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POTENTIAL HERBAL REMEDIES FOR ALZHEIMER'S DISEASE: A TYPE OF DEMENTIA

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ABSTRACT

Dementia is a progressive neurological disorder characterized by a decline in cognitive function, affecting memory, reasoning, and daily functioning. With an aging global population, dementia has become a growing concern, leading to the need for effective treatment strategies. This review explores the various types of dementia, including Alzheimer's disease, vascular dementia, and Lewy body dementia, each with distinct pathophysiological mechanisms and clinical manifestations. Current treatment approaches primarily focus on symptomatic management, utilizing pharmacological agents such as cholinesterase inhibitors and glutamate regulators, though these therapies offer limited disease-modifying effects. In recent years, herbal remedies have gained attention as potential adjuncts or alternatives to conventional treatments. This article examines the Curcuma longa, highlighting their potential neuroprotective properties. The review further assesses the scientific evidence supporting the use of these herbs, evaluating both preclinical and clinical studies, and discusses the challenges in interpreting the results. The conclusion underscores the need for rigorous, large-scale clinical trials to validate the therapeutic potential of herbal remedies in dementia management and emphasizes the importance of an integrated approach combining conventional and alternative treatments.

Keywords: *Alzheimer's, Cognitive, Herbs, Vascular dementia, Lewy body dementia.*

I. INTRODUCTION

Dementia is a widespread neurodegenerative condition that primarily affects older adults, contributing to a significant public health challenge globally. As the global population ages, the number of people with dementia is rising rapidly. The World Health Organization predicts that by 2050, the number of individuals living with dementia will reach 115.4 million. Despite this alarming trend, the issue often goes unnoticed or underappreciated.[1]

Dementia is a progressive neurological condition that damages crucial brain cells, affecting memory, thinking, and behavior to the point that it disrupts work, hobbies, and social interactions. To help manage dementia, various drugs and natural

remedies have been used to improve memory and protect cognitive function. Traditional herbal medicine, with its many plant-based treatments, has been widely utilized for age-related cognitive issues and is gaining popularity globally due to its proven effectiveness.

Drugs that act on the brain to enhance memory are known as nootropic drugs. Many natural memory boosters work by regulating the activity of acetylcholinesterase (AChE), an enzyme that controls the levels of acetylcholine (ACh), a neurotransmitter important for memory. When AChE is too active, it leads to a depletion of acetylcholine, causing memory and cognitive problems. Natural substances that inhibit excessive AChE activity can help protect individuals with dementia by maintaining better acetylcholine levels and supporting cognitive health.[2]

II. What is dementia?

Dementia is a condition where a person's cognitive functions, such as memory, thinking, and reasoning, begin to decline to the extent that it impacts their daily life. It's not a singular condition, but rather a group of symptoms linked to various underlying disorders, such as Alzheimer's disease, vascular dementia, frontotemporal dementia, and Lewy body dementia.

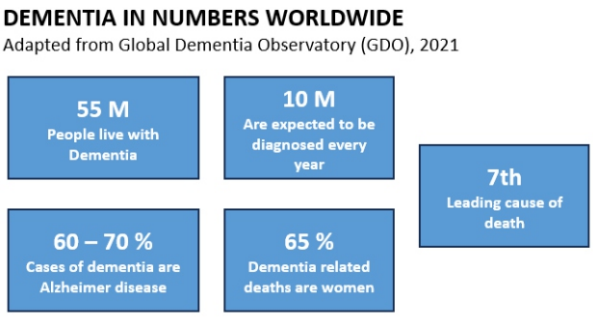
In addition to memory loss, those with dementia may struggle with communication, have trouble with decision-making, and experience shifts in mood or behavior. Everyday tasks that were once simple can become increasingly difficult. Over time, these symptoms typically get worse and can greatly affect a person's independence and overall well-being.

While dementia can affect people at any age, the risk increases as we get older, especially in individuals over 60. In addition to age, other factors like genetics, high BP, Smoking, Diabetes, and Obesity can also raise the likelihood of developing dementia.[3]

SIGNS AND SYMPTOMS

A person with dementia typically:

- Struggles with completing everyday tasks.
- Has trouble remembering recent events.
- Finds it hard to make logical decisions and may act in ways that seem inappropriate.
- Difficulty in Communication and understanding the information.
- Loses their thought easily, often repeating phrases or questions in conversations without realizing it.
- Appears confused or disoriented, even in familiar environments.[3]



1: Dementia in numbers worldwide

TYPES OF DEMENTIA

I. Alzheimer's Disease[4]

AD(AD) is a condition that leads to the breakdown of brain cells and is the major cause of dementia. It progressively affects older adults by impairing their ability to think, learn, and perform daily tasks independently. In the early stages of AD, memory loss is typically the first noticeable symptom, and dementia develops as the disease advances.Alzheimer's causes changes in the brain, such as the buildup of abnormal β-amyloid and tau proteins, inflammation, and damage from free radicals and cholinergic dysfunction. These changes contribute to the decline in cognitive and behavioral functions. Here are the main causes of Alzheimer's disease: -

a. Neuritic plaques or senile plaques:

Large, insoluble amyloid fibrils and smaller, soluble oligomers make up amyloid beta (Aβ) monomers, which can build up in the brain and create amyloid plaques that spread throughout the body. Aβ is a major factor in brain cell damage and neural function disruption. Denser plaque accumulation in areas like the cerebral cortex, hippocampus, and amygdala causes astrocytes and microglia to become activated, which damages axons and dendritic fibers, destroys synapses, and impairs cognitive function. Brain function and health are severely harmed by this process.

b. Neurofibrillary tangles:

Neurofibrillary tangles are twisted clumps of tau protein that have become abnormally phosphorylated. These tangles build up inside nerve cell bodies (perikarya), as well as in axons and dendrites. At certain stages, they twist together to form paired helical filaments. The presence of these tangles disrupts the normal structure of the cell, leading to the loss of important components like microtubules and tubulin-associated proteins, which are crucial for maintaining the cell's structure and function.

c. Synaptic Loss:

In the early stages of Alzheimer's disease, damage to synapses in the neocortex and limbic system leads to memory problems. This synaptic loss occurs because of several factors, including mitochondrial damage, issues with axonal transport, oxidative stress, and the buildup of Aβ and tau proteins at synaptic sites. Over time, these disruptions cause the loss of dendritic spines and presynaptic terminals, further impairing brain function.

ii. Frontotemporal Dementia:

Frontotemporal dementia (FTD) is a less common form of dementia, but it specifically impacts the front regions of the brain that control emotions, planning, language, and motivation. There are different types of frontotemporal dementia, depending on which part of the frontal or temporal lobes is most affected. A common feature of FTD is the degeneration of these lobes, and this condition is often referred to as frontotemporal lobar degeneration (FTLD). In most cases of FTD, the pathology involves the abnormal buildup of specific proteins inside the cells, which are unique to the disease.[5]

iii. Semantic Dementia:

Semantic dementia is a form of dementia that primarily affects semantic memory, which includes knowledge of objects, concepts, and familiarity with people. This type of dementia leads to a decline in the ability to remember facts, understand objects, and grasp the meaning behind words and language. Patients with semantic dementia often struggle to recall the names of places, people, and things. The condition is linked to asymmetrical atrophy of the temporal lobes, with more significant damage typically occurring on the left side. Severe neuronal degradation is commonly observed in areas associated with the left anterior temporal lobe.[6]

iv. Vascular Dementia

Vascular dementia is a condition where cognitive abilities decline due to reduced or blocked blood flow to parts of the brain, which limits the supply of oxygen and nutrients. When blood flow is inadequate, brain cells can become damaged and eventually die, with the brain being particularly vulnerable to this type of damage. In vascular dementia, cognitive changes typically occur after a stroke, which blocks blood flow in the brain's major blood vessels. These brain changes often overlap with those seen in Alzheimer's disease, Lewy body dementia, and other types of dementia. Vascular dementia is thought to be the second

most common form of dementia, accounting for 10-20% of all dementia cases.[7]

v. Lewy bodies Dementia:

