and moisture content.
- Physical Evaluation: The method of microscopy was used to test the particle size. Using the funnel method, bulk density, and tapping method, the flow property of the dried powder in mixed form was assessed.
- Phytochemical Evaluation: The presence of several phytoconstituents was assessed in the herbal face pack's aqueous extract using established protocols.
- Irritancy Test: On the dorsal surface of your left hand, mark a square centimetre. A certain amount of ready-made face packs was applied to the designated region, and the time was recorded. For a full day, irritability, erythema, and edema were monitored at regular intervals and reported.
- Stability Studies: A month-long stability test of the obtained formulation was carried out by storing it at various temperatures. The formulation's packed glass vials were kept at various temperatures. Stability analyses A month-long stability test of the obtained formulation was carried out by storing it at various temperatures. The glass vials containing the formulation were stored at different temperatures.(33)

CONCLUSION:

People now a days require side-effect-free treatments for a variety of skin conditions. Given that natural medicines are safer and have less adverse effects than synthetic ones, they are considered more appropriate. In the global market, herbal formulations are in demand. The face pack made of herbs is quite beneficial and includes ingredients such as rose water, aloe vera, gram flour, nutmeg, sandal wood, and charcoal. It is suggested that the developed formulation had characteristics of a typical cosmeceutical formulation for cosmetics and was both physically and microbiologically stable. It effectively gives the skin a radiant

appearance. A face pack made of herbs is used to restore muscle flexibility, eliminate stuck-on dirt particles, and enhance blood flow. One of the advantages of herbal-based cosmetics is their non-toxic composition. The facial skin is nourished by it. This face pack gives the skin essential nutrients. Acne, pimples, scars, and markings are all reduced by it. A face pack has the dual benefits of exfoliating the skin and cooling, relaxing, and soothing it. They give skin its ideal radiance back in the shortest amount of time. Natural medicines are becoming widely accepted because they are less harmful and have less adverse effects than solutions made of chemicals. To meet the demands of the expanding global market, a significant volume of herbal formulation was needed.

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Over-The-Counter Cold Remedies: Origins And Impact On Different Age Groups

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Abstract:

Introduction: Over-the-counter (OTC) medications are commonly utilized for treating the symptoms of the common cold due to their accessibility and affordability, especially in regions where healthcare access is limited. This study aims to gather data on the usage of OTC medications, specifically focusing on cetirizine, levocetirizine, phenylephrine, paracetamol, and other commonly used remedies for cold relief.
Methods: Data collection involved surveying individuals to ascertain their utilization of OTC medications for treating common cold symptoms. Additionally, therapeutic effects reported in published articles regarding various OTC drugs were analyzed to determine their efficacy in alleviating cold symptoms.
Results: Our analysis revealed widespread use of OTC medications for the common cold. The data obtained from published studies provided insights into the therapeutic effects of various OTC drugs on the body. Through statistical analysis, we evaluated the effectiveness of these medications for cold remedies.
Discussion: The findings of this study shed light on the efficacy of OTC medications for treating the common cold. Furthermore, the study highlights the potential risks associated with overuse of these medications, particularly among different age groups. Awareness regarding appropriate OTC medication usage and its effects across extreme ages is crucial for optimizing healthcare practices.
Conclusion: This study contributes to the understanding of OTC medication usage for cold remedies and emphasizes the importance of responsible usage, especially considering the potential impact on individuals across different age groups. Further research and awareness efforts are warranted to promote safe and effective usage of OTC medications for cold relief.

Keywords: OTC, non-prescription, cetirizine, levocetirizine, common cold.

Introduction:

OTC drugs stand for Over-the-Counter Drugs. OTC drugs are meant to be unprescribed or self- medication drugs. Over-the-counter (OTC) drugs are those drugs that are sold without a prescription by ordinary retail purchase, with no need for a prescription or a license(1).OTC medicines are nonprescription medicines; they are used interchangeably to refer to medicines that can be bought without a prescription. The drugs that come under schedules H and X are prescribed drugs according to the Drugs and Cosmetics Act of 1945, but these drugs are also sold as OTC drugs(1).