A protein called alpha-synuclein accumulates abnormally in neurons to create aggregates called Lewy bodies, which can spread to other areas of the brain in Lewy body dementia. These deposits interfere with brain chemicals, leading to disruptions that affect movement, thinking, mood, and behavior. Alpha-synuclein is an important protein in nerve cells, especially at synapses, where communication between brain cells takes place. In Lewy body dementia, this protein clumps together inside neurons in areas of the brain responsible for movement and memory. Over time, these clumps hinder the function of neurons, causing them to gradually become less effective and eventually die.[8]

vi. Mixed Dementia:

Mixed dementia refers to the presence of more than one type of dementia in a single individual. The most common combination is ADand Vascular dementia, where both conditions contribute to the clinical symptoms and changes observed in the brain. In mixed dementia, there is often a progressive decline in cognitive abilities similar to Alzheimer's disease, but with strokes also playing a role in worsening the condition. The combination of these two types of dementia can make the symptoms more complex and challenging to manage.[9]

III. CURRENT TREATMENT APPROACHES FOR DEMENTIA

Because dementia causes the loss of brain cells, there is currently no cure. As a result, the focus of treatment is on managing symptoms. This includes addressing behavioral issues, making environmental changes to help maintain function, and providing guidance on safety concerns.[10]

The main goal in managing dementia is to slow down cognitive decline and ease the cognitive distress that patients experience. Both non-drug and drug treatments are used, either separately or together. The specific treatment options can vary depending on the type of dementia. Cholinesterase inhibitors and memantine are the two primary drug classes authorized for the treatment of dementia. Acetylcholinesterase inhibitors (AChEIs), such as galantamine, donepezil, and rivastigmine galantamine, are prescribed for Alzheimer's-related dementia; doses are modified according on the severity of the illness. Additionally, memantine, an NMDA receptor antagonist, may also be used. Other types of dementia, including vascular dementia, Parkinson's disease dementia, Down syndrome-related dementia, Lewy body dementia (LBD), and frontotemporal dementia, can also be treated with these medications.[10]

I. AChEIs

Research shows that AChEIs like galantamine, rivastigmine, and donepezil work by increasing cholinergic transmission. They do this by blocking cholinesterase at the synaptic cleft, offering modest relief from symptoms in some dementia patients. These medications are particularly important for Alzheimer's patients, who have reduced levels of choline acetyltransferase in the brain, leading to lower acetylcholine production and impaired brain function. Donepezil has shown significant improvement in cognition, clinical assessments, and overall functional outcomes in patients taking higher doses.[11–14] Currently, AChEIs are considered the gold standard for managing cognitive and psychiatric symptoms in Lewy body dementia (LBD). Among these, rivastigmine is the only one approved by the FDA specifically for treating LBD.[15–17]

In Parkinson's disease dementia, treatment

mainly focuses on using AChEIs. While most clinical trials have shown a slight to moderate benefit from AChEIs, these benefits often come with an increased risk of side effects, such as worsened tremors and nausea. However, not all trials have had the same results.[18,19]

ii. Memantine

Memantine is an NMDA receptor antagonist that works differently from cholinergic medications by offering neuroprotection. Glutamate, the brain's primary excitatory neurotransmitter, activates NMDA receptors, which play a key role in memory and learning. Memantine is commonly used alongside AChEIs, particularly in advanced Alzheimer's disease, to help manage symptoms. It can also be helpful in treating vascular dementia (VaD) by blocking excessive NMDA receptor stimulation caused by ischemia, which could otherwise lead to excitotoxicity and further brain damage. This blockage may help preserve the function of remaining neurons and improve symptoms.[20] Given the lack of other effective treatments for VaD, many clinicians are increasingly turning to memantine, especially when used with AChEIs. For Lewy body dementia (LBD), the 2020 treatment guidelines suggest that while AChEIs have the strongest evidence for treating cognitive impairment, memantine's effectiveness is less clear and mixed.[21]

iii. Antioxidants.

Both selegiline, a monoamine oxidase inhibitor, and vitamin E (alpha-tocopherol) have been investigated as possible AD therapies. Although it has little effect on cognitive performance, studies indicate that vitamin E, when given at a certain level, may somewhat reduce functional loss in those with mild to severe Alzheimer's disease.[22,23] On the other hand, drugs that target serotonergic pathways, such as trazodone, atypical antipsychotics, and selective serotonin reuptake inhibitors (SSRIs), are better in treating particular behavioral symptoms of Alzheimer's disease. These drugs don't, however, enhance general cognitive function. Based on case reports and brief observational trials, SSRIs like sertraline and fluvoxamine have demonstrated some advantages in treating anxiety, eating problems, and impulsivity in patients with frontotemporal dementia.[24]

iv. Recent Drugs

Lecanemab, an anti-amyloid monoclonal antibody, was recently licensed by the FDA to treat mild dementia and moderate cognitive impairment (MCI) brought on by Alzheimer's disease.[25] a crucial turning point in the treatment of dementia has been reached with this approval. Lecanemab functions by attaching itself to amyloid-beta plaques, one of the leading causes of Alzheimer's, and assisting in the treatment of this important pathological characteristic of the illness. [26]

A significant study highlighted the effectiveness of lecanemab in reducing amyloid markers in people with early-stage Alzheimer's. The results showed that those treated with lecanemab experienced slower cognitive and functional decline over 18 months compared to those who received a placebo. However, it's important to note that adverse events were a concern with lecanemab treatment, emphasizing the need for close monitoring and management of potential side effects.[27]

Similarly, the effectiveness of another anti-amyloid-beta monoclonal antibody, aducanumab, has been well-documented in research. A systematic review by Rahman et al. found that aducanumab helped reduce amyloid-beta plaques and significantly slowed cognitive decline in Alzheimer's patients. The FDA's approval of aducanumab in June 2021 further supports its role as a viable treatment option for Alzheimer's disease.

v. Non-Pharmacological Treatments

While no single diet has been proven to directly prevent cognitive decline or dementia, several lifestyle factors can help maintain brain health and lower the risk of Alzheimer's disease. In addition to eating a balanced, healthy diet, regular physical activity, adequate sleep, and effective stress management are all important habits linked to a reduced risk of cognitive decline.[28]

IV. Herbal remedies for dementia.

Herbal medicines have become highly effective in treating and slowing the progression of various diseases, including diabetes, cancer, and neurodegenerative disorders like Alzheimer's. In recent years, natural products have gained widespread popularity as supplements or alternative therapies due to their effectiveness and lower risk of side effects.[29]

PROMISING HERBS AGAINST ALZHEIMER'S DISEASE

i. Salvia officinalis L

Salvia officinalis L. and S. lavandulifolia Vahl. have long been recognized in European herbal texts for their ability to enhance memory. These plants exhibit a range of neurological effects, including anti-AChE and anti-BuChE activity in laboratory settings, along with anti-inflammatory, estrogenic, antioxidant, and anti-amyloidogenic properties. Additionally, research on healthy young individuals has shown that a standardized oil extract of S. lavandulifolia can improve short-term word recall and other cognitive functions. Another study also demonstrated that using the essential oil of S. lavandulifolia boosted both mood and cognitive performance in healthy individuals.[30]

ii. Areca catechu L.

Areca nuts, the fruit of the Areca catechu L. palm tree (Arecaceae), are widely consumed across the Indian subcontinent and Southeast Asia to promote euphoria and increase salivation. The main alkaloid in these nuts is arecoline, which has cholinergic effects that stimulate excessive salivation through a muscarinic mechanism, activating the central nervous system. Arecoline binds to M2 muscarinic receptors and acts as a partial agonist at M1/M3 receptors. It has been studied for its potential in treating cognitive impairments, as it has shown to improve scopolamine-induced cognitive deficits and passive avoidance behavior in animal studies, indicating cholinergic activity.[31] In Alzheimer's patients, arecoline has been found to enhance verbal memory and provide modest improvements in cognitive function and recognition. Xanomeline, a derivative of arecoline, exhibits functional selectivity for the M1 receptor. It has been shown to slow cognitive decline while also reducing delusions and hallucinations in Alzheimer's patients.[31]

iii. Clitoria ternatea L.

The roots of *Clitoria ternatea* L. (Leguminosae), a well-known Indian botanical remedy, are traditionally believed to enhance intelligence. Some research suggests that this effect is connected to changes in cholinergic activity within the central nervous system. A study comparing the aerial and root parts of *C. ternatea* found that alcoholic extracts from the roots were more effective in improving memory deficits in rats. When the root extract was administered orally, it resulted in higher levels of acetylcholine (ACh) and choline acetyltransferase (ChAT) in the rat brain, which enhanced memory recall. However, this effect was not linked to AChE inhibition; instead, an increase in cortical AChE activity was observed. Similarly, an aqueous extract from the root raised ACh levels in the rat hippocampus, likely due to the activation of

enzymes involved in ACh production.[29]

iv. Lesser periwinkle.