In day-to-day life, the use of OTC medicines is increasing continuously. OTC drugs are easily available and easily affordable; that's why the use of OTC medicines has increased in the last few years. Self-medications are the drugs that are obtained by patients for the recovery or treatment of common diseases and the treatment of a wide range of conditions, such as headaches, common colds, coughs, and musculoskeletal pain. These are the drugs that are not prescribed bythe physician and are sold out without a prescription. The World Health

Organization (WHO) considers that the self-medication of patients is helpful in reducing the load on the health care system(2).OTC drugs are useful for a wide range of treatments for various conditions, like the common cold, cough, headache, muscle pain, allergies, tobacco dependence, acidity, heartburn, etc(3). The cost of the medicines is very high at present, and the doctors are also not easily available for treatment, so this condition makes health care costly and unaffordable for the patient(4). OTC medications have some advantages, like being easily available everywhere, the cost of the OTC drugs being affordable to the patient, and time management or less time required to take OTC medication as compared to prescribed medications. That is why people's rational use of OTC drugs is increasing every day (1).

The common cold is defined as the term for an illness of the mild upper respiratory track. Which show symptoms like sneezing, sore throat, etc. The common cold is a disease that is caused by numerous viruses that belong to several different families and come under the heterogeneous group of diseases(5). The common cold is a self-limited illness. In a few of the patients, the viral infection spreads to adjacent organs in various clinical manifestations. The common cold is caused by the different viruses that are surrounded around us and passed from one person to another, and most of the cold viruses spread from one body to another due to contact with the fluids from the mouth and nose(5).

The common cold shows various symptoms such as runny or stuffy nose, sneezing, headache, and fever. These symptoms offer changes every few days. There is only one option, which is an antibiotic that is used to fight with the infection that is caused by the bacteria. But antibiotics do not work against the viruses that caused the common cold; they last for 7 to 10 days, and our body is capable of fighting with the viruses that caused the common cold, so there is no need for antibiotics(5). The regular cause of the common cold is rhinoviruses (30–50%) and influenza viruses (5–15%). Most of the common cold viruses are spread through the floating of droplets or hand-to-hand contact.

A cold is not the same as the flu, sinusitis, bronchitis, or strep throat. Other types of URIs are those caused by a flu virus or bacteria. If you have a URI that is not caused by a cold, you may require medicine to help you recover. Many of these additional URIs begin with cold-like symptoms. Other URI symptoms, on the other hand, are more severe or continue to worsen after week to ten days(5).

There are no tests to determine if you have a cold. Your doctor can diagnose a cold by asking about your symptoms and performing a physical check. To ensure that you do not have the flu or strep throat, your provider may perform a flu or strep throat test on you.

Antibiotics are only effective against bacterial infections. The viruses that cause the common cold are not cured by antibiotics. Our bodies are capable of fighting cold virus without the use of drugs. The majority of healthy people recover from a cold without treatment. Although medicines will not cure a cold, there are other treatments that can alleviate your symptoms(5).

Treatment options for cold

Symptoms	**Treatment**	**Important Notes**
Non-Medication Treatments		
Any cold or infection	Sleep, rest, extra water	Very important

Runny or stuffy nose	Clean or flush the nose	Use a saline nasal spray or net pot
Runny or stuffy nose	Humidified (wet) air	Good for children

Table 1 Treatment options for cold (6)

Over-the-Counter Medication Treatments*		
Fever, chills, pain, sore throat	Ibuprofen (Advil) or acetaminophen (Tylenol)	Do not take more than 3000mg of Tylenol in one day. Do not take more than 6 pills with 500 mg of Tylenol in 24 hours. Do not take more than 10 pills with 325 mg of Tylenol in 24 hours.
Runny or stuffy nose, sinus pressure	Fluticasone propionate nasal(Flonase)	
Runny nose, wet cough	Pseudo ephedrine (Sudafed)	Don't use for more than 3 days
Sore throat	Throat lozenges or spray	
Cough	Dextromethorphan (Robitussin)	
Dry cough	Guaifenesin (Mucinex)	

Table 2 Over-the-Counter Medication Treatments (7)

Most over-the-counter cold treatments include mixtures of two or more drugs, which is especially important for children. The elderly person, who may already be using numerous medicines. Individual reactions to medications will always vary, and the reactions become even more unpredictable when a single product has multiple active components. The risk to the consumer grows as the number of drugs in a regimen increases. Adding just one of the common cold treatments to an elderly person's medicine regimen may quadruple or even triple the amount of drugs that individual is taking. Most cough and cold treatments are a fixed-dose combo, which means that there is always a specific amount of each ingredient in the package. If a stronger decongestant is required, it is not possible to take more of that one substance if alleviation, cough suppression, or analgesia is required(8).

Factors of Growth

The worldwide over-the-counter pharmaceuticals business is expanding due to rising demand for self-medication and drugs. According to the Pharmacoepidemiology and Drug Safety, around 20% of the Spanish population consumes non prescribed medicine, with females being more probable.

Furthermore, rising approvals for over-the-counter pharmaceuticals are propelling the worldwide over-the-

counter drugs market forward. Sanofi, for example, announced in February 2017 that the Food and Drug Administration has approved Xyzal Allergy 24HR as an over-the-counter medication for seasonal allergies. The worldwide over-the-counter pharmaceuticals industry is being propelled by an increase in demand for personalized medications for minor ailments and the deployment of treatment processes by healthcare payers.

CATEGORY	EXAMPLES OF INGREDIENTS
Antihistamines	Chlorpheniramine, diphenhydramine, hydroxyzine
Antipyretics	Acetaminophen, ibuprofen
Antitussives	Dextromethorphan
Decongestants	Pseudo ephedrine, phenyl propanolamine, phenylephrine
Expectorants	Guaifenesin

Table 3 Examples of over-the-counter medications categorized according their medication(9)

Over-the-counter cough and cold drugs (OTC CCM) will be used by youngsters. OTC CCM remedies are often a blend of at least two drugs, such as antihistamines, antitussives, expectorants, decongestants, and antipyretics. youngsters aged 2 to 5 years are the most likely to utilize such preparations, followed by youngsters less than 2 years

Various Types of OTC Drugs Consumed:

Antidepressants were the least regularly taken OTC medications (n = 3; 0.4%), whereas analgesics were the most commonly consumed (n = 357; 49.1%). Although antidepressants are not considered OTC, they have been included in this research since they are available from some internet "pharmacies" and have been acquired from traditional pharmacies on Occasion(9).

Drugs used for over-the-counter medication

The medications were non steroidal anti-most widely utilized OTC inflammatory medicines (NSAIDs) (38%), gastrointestinal treatments (16%), cough cures (14%), and antimicrobials (10%). 1.5% of individuals in this group used OTC medicine containing atenolol and amlodipine for the treatment of chronic cardiovascular diseases such as hypertension.(4)

Indications for over-the-counter medication

Fever was the most prevalent reason for using OTC medicine (22.42%), followed by pain (15.75%) and gastrointestinal problems (15.75%). The most prevalent reason for non-OTC medicine was pain (20.27%), followed by infection control (16.22%)(4)

INDICATION	OTCn=165(%)	N-OTCn=715(%)
Pain (include headache)	26(15.75)	145(20.27)
Fever	37(22.42)	104(14.54)
Infection	17(10.32)	116(16.22)
Gastrointestinal Disorders	2615.75)	74(10.34)
Respiratory Symptoms	22(13.33)	42(5.87)
Skin Disease	4(2.4)	13(1.81)
Eye Disease	1(0.60)	6(0.83)
Ear Disease	3(1.81)	9(1.25)
CVS Disease	2(1.21)	74(10.34)
Urogenital Disease	6(3.63)	28(3.91)
Insomnia	9(5.45)	14(1.95)
Miscellaneous	12(7.27)	90(12.58)

Table 4 Indications for medication in over-the-counter and non-over-the-counter group(8)

Category (name of drugs)	Number of OTC request (n=165)
NSAIDs (paracetamol, diclofenac and their FDC)	63(38)
Antimicrobial (cefpodoxime, ciprofloxacin, norfloxacin, amoxicillin-clavulanic)	17(10)
Gastrointestinal drugs (ondansetron, proton-pump-inhibitors)	26(16)
Cough remedies (dextromethorphan, bromhexine)	23(14)
Cold remedies (cetirizine, levocetirizine)	3(2)
Central nervous system drugs (lorazepam)	1(0.6)
Eardrops (ciprofloxacin)	8(5)
Eyedrops (dexamethasone)	3(2)
Cardiovascular drugs (amlodipine)	1(0.6)
Uro genital disease (alkalizer)	2(1.2)
Others	5(3)

Table 5 Drugs used for over-the-counter medication(8)