Vinca minor L. (Apocynaceae) contains alkaloids like vincamine and its derivatives, vinpocetine and vincanol, which have neuroprotective properties. These compounds block voltage-gated Na+ channels and have cerebral vasodilatory and nootropic effects. Vincamine helps regulate brain circulation, maintain neuronal balance, and offers antihypoxic benefits. A Cochrane review highlighted that vinpocetine has shown promising results in clinical trials for improving cognitive function in people with dementia. However, while it shows potential in enhancing memory and learning in vascular dementia (VaD), the evidence is still insufficient to recommend it for widespread clinical use.[32]

v. Amaryllidaceae family.

Originally isolated from the bulbs of Galanthus woronowii, galanthamine is a tertiary alkaloid and one of the well-researched alkaloids from the Amaryllidaceae family. Additionally, galanthamine was recovered from several Amaryllidaceae plants, including Lycoris radiate, Lycoris aruea, and Lycoris squamigeric. It inhibits AchE in a competitive, reversible, and selective manner. Prior research has suggested that galanthamine might exacerbate memory impairments.[33] Additionally, the molecule can selectively activate or modify the nicotinic acetylcholine receptor in neurons, which may promote the creation of neurotrophic factors and shield neurons from the damaging effects of damage and oxidative stress. Additionally, nicotine and galanthamine operate together to suppress the activation of microglia.

The effectiveness and safety of galanthamine in the treatment of AD have been validated by a clinical investigation. Therefore, the FDA in the United States and the State Food and Drug Administration in China have authorized the use of galanthamine in the management of moderate to mild AD. In general, galanthamine is a naturally occurring substance that has several molecular targets because it reduces oxidative stress and regulates cholinergic transmission.

vi. Polygala tenuifolia.

Herbal remedies have been traditionally used to treat memory loss and improve cognitive function. In Traditional Chinese Medicine (TCM), *Polygala tenuifolia* Willdenow is one of the most commonly utilized medicinal herbs for memory impairment. Beyond its cognitive benefits, *P. tenuifolia* also exhibits antipsychotic, anti-inflammatory, sedative, and expectorant properties. The dried root of this plant contains polygalasaponins (oleanane-type saponins), which can inhibit cyclic adenosine monophosphate (cAMP) synthesis. Additionally, tenuifolin, a key bioactive compound derived from the dried root of *P. tenuifolia*, is believed to enhance cholinergic neurotransmission and inhibit acetylcholinesterase (AChE) activity. Tenuifolin has also been shown to strengthen the cholinergic system by preventing acetylcholine hydrolysis, allowing it to cross the blood-brain barrier and mitigate cognitive decline. Moreover, studies have indicated that tenuifolin reduces the secretion of Aβ1-40 and Aβ1-42, proteins associated with AD pathology.

vii. Ginseng

Chinese ginseng, or ginseng (Panax ginseng), is a well-liked medicinal plant that has long been used to improve memory and vitality in China, Japan, and Korea. It contains natural compounds called ginsenosides, which help manage AD in several ways. Ginsenosides prevent harmful protein deposits (amyloid-beta) in the brain, help remove these proteins from nerve cells, and support the production of substances that protect and repair neurons. They also improve how cells produce

energy by fixing issues with mitochondria. Additionally, ginsenosides block an enzyme (AChE) that breaks down a key brain chemical, acetylcholine, helping to reduce symptoms of AD. These benefits make ginseng an effective natural option for managing Alzheimer's Disease.[30]

Gintonin, a bioactive glycoprotein found in ginseng, plays a significant role in reducing amyloid-beta (Aβ) formation and enhancing learning and memory by activating phosphatidic acid receptors involved in hemolysis. It helps alleviate AD symptoms by promoting autophagy, reducing inflammation, preventing cell death (anti-apoptosis), and regulating oxidative stress. These effects have been confirmed through extensive in vivo and in vitro studies. Furthermore, gintonin affects G protein-coupled receptors, which in turn affects neurotrophic elements and the cholinergic framework, hence reducing the formation of plaque. This demonstrates its promise for managing AD, which has been demonstrated by science.[30]

viii. Ashwagandha (Withania somnifera)

The popular herb ashwagandha, sometimes referred to as winter cherry or Indian ginseng, has long been utilized as a brain tonic to treat AD. It is frequently advised to support nerve function, increase energy levels, and encourage general health and longevity. Ashwagandha, which is abundant in bioactive substances like alkaloids, phytosterols (like sitoindosides VII-X and beta-sitosterol), and ergostane-type steroidal lactones (including withanolides A-Y, dehydrowithanolide-R, withaferin A, and withanone), has strong antioxidant and free radical scavenging properties. These qualities support brain health and strengthen the immune system. In an APP/PS1 animal model of Alzheimer's disease, studies have demonstrated that oral treatment of a semi-purified ashwagandha extract can correct behavioral impairments and prevent the accumulation of amyloid-beta (Aβ) peptides, hence bolstering its potential for managing AD.

The liver's cholesterol receptor-related protein mediates this therapeutic action. Furthermore, research employing a Drosophila melanogaster AD model shown that ashwagandha administration decreased amyloid-beta toxicity and increased longevity, underscoring its potential as a successful AD treatment.[34]

ix. Ginkgo Biloba.

Ginkgo biloba (Gb) is widely recognized for its efficacy in healing AD and has also shown promise as an herbal Remedy for various acute and chronic conditions. Its primary pharmacologically active components are flavonoids and terpenoids, typically present in the standardized extract used in most clinical studies. This extract combines ginkgoid acids, glycosides, terpene, lactones and flavonoid.[34]

Ginkgo biloba extract has shown promise in the treatment of tinnitus, cancer, heart disease, AD, and other age-related conditions.[35] Its anti-platelet activating factor qualities (helpful for vascular diseases), antioxidant activity, inhibition of amyloid-beta aggregation (related to AD), and decreased expression of peripheral benzodiazepine receptors (which reduce stress) are some of the mechanisms that are thought to be responsible for its therapeutic effects. Given its significance in age-related cognitive health, GB is especially well-liked for treating AD and early-stage AD.[34,36]

x. Gotu Kola (Centella asiatica)

Gotu kola (Gk), known for its use in traditional Chinese, Indonesian, and Ayurvedic medicine, is considered both a nutraceutical and a cognitive enhancer. It has been traditionally used to improve brain function, treat skin problems, and support liver and kidney health. Gotu kola is

valued for its ability to rejuvenate nerve and brain cells, enhancing intelligence and memory, making it an important herb for cognitive and overall health.[32,37] Compounds found in Gotu kola, such as asiaticosides, asiatic acid, madecassoside, and madasiatic acid, have shown promising neuroprotective effects. These compounds can prevent cell death caused by hydrogen peroxide (H_2O_2), reduce free radicals, and block amyloid-beta-induced cell damage, suggesting that Gotu kola may act as a significant impact in treating and preventing Alzheimer's Disease.Gotu kola (Gk), known for its use in traditional Chinese, Indonesian, and Ayurvedic medicine, is considered both a nutraceutical and a cognitive enhancer. It has been traditionally used to improve brain function, treat skin problems, and support liver and kidney health. Gotu kola is valued for its ability to rejuvenate nerve and brain cells, enhancing intelligence and memory, making it an important herb for cognitive and overall health.[32,37] Compounds found in Gotu kola, such as asiaticosides, asiatic acid, madecassoside, and madasiatic acid, have shown promising neuroprotective effects. These compounds can prevent cell death caused by hydrogen peroxide (H_2O_2), reduce free radicals, and block amyloid-beta-induced cell damage, suggesting that Gotu kola may act as a significant impact in treating and preventing Alzheimer's Disease.

Additionally, the ethanolic solution or extract of Gotu kola (Gk) has been demonstrated to promote the growth of nerve cell extensions (neurite outgrowth) in human SH-SY5Y cells when combined with nerve growth factor (NGF). It also helps accelerate axonal regeneration in rats. Research using Gotu kola leaf extract has demonstrated improvements in memory and learning in rats by influencing important neuron transmitters including serotonin, dopamine and noradrenaline. These findings emphasize Gotu kola's potential as a therapeutic option for managing cognitive changes releated with AD.[32]

xi. Shankhpushpi (Convolvulus pluricaulis).