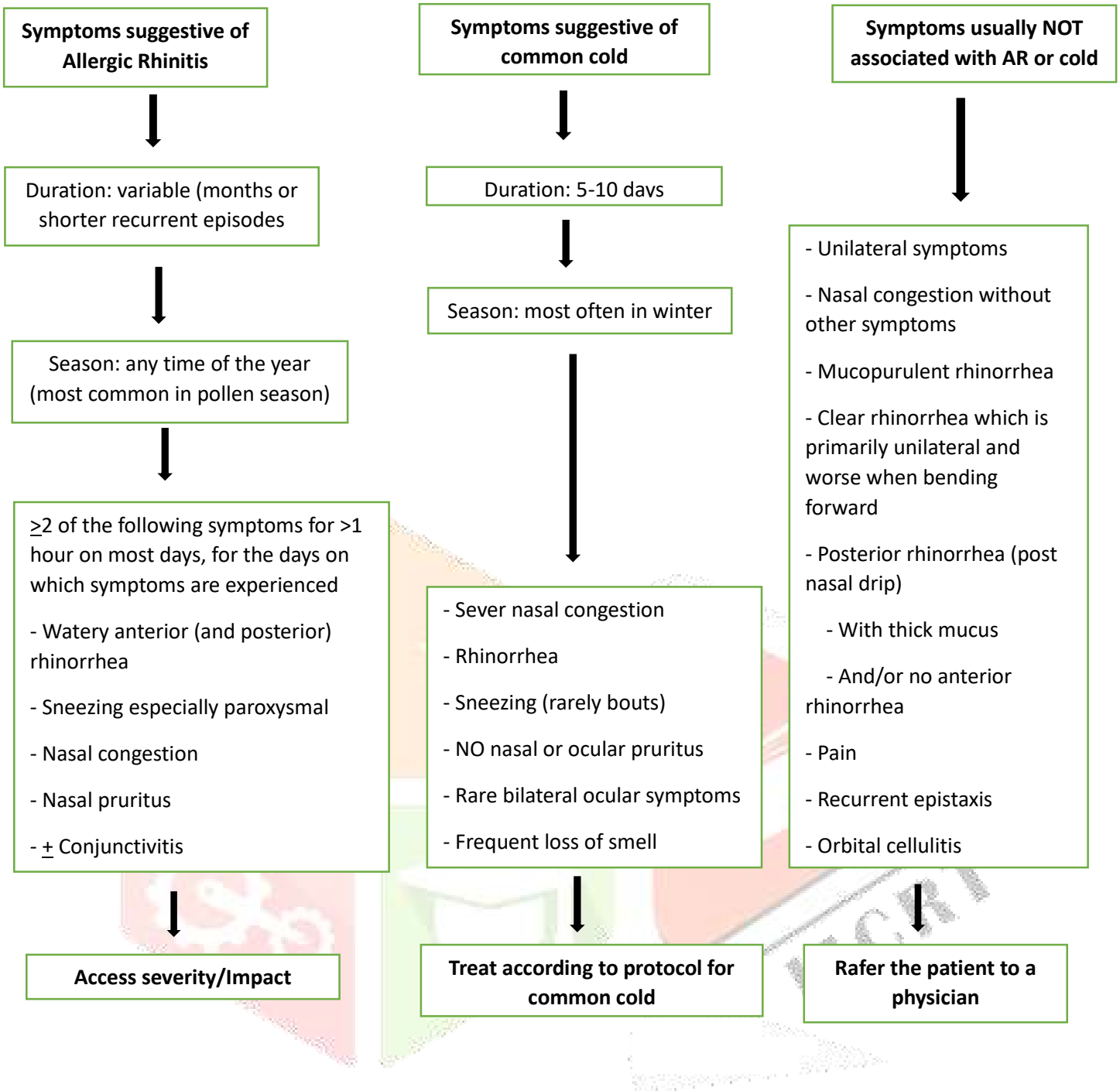

Figure 1 Recognizing allergic rhinitis in the pharmacy

Mechanism of Action of Paracetamol

The most often used analgesic/antipyretic in children is paracetamol (acetaminophen). The product was introduced in the United States in 1955 and in the United Kingdom the following year. Its elevation followed the discovery of a link between Reye's syndrome and aspirin(1) Despite its ubiquity, the mechanism by which paracetamol works to reduce fever and discomfort remains unknown(9).

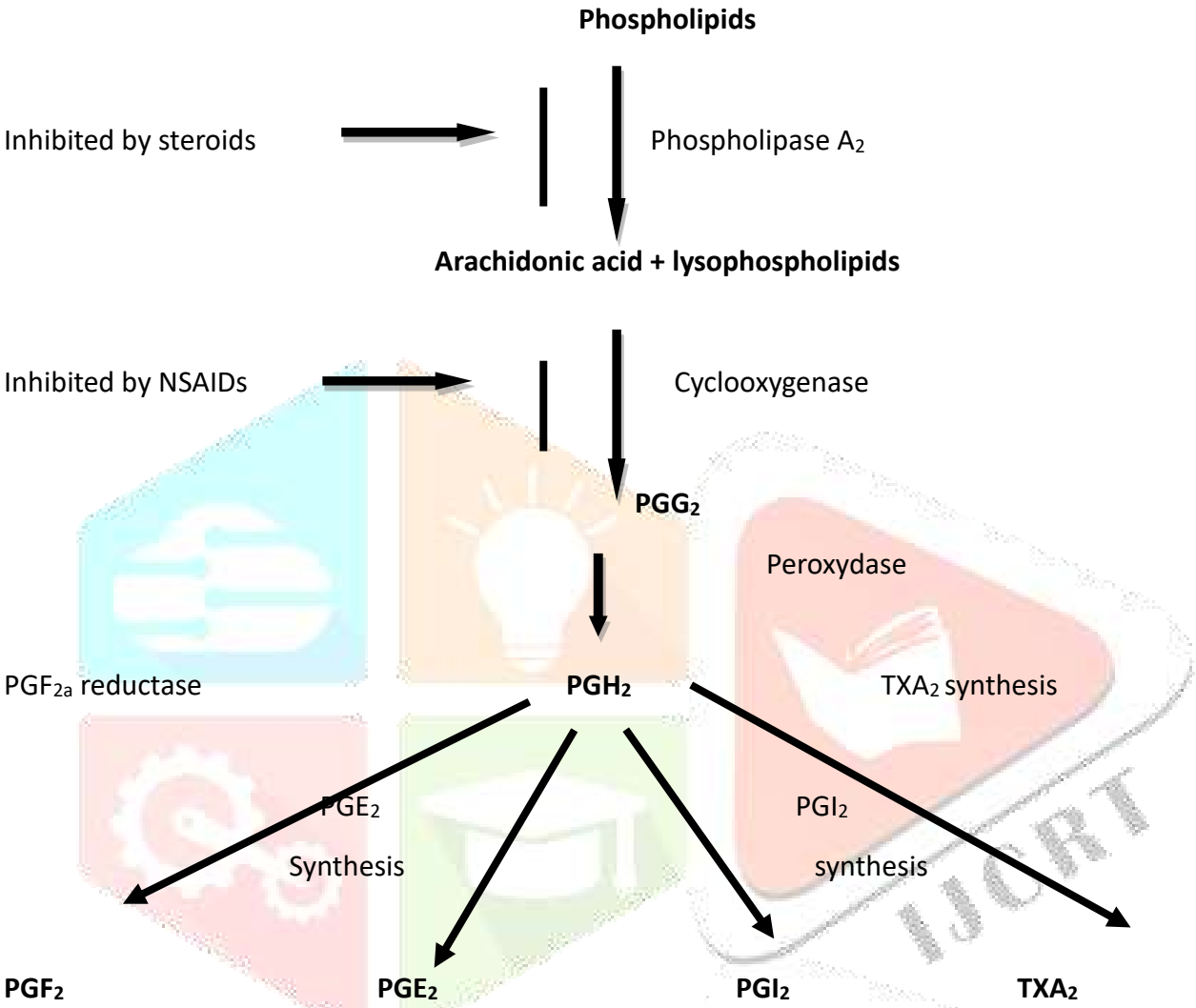

Figure 2 Schematic diagram of arachidonic acid metabolism.

Prostaglandin H2 synthetase inhibition

Prostaglandin H2 synthetase is the enzyme that converts arachidonic acid to the unstable PGH2. This enzyme exists in two forms: constitutive PGHS-1and inducible PGHS-2. COX-1and COX- 2 are the common names for these two enzymes However, the abbreviation PGHS is recommended since this enzyme has two active sites: a COX site and a POX site. The COX enzyme's activity is dependent on its being in the oxidized state, and it has been proposed that paracetamol lowers the quantity of the oxidized form by acting on the POX site (10). Another possibility is that the central nervous system (CNS) contains a PGHS variation (COX-3) that is extremely susceptible to paracetamol.

Paracetamol activity at the POX site

Arachidonic acid to PGH2 conversion is a two-step process. Arachidonic acid first absorbs two molecules of O2 to generate PGG2 (by COX), and then PGG2 is reduced by two electrons (via POX). These responses take place at two separate locations. POX occurs in a heme-containing active site on the protein surface, whereas

COX occurs in a hydrophobic channel in the enzyme's core (10). COX is reliant on POX, while POX may function on its own (9).