Shankh Pushpi (Convolvulus pluricaulis, Cp) is frequently used to enhance memory and encourage neuron regeneration. Triterpenoids, flavanol,glycosides,steroids and anthocyanins are among the chemical constituents that give it its memory-boosting properties. A class of nutraceuticals called racetams, which improve glutamatergic and cholinergic signaling, has several characteristics in common with Cp. Furthermore, Cp aids in controlling the body's synthesis of cortisol and adrenaline.[34]

Insomnia, anxiety, exhaustion, and mental stress are also treated with cp. According to studies, an ethanolic extract of Cp significantly enhances rat learning and memory and has strong antioxidant activity in in vitro experiments. When an aqueous root extract was given to newborn rat pups, their retention and spatial learning skills improved. Additionally, there was a notable rise in acetylcholine (ACh) activity and content, which may account for the learning and memory gains. Furthermore, compared to control rats, rats given Cp extract showed an enhance in dendritic bifurcation sites and operations indicating that the coefficient Cp boost memory and learning by promoting dendritic neurotization.[34]

xii. Turmeric (Curcuma longa)

Originating in Southeast Asia and the Indian subcontinent, turmeric is a plant with blossoms belonging to the Zingiberaceae genus. Curcuminoids are polyphenolic chemicals that give its tuber its vivid orange-yellow hue. The antibacterial, antimicrobial, and anti-inflammatory qualities of turmeric have been utilized for a very long time. It is frequently used to treat a variety of illnesses, such as liver detoxification, immune system stimulation, cholesterol balance, allergy treatment, inflammation and infection prevention, and

digestive aids.Turmeric's primary active ingredients are water-soluble curcuminoids, such as curcumin, demethoxycurcumin (DMC), cyclocurcuminand bisdemethoxycurcumin (BDMC), as well as turmerone oil. The most significant curcuminoid, turmeric, has anti-inflammatory characteristics and is associated with a decreased risk of AD. Studies have demonstrated that curcumin is far more effective than the antioxidant vitamin E at neutralizing oxygen species that are reactive and preventing lipid peroxidation. Curcumin has been proven to cure cognitive abnormalities in a number of animal models of AD. Greater dosages of curcumin are more beneficial than smaller amounts, and cognitive gains are even more pronounced when piperine, an active ingredient with well-established health benefits, especially against chronic illnesses, is added. Metals like iron, copper, and zinc are believed to play an integral part in the development of Alzheimer disease.[38]

xiiiTriphala.

Triphala, which comes from the Sanskrit words Tri, which means "three," and Phala, which means "fruits," is a traditional herbal remedy made by combining three fruits, called Bibhitaki (Terminalia bellerica), myrobalans: Amalaki (Emblica officinalis) and Haritaki (Terminalia chebula). These fruits tend to be combined in equal amounts and are used to treat a variety of health conditions, such as metabolic disorders, dental issues,eye diseases, skin conditions, heart conditions, high cholesterol, intestinal problems, gingivitis as dental cavities, and even malignancy. Research indicates that triphala may have a number of health benefit including anti-inflammatory, immunomodulatory, antioxidant, antibacterial, hypoglycemic, antimutagenic and antineoplastic (anti-cancer) repercussions.[39]

Each of the three fruits in Triphala provides unique bioactive compounds with specific benefits. Amalaki, for instance, is high in vitamin C and contains tannins, phenols and other components recognized for their anti-melanogenisis properties. Research has also shown that Amalaki can help reduce neurodementia in animals' model of Huntington's and Alzheimer's illness, highlighting its wide-ranging therapeutic potential. The anti-inflammatory and antidiabetic properties of tannins, lignans, ellagic acid, flavones and gallic acid are all abundant in bibhitaki.[34]

V. SAFETY & CONSIDERATIONS POTENTIAL ADVANTAGES & DISADVANTAGES OF HERBAL TREATMENT & NUTRIENTS FOR ALZHEIMER DISEASE

I. Polyphenols:

ADVANTAGES: Curcumin offers at least ten neuroprotective benefits, such as reducing oxidative stress, inflammation, and brain aging (BA), and it supports cognitive function. Resveratrol provides similar advantages. Both compounds are generally well tolerated.

DISADVANTAGES: Curcumin has poor absorption on its own, but its effectiveness can be enhanced when combined with bioavailability boosters. There is a need for more human studies, as research on the use of resveratrol for AD is still limited.

ii. Gingiko biloba

ADVANTAGES: It has an antioxidant and anti-inflammatory effects; which slows cell death; and is well tolerated. Has significant study supporting cognitive benefit.

DISADVANTAGES: It seems that curcumin may be effective for AD but not for mild cognitive impairment (MCI). Additionally, it doesn't appear to reduce the chances of developing Alzheimer disease.[40,41]

iii. Panax ginseng.

ADVANTAGES: It possesses neuro-preventative

characteristics, especially a decrease in BA, but its mechanisms are mostly unknown. Cognitive benefits have been claimed. Well, accepted.

DISADVANTAGES: There is few human research on this topic, and those that do exist have poor methods.[42,43]

iv. Withania somnifera

ADVANTAGES: Several neuro-preventative qualities, including reducing oxidative stress, inflammation, calcium levels (Ca2+), BA, acetylcholinesterase (ACHE) activity, and cell death, help repair neurons.

DISADVANTAGES: There are no studies on humans with AD available at this time.[44]

v. Vitamins & minerals.

ADVANTAGES: AD patients often have low levels of certain nutrients, and supplementation with substances like vitamin E, lithium, and other nutritional combinations has shown effectiveness in some cases.

DISADVANTAGES: While it is reasonable to supplement when deficiencies are present, there is insufficient research to make definitive conclusions in most cases.[45,46]

VI. CONCLUSION.

To summarize, dementia is an intricate and degenerative neurological disorder that affects cognitive function, memory, and behavior. Dementia is classified into three types: Alzheimer's disease, Lewy body dementia and vascular dementia each with its own set of characteristics but all facing the same challenge: cognitive decline. While conventional treatments focus on symptom management and slowing disease progression through medications, there is growing interest in alternative approaches, such as herbal remedies, for managing dementia symptoms.

Herbal remedies, including ginkgo biloba, turmeric, etc. have shown promise in scientific studies for their potential neuroprotective and cognitive-enhancing properties. These remedies are believed to work through various mechanisms, such as improving blood circulation to the brain, reducing inflammation, and protecting against oxidative stress. While research into herbal treatments is still ongoing, the benefits they offer, such as fewer side effects compared to traditional medications and potential enhancement of cognitive function, make them an attractive complementary option.

Incorporating herbal remedies into dementia care may provide additional support alongside conventional treatments, offering patients a holistic approach to managing symptoms and improving quality of life. However, it is crucial to continue rigorous scientific exploration to fully understand the efficacy, safety, and appropriate dosages of these herbal treatments, ensuring they can be used effectively in clinical practice.

VII. ACKNOWLEDGEMENT

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VIII. CONFLICT OF INTEREST

None to declare

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SCAFFOLD HOPPING: A BLESSING TO MEDICINAL CHEMIST

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ABSTRACT

Scaffold hopping also known as lead hopping is an important strategy used in lead optimization during drug discovery. It includes conversion of an explicit part of a potentially active compound to an alternative structure to discover isofunctional structure. The main goal of scaffold hopping is of creating a structurally different template of chemical structure while safeguarding desired biological activity. It helps in reducing various toxicity issues, obtaining an intellectual property, and addresses issues related to less potency or stability of the drug. Scaffold hopping tools such as isosteric ring replacement include ring opening and closing, functional group isosterism, functional group reversion, chain shortening, chain elongation, and scaffolding. It has truly been a blessing to medicinal chemist since it provides a means to modify the structure and improve physicochemical properties. It also opens the scope for intellectual property if the designed structure is novel.