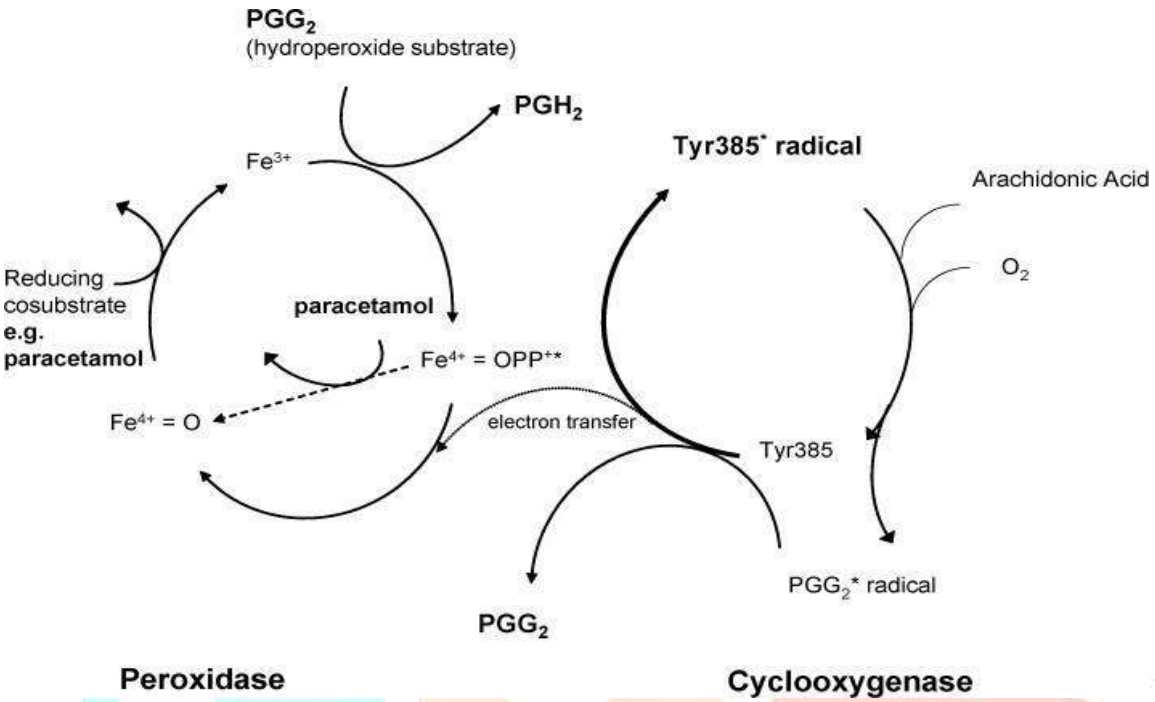

Figure 3 Paracetamol activity at the POX site

Etiology:

The genesis of the common cold was studied in young children who were newly sick but did not require hospitalization. We predicted that by testing for 16 viruses in outpatients, we might determine the etiology in all instances.

The common cold is considered a viral illness. Several novel respiratory viruses have been found in the opening years of the twenty-first century, including human Meta pneumo virus (hMPV), corona viruses NL63 and HKU1, and human bocavirus (HBoV). Many research has been undertaken on the role of these viruses in hospital settings, but few investigations have been conducted on outpatients. We investigated the genesis of the common cold in young children who were newly sick but did not require hospital treatment. We expected that the etiology might be found in all instances by employing contemporary diagnostics that test for 16 viruses in outpatients. We collected nasopharyngeal aspirate samples in outpatient setting from 194 Finnish children with freshly onset (48 h) symptoms of a common cold without acute otitis media (AOM) or other symptoms necessitating antibiotic treatment(11).

We collected nasopharyngeal aspirate samples in an outpatient environment from 194 Finnish children with freshly on set (48h) symptoms of common cold but no acute otitis media (AOM) or other symptoms requiring antimicrobial therapy between February 1996 and April 1998 (1) The research population's average age was 2.1 years (range 0.7-3.9 years), and 81% attended day care. All participants' parents submitted written informed consent, and the study procedure was approved by Turku University's Ethics Committee. Fresh nasopharyngeal aspirate samples were processed for antigen identification (RSV, parainfluenza viruses 1, 2,and 3, influenza A and B viruses, and adenovirus) using time-resolved fluor immunoassay(11).