Keywords: *Scaffold hopping, isosteric ring replacement, functional group isosterism, optimization, core structure, lead optimization.*

INTRODUCTION:

Scaffold hopping known as lead hopping is widely used during drug discovery [1]. Schneider et al. in 1999 coined the term scaffold hopping for referring to a compound that have same activity but different key structures. Scaffolding techniques usually involves a novel chemotype obtained by linking different functionalities to the central structure of the molecule. [2]. In such a case the bioactivity is maintained or enhanced [3].

Scaffold is obtained from the compound by removing substituent group and retaining ring system and linker fragment between rings. Several different scaffold hopping techniques are used, including closing / opening the ring, and topology-based scaffold-hopping. The most used method is heterocycle replacement which involves a rearrangement or change in the quantity of heteroatoms within the core [1]. Because many compounds create negative physicochemical and pharmacokinetic properties,

molecules can inherit many undesirable characteristics. In some cases, modifying a side chain is sufficient to overcome the undesirable properties of structures associated with the parent molecule, and in some cases, the basic structure or scaffolding of the parent molecule must be altered. There are many methods that allow the production of scaffold hops. This includes the use of 2D fingerprints and 3D pharmacophores [5].

Compounds with similar structures have identical physicochemical as well as biological activities [6].

CLASSIFICATION OF SCAFFOLD HOPPING APPROACHES:

Scaffold hopping approaches can be classified based on how different the structures are generated by scaffold hops.

Boehm et al. categorised two scaffolds differently when synthesized from two different synthetic routes irrespective of small changes. This has been verified to be correct since the organic properties are interconnected and the applications for new drugs may be accepted by the USFDA. For example, there is a significant structural difference among the two phosphodiesterase 5 (PDE5) inhibitors namely sildenafil and vardenafil (Figure 1a and 1b) but the modification is sufficient for two molecules to be covered through two different patents. Similarly, two cyclooxygenase 2 (COX-2) inhibitors of rofecoxib and valdecoxib (Figure 1c and 1d) are distinguished by hetero rings connected via two phenyl rings [2].

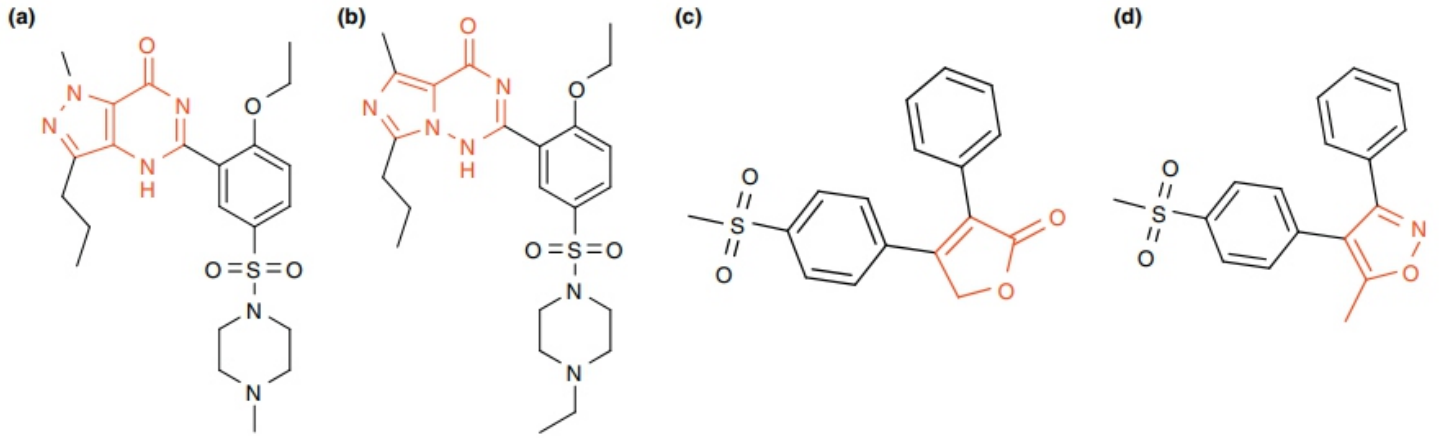

Figure 1: Phosphodiesterase type 5 enzymes inhibitors (a) sildenafil, (b) vardenafil and cyclooxygenase (COX-2) inhibitors, (c) rofecoxib and (d) valdecoxib.

This type of scaffold hopping is classified as 1° hop. The opening and closing of the ring are called as a 2° hop. Replacing the peptide framework to a nonpeptide moiety is 3° hop. Eventually, a novel chemical backbone is 4º hop [2].

1°HOP: HETEROCYCLE REPLACEMENT:

In general, heterocyclic ring act like a backbone of drug molecule. Replacement of carbon, nitrogen, oxygen, and sulphur atoms in the heterocyclic ring can lead to novel scaffolds. Enhanced binding interactions can be possibly achieved when the heterocyclic ring is involved in the interaction with targeted protein.

Rimonabant is an anorexic anti-obesity medicament which inhibits cannabinoid 1 (CB1) receptor. It acts as an appetite suppressant. This drug was not approved by U.S. FDA due to the associated safety concerns. Team at AstraZeneca started working for scaffold hopping technique, by improving physicochemical property, drug metabolism and pharmacokinetic properties. The strategy of scaffold hopping used resulted in novel

classes of CB1 inhibitors [7]. Replacement of the methyl pyrazole backbone of rimonabant with a variety of five and six membered rings was carried out as depicted in Figure 2 [8].

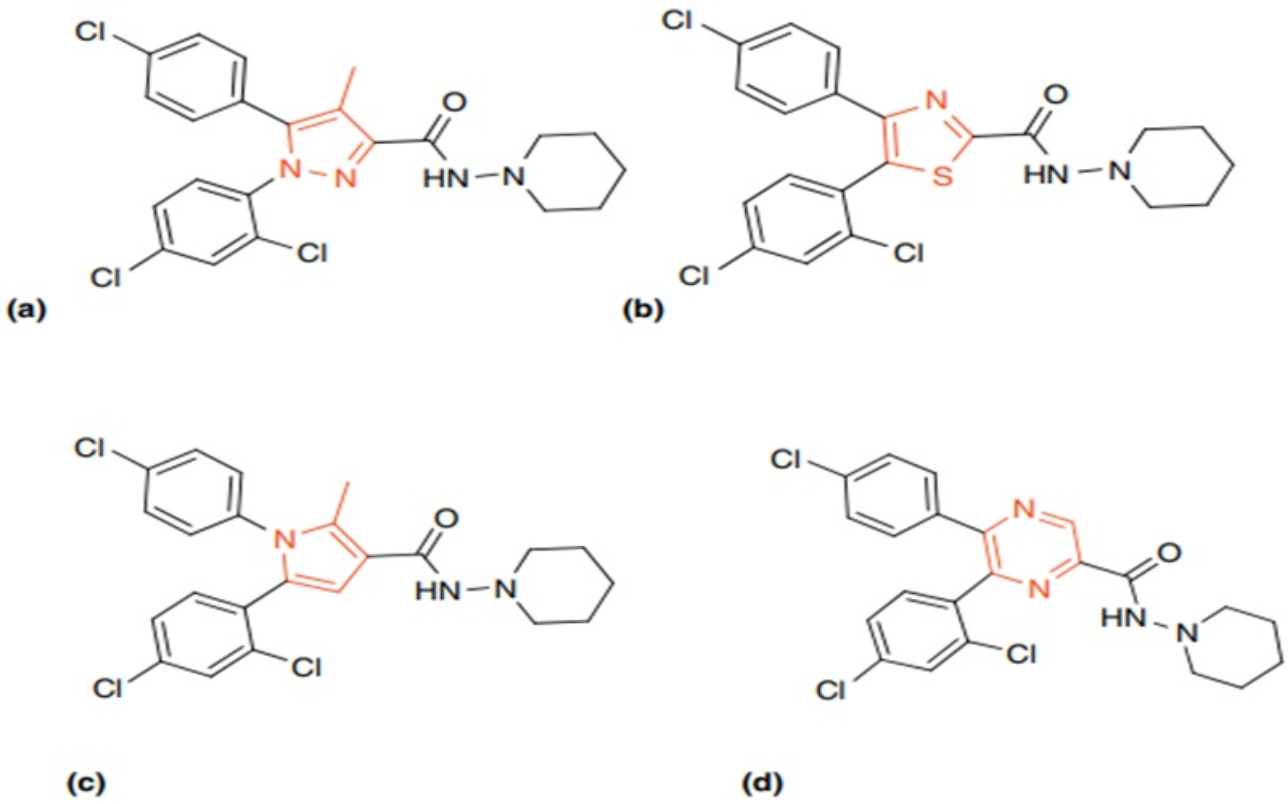

Figure 2: Structure of the CB1 antagonists (a) rimonabant, (b) thiazole derivative, (c) pyrrole derivative, and (d) pyrazine derivative.

Cannabinoid 2 receptor inhibitor is having 44% of sequence resemblance like CB1 receptor. Merck scientists optimized potent as well as triaryl bis-sulfone CB2 inhibitor, to modify some unfavoured conditions like blocking of calcium channels and cytochrome P450 [1].

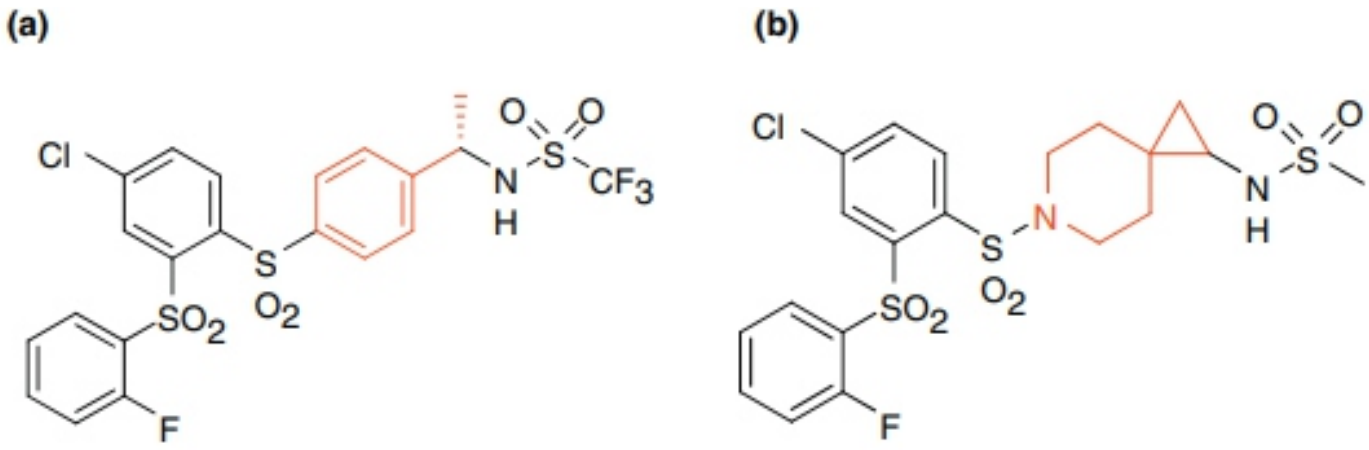

Figure 3: Triaryl bis-sulfone CB2 receptor inhibitor (a) its biaryl analogy (b). The superposition.

2 °HOP- RING CLOSING AND RING OPENING-

Opening and closing of ring is an approach for enhancing physicochemical features of a molecule. Ring opening and closure alters the flexibility of molecule [1].

Ring closure- Intramolecular hydrogen bonds

(HBs) generally intimate where to close a ring. The below example shows a possible hydrogen bonding among the alkoxy compound and biaryl group [4]. Most common concept comprises conversion of an alkyl chain to cyclic hexane ring, converting o-hydroxylbenzoyl to quinazoline, and altering an arylamine to linked ring structure[5]. There will be no entropy loss because of limited binding, as the intramolecular HBs have reduced molecular flexibility of the parent compound.

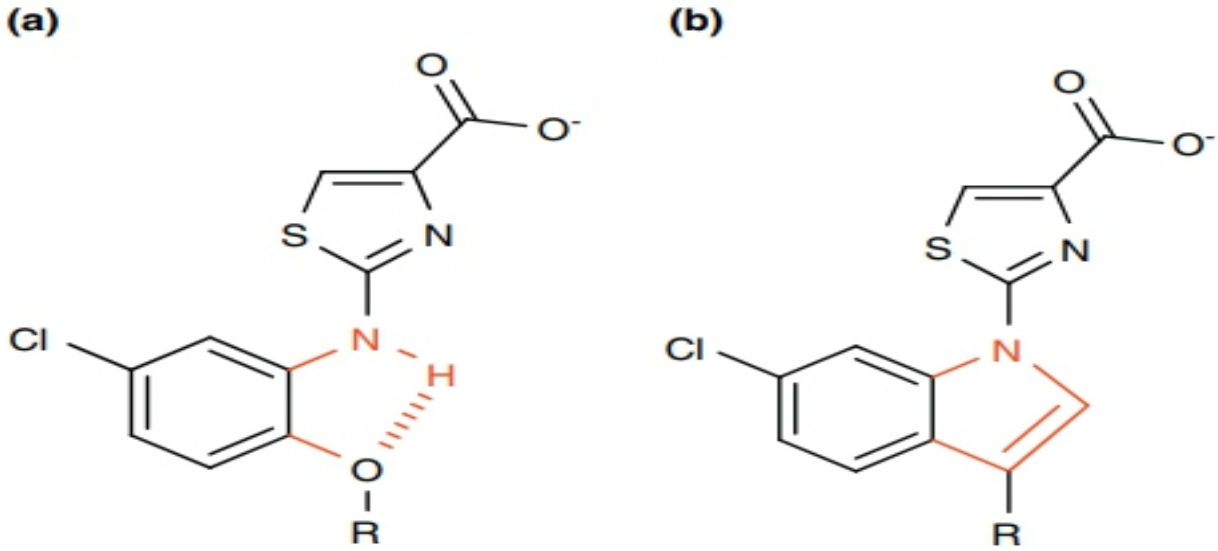

Figure 4: PG EP1 receptor antagonists: (a) biaryl amine series and (b) indole series.

Ring opening- Ring opening enhances the physicochemical as well as kinetic properties of a molecule. Pyridopyrimidinone [Fig (4a)] is an antineoplastic agent that specifically targets protein kinase; used for treating cancer, PD166285 target is used as a template for designing a novel tyrosine kinase inhibitor, the opening of pyrimidone ring migrates the N atom from the 1st to 5th position of the pyrimidine ring forming a six-membered ring [6]. The observed log P value of the urea derivative is 1 log unit less than that of the molecule which is derived

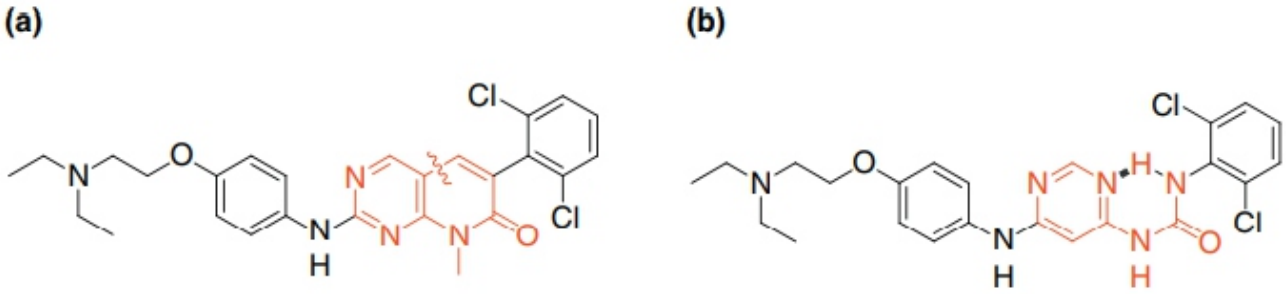

Figure 5: Tyrosine kinase inhibitors: (a) pyridopyrimidinone PD 166285 and (b) corresponding urea derivative.

[7].Many rings like aromatic rings, tends to reduce the physicochemical properties of drug. Adding a cycloalkane ring can reduce the molecular flexibility and maintain ADME properties.[8].

3°HOP: PSEUDOPEPTIDES AND PEPTIDOMIMETICS-

We can design a small compound by taking into consideration the structural properties of peptides by use of conformations of a peptide which is vital. This complies with targets having

protein-protein interactions [9]. Scaffold hopping is a characteristic process that converts peptides into small compounds. 2º structures for example alpha helix, beta-sheet and beta-gamma turn are commonly seen in peptide-protein interface [8].