Nucleic acid testing (NAT) was performed on stored samples to detect picorna viruses, RSV, corona viruses 229E, OC43, NL63, and HKU1; influenza C virus; HBoV; hMPV; and adenovirus. These samples were just retested for rhinovirus. 179 (92%) of the 194 children tested positive for at least one respiratory infection. The most frequent respiratory infection, rhinovirus, was detected in 138 (71%) of the children (Table). Other viruses were discovered in varying proportions: HBoV was found in 27 (14%) of the children; adenovirus

was found in 23 (12%) (3 were positive by antigen detection, and 23 by NAT); entero virus was found in 20 (10%); corona viruses were found in 11 (6%) (NL63:7; HKU1:2; 229E/OC43:2); influenza viruses were found in 11 (6%) (A:4; B:1; C:6) Para influenza viruses were detected in 7(4%) (1:1;3:6) cases, and hMPV in 3(2%). 46(26%) of children with a positive viral result had two viruses, while 10 (6%) had three or four viruses. The viruses that co-occurred the most commonly with other viruses were adenovirus (100%), HBoV (81%), and entero virus (75%) (11). Positive viral findings in 194 children with newly onset uncomplicated common cold, Finland, 1996–1998.

Mechanism of action of cetirizine:

Cetirizine is an antihistamine that is used to treat allergic rhinitis and urticaria. It belongs to the second generation of antihistamines. Cetirizine was FDA-approved as a prescription-only medicine in the United States in 1995, and it was later authorized as an over-the-counter drug in 2007. Cetirizine is a potent and highly specific antagonist of the peripheral histamine H1 receptor. Cetirizine inhibits H1-receptors particularly in respiratory smooth muscle cells, vascular endothelial cells, immunological cells, and the gastrointestinal tract. Cetirizine, unlike first-generation antihistamines such as diphenhydramine and doxylamine, does not pass the blood-brain barrier very well, avoiding the neurons of the central nervous system.

Because of its antagonistic impact on histamine H1-receptors, cetirizine efficiently reverses many of histamine's effects. Cetirizine, like other second-generation antihistamines, reduces vascular permeability, which reduces fluid leaking from capillaries to tissues. Cetirizine also inhibits histamine-induced bronchospasm. Cetirizine has been shown to have strong anti- inflammatory effect, lowering inflammatory cell infiltration in the context of allergic rhinitis. Cetirizine, in particular, has been shown in studies to reduce neutrophil and eosinophil migration.

Pharmacokinetics:

Absorption: Cetirizine is readily absorbed in the gastrointestinal system and excreted extensively by the kidney. After about an hour, cetirizine achieves its highest plasma concentration. Its effects usually start within 20 to 60 minutes and last at least 24 hours. Food has no effect on the amount of exposure (AUC) of cetirizine, although it did delay the time to peak concentration by 1.7hours(12).

Distribution: Cetirizine has an average plasma protein binding of 93%.

Metabolism: Cetirizine is oxidatively O-dealkylated to produce a metabolite with little antihistaminic action. Cetirizine is not a CYP450 system substrate. Evidence suggests that cetirizine is a P-glycoprotein substrate, which should be noted when using cetirizine in conjunction with P-gp inhibitors.

Excretion: Cetirizine has an elimination half-life of 8.3 hours.

Administration: Cetirizine is available in the form of pills, capsules, liquids, and orally disintegrating tablets. Cetirizine dose is determined on the patient's age. The suggested dose for adults and children 12 years and older is 5 or 10 mg per day orally, depending on symptom severity(6). It is available in 5mg and 10mg tablets, as well as a 5mg/5ml oral solution and elixir. The 0.24% cetirizine hydrochloride eye drops are available in 5 mL and 7.5 mL vials.

Depending on the severity of the symptoms, 5 or 10mg (1 or 2 teaspoons) once day in syrup form is indicated for children aged 6 to 11 years old. The suggested dose for children aged 2 to 5 years old is 2.5 milligrams (half a teaspoon) once day in syrup form. For individuals with allergic conjunctivitis, one drop (0.24% cetirizine hydrochloride ophthalmic solution) is administered twice day in the afflicted eye(12).