4° HOP- TOPOLOGY/SHAPE-BASED SCAFFOLD HOPPING-

This type of scaffold hopping can be brought forth by virtual screening. Scaffold hopping concentrates mainly on optimizing new core structures, by ignoring probable clashing between adjacent side chains [1].

A 5,6-membered fused heteroaromatic scaffolds which represent some essential structural similarities for optimum anticancer activity depending on the lead containing an indole ring was optimized. Suitable replacement of -OCH_3 and trimethoxybenzoyl groups (required groups for anticancer activity)[10]. Amongst the molecules that are synthesized from the core scaffold, NH group at 1st position of the heteroaromatic core forms non potent anticancer activity and N atom at 7th position have a good stability. The 7-azaindole 9 and pyrazolo- [1,5-b]pyridazine 10 core comprised molecule have an effective anticancer activity than the indole core. Most remarkably, 7-azaindole core with 6-methyl substitution show a potent in vitro anticancer activity with good metabolic stability and solubility. Therefore, scaffold hopping strategy helps to design a compound which is an oral administrated drug that reaches systemic circulation , with reformed pharmacokinetic and pharmacodynamic properties and wider intellectual property right[10].

SCAFFOLD HOPPING VIA CHAIN SHORTENING AND CHAIN LENGTHENING:

Another effective strategy for obtaining a potential compound can be done by chain lengthening and shortening process. In pyrithiobac, a chain shortening process is observed where in the removal of diamino carbamate takes place by forming a sulfur bridge (Fig:6). In the next example chain lengthening is observed by adding O and CH_2 in mandipropamide resulting in similar potent activity [2].

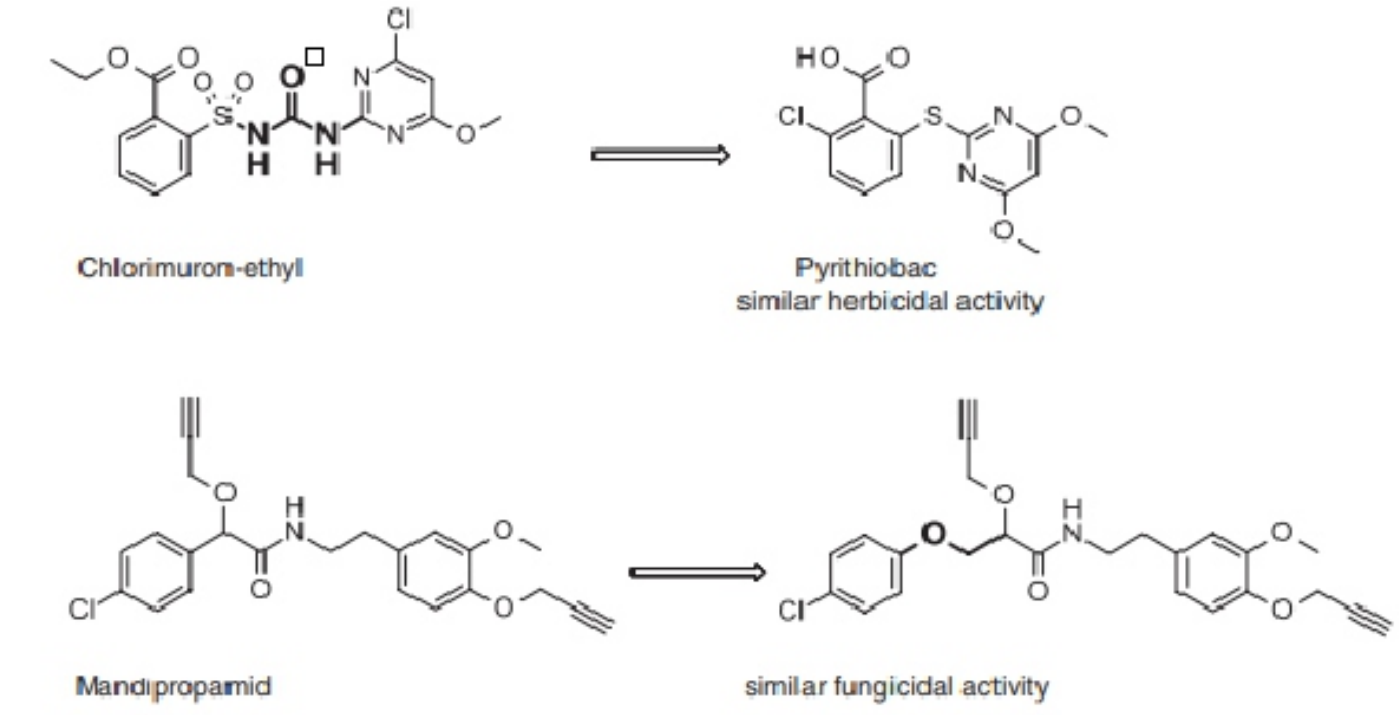

Figure 6: Scaffold hopping by altering chain shortening and chain lengthening process.

SCAFFOLD HOPPING BY TOPOLOGICAL PHARMACOPHORE SEARCH:

Pharmacophore features are very important as it gives us information about the chemical property of a drug having a specific biological activity which acts as a boon for determining the change we can make in the structure so it can be more acceptable with a potent activity, by considering two methods core replacement and virtual screening.

Virtual screening mainly focuses on finding novel chemical structures, core replacement is the one which is focusing only on the part of the molecule to be replaced, techniques have been invented based on two- or three-dimensional representations of molecular structures and various definitions of biophore / pharmacophores [9].

SCAFFOLD HOPPING BY CORE REPLACEMENT:

The program CAVEAT helps to understand the basics before carrying out the procedure. CAVEAT helps in identifying the framework of molecule make a template which can for understanding the position of a functional group in different confirmation. It searches 3D database for a compound It can classify structural backbone [5].

SCAFFOLD HOPPING BY VIRTUAL SCREENING:

Scaffolding is able to be completed via virtual screening. With help of its entire molecule not just its scaffold can be useful to undergo changes. A novel scaffolding idea could be confirmed irrespective of its chemical background. It aims at whole molecule rather than its core[5].

PHARMACOPHORE-BASED TWO-DIMENSIONAL DESCRIPTORS-

CATS (Chemically Advanced Template Search) is the first tool to be used for hopping studies [5].CATS retrieved a larger number of relevant structures than a conventional fingerprint-based search thus CATS seems to be a useful tool for database mining [1]

In a potential test, CATS was applied for predicting a novel cardiac Ca^{2+} channel blocking agents. Mibefradil, a well-known T-channel antagonist (IC50 1.7 mm) (Figure7) 1can be operated as the main structure for CATS, twelve compounds were chosen, among them nine compounds have potent activity (75%)[1].

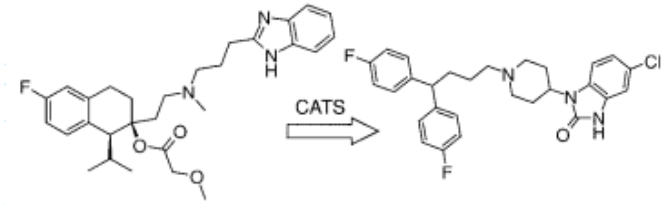

Figure7: Mibefradil structure derived from CATS

STUDY OF INSILICO SCAFFOLD HOPPING:

FIRST CASE STUDY- The quinoline-4-acyloxy scaffold is mainly taken into consideration for study. The Derivatives 1 and 2 both are strong-acting nor epinephrine analogs. The derivative 2 acts as a lead of quinolin-4-yloxy class and has less toxicity even at greater concentrations [11].

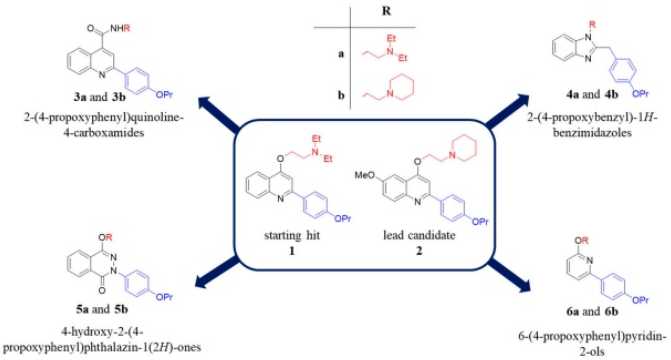

Figure 8: Structures of the derivatives 1 and 2, novel synthesized molecules obtained from the *in silico* scaffold hopping.