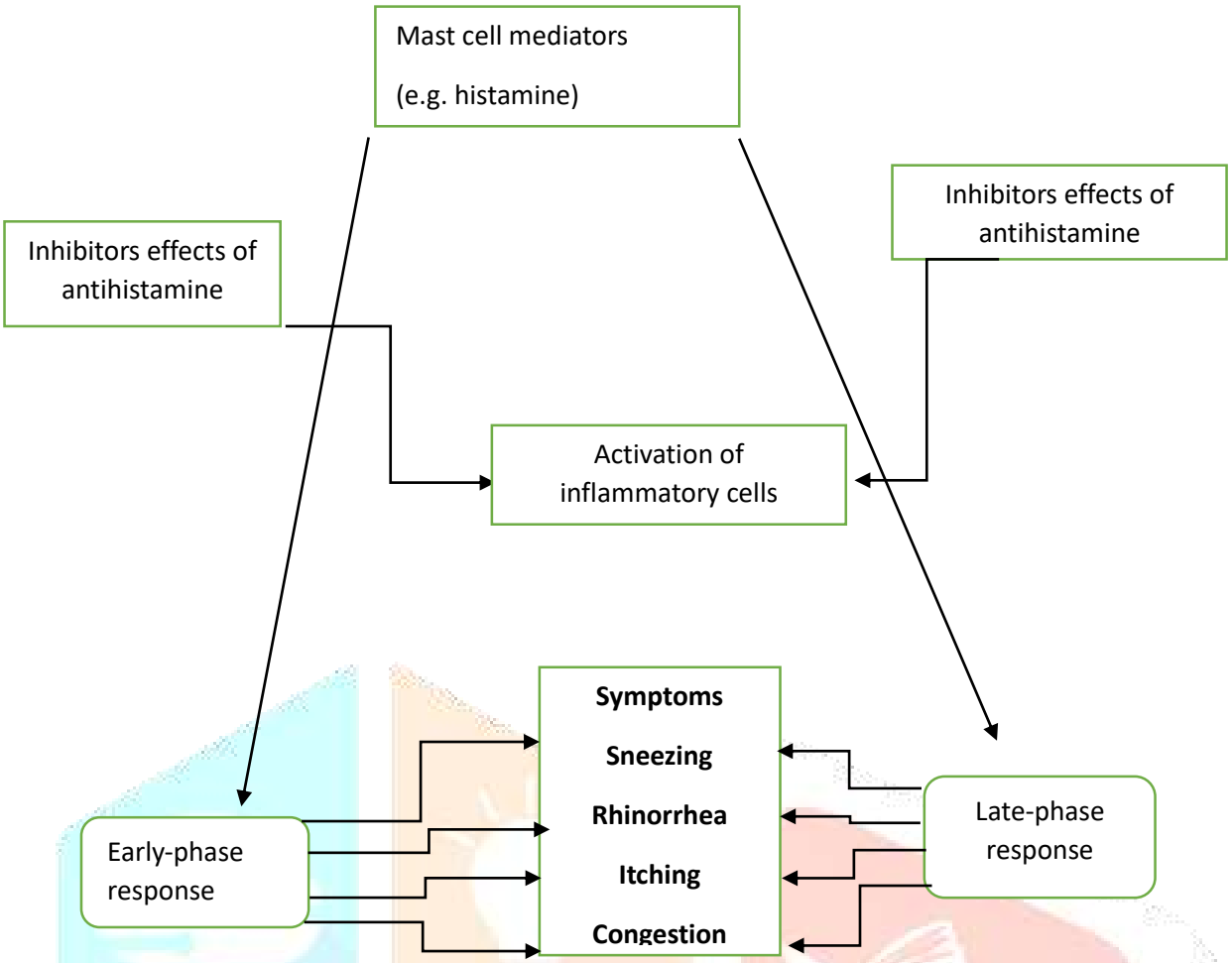

Figure 4 Mechanism of Cetirizine

Result: The study shows that over-the-counter (OTC) drugs are used commonly for the treatment of common cold or get relief from the cold The OTC drugs are mostly available, affordable to the patient, so peoples are mostly taking non-prescription drugs as compared to prescription drugs.

The consumption OTC drugs without knowing the dose level or about drug is can led to severe consequences on patients.

Conclusion: According to research, the majority of individuals take over-the-counter medications for pain and other ailments. In the future, we may educate patients about the dangers of taking over-the-counter medications. This will assist patients in obtaining safe and effective over-the-counter medications.

OTC medicines are ones that may be purchased without a prescription or as non-prescription drugs. The usage of OTC medications is examined in this review. Data was acquired through an examination of several published papers.

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