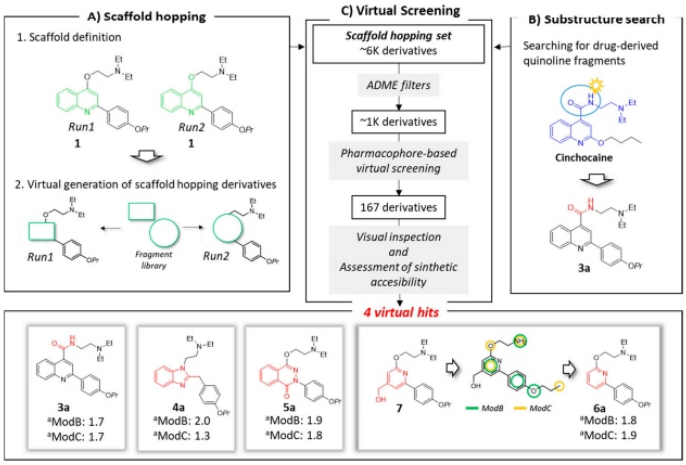

Figure 9: In silico scaffold hopping approach A): two runs performed on 1st derivative. green color indicates replacing is been carried B): previously obtained drug is been searched blue color is used for highlighting fragment C): virtual screening method, ModB and ModC are represented in green and yellow color shows its chemical properties.

Derivative 1 is selected as quinoline representative directing scaffold hopping approach Replacement of only the quinoline framework with 1456 smaller compounds, no changes were made at the 2nd and 4th position of quinoline ring (run-1).

Derivative 2 quinoline ring along with the oxygen on 4th position is considered for scaffold hopping (run-2). Then the hopping of both the derivatives is carried out independently by ligand based virtual screening [12].

Two libraries were merged to find 6393 scaffold hopping sets (panel C) in correlation with this a substructure search from 1456 compounds is carried out with quinolone ring as reference showing the previously available drug of cinchocaine mixed with the previous database and sets are formed.

In second, 1089 derivatives were successively virtually analyzed by using the two pharmacophore models as references. From a single pharmacophore, only compounds presenting a fitness score of 1.7 were preserved and select a compound fitting both models.

In third procedure, the obtained molecule (167 molecules) analyzed by observing a novel compound with a new scaffold with required pharmacophoric properties.

Considering in silico results, four hits obtained (3a–6a), each one having a contrasting core, were considered liable for the further experiment, hit 6a was customized initially from the 7th derivative, presence of methyl hydroxy group greatly reduces the chemical synthetic property of drug. Hence the hydroxy-methyl removal takes place, only the pyridine ring is considered to optimize compound 6a (Fig9) [12].

SECOND CASE STUDY- In this study PIM-kinase is antitumor drug target. Saluste and co-workers by keeping in consideration the primary activity and high target selectivity as well as ADMET properties found a scaffold by replacing imidazopyridazine scaffold with triazolopyridine [13].

Seed 1st has a 0.024 nM value of half-maximal inhibitory concentration (IC50). Seed 2nd with IC50=155 nM. Seed 3rd having IC50=130 nM, focused mainly on improving its pharmaceutical properties, using 500 molecules from three seed compounds for carrying out its molecular docking. As shown in table 2 potent novel hops are generated from every sample compound [13].

There are approximately 51,66,40 successful structurally hoped molecules from all three seeds. Seed 1 which shows high activity has total 11 compounds with good pharmacological activity and 102 of them have a good docking score, so here we can conclude that scaffold hopping is a dynamic tool in optimizing molecules [13].

CONCLUSION:

Numerous amounts of tools are present till date, but scaffold hopping is a very potent tool for the

optimization of a novel potent compound. In this article most of the possible strategies of scaffold hopping are studied along with their successful implementation. Scaffold hopping mainly changes the backbone or framework of a molecule with similar biological activity**.** It has proved to be successful in optimizing the molecules in terms of their properties, activity, potency as well as opened doors for intellectual property.

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IMMUNOTHERAPY -A LIFE SAVIOUR APPROACH IN CANCER

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ABSTRACT

Immunotherapy has revolutionized the field of cancer treatment, offering new avenues for combating various malignancies. This systematic review seeks to offer a comprehensive overview of recent advancements within immunotherapy, highlighting the development of novel approaches and their potential for future clinical applications. We examine immunotherapy concepts such as immune checkpoint inhibitors, adoptive cell treatment, cancer vaccinations, and oncolytic viruses. Additionally, we explore emerging areas of research, such as combination therapies, personalized medicine, and the utilization of artificial intelligence in optimizing immunotherapeutic strategies. By understanding the current landscape of immunotherapy, we can envision a future where these innovative approaches will significantly impact patient outcomes and reshape the field of oncology.

INTRODUCTION

Cancer is a complicated disease characterized by uncontrolled cell proliferation and the spread of these abnormal cells within the body. Based on the American Cancer Society's projection for 2023, approximately 1.9 million individuals are expected to be diagnosed with cancer, with 608,570 dying as a result. By 2030, cancer-related fatalities are expected to exceed 23 million.

Amongst the several techniques employed for the treatment of cancer, surgery is often the primary method of choice. The treatment strategy is tailored to the specific type and phase of cancer. Chemotherapy, radiation, and combinations of these therapies are also employed in clinical practice. Chemotherapy involving different antineoplastic medications may be used as a choice of treatment not only for the intent of therapy but also to avoid the multiplication of cancerous cells following surgical treatment or radiation therapy, or to reduce the dimensions of cancerous tissue before surgery. Whether now it is feasible to cure cancer utilizing one curative methodology along with a combination of various therapy modalities, needed success rate in the

management of cancer is still yet to be achieved. The primary cause of this lack of success is systemic toxicities along with unwanted side effects caused by the course of therapy plan particularly. Various therapeutic strategies have been developed in order to avoid these adverse reactions and provide improved treatment for cancer with lower active component levels. Immunotherapy is the utilization of immune system features in cancer treatment, which has gained prominence in recent years. In simple terms, immunotherapy is a type of biotherapy that involves sensitizing the immune system of the individual to cancer in order to improve selectivity and reduce side effects.

A recent clinical success of the immune checkpoint medical treatment, that employs inhibiting antibodies to Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and programmed death-1 (PD-1) and (PD-2), as well as oncolytic viruses and Adoptive Cell Therapy, reflects an attempt to shift the balance in cancer cell removal to the advantage of the immune system. Clinical trials have shown that they have the potential to save lives; as a result, “cancer immunotherapy” was named Science's Breakthrough of the Year in 2013. Furthermore, the achievement of these drugs underlines the importance of rigorous interpretation of basic immunological sciences in cancer treatment. The goal of this Review Series is to offer a concise summary of current achievements in immunology of cancer and immunotherapy, as well as demonstrate how fresh discoveries about the processes underlying cancer immune protection may lead to novel and effective treatments. We expect that by putting basic mechanistic investigations in a therapeutic perspective, these summaries will be of interest to both cancer immunologists and practicing oncologists.

STRATEGIES IN CANCER IMMUNOTHERAPY

Immune Checkpoint Inhibitors (ICIs)

Cancer immunotherapies that target immunological receptors on the surface of T cell lymphocytes are known as ICIs. As a result, when ipilimumab was approved in 2011, it was considered a breakthrough therapy strategy that would alter cancer treatment. In some situations, these medicines provided long-term benefits while having a reduced toxicology profile. Contrary to traditional therapeutic methods, ICIs kill tumour cells by stimulating the body's own immune system. Immune checkpoints establish a proper equilibrium of anti-inflammatory and pro-inflammatory responses within stable settings. Such immunological checkpoints include a group of stimulatory as well as inhibitory processes which regulate immune cell function.

Antibodies addressing immune-related inhibiting receptors including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1) became among the widely employed immunotherapy medicines during the past few years. Various antibodies along with minor substances addressing immunological checkpoint proteins are recently present under clinical trials, such as adenosine receptor (A2A), B7H3, CD47, and Cd39.

Current discoveries include T cell immunoglobulin and mucin-domain containing-3 (TIM-3), V-domain Ig suppressor of T cell activation (VISTA), T cell immunoglobulin and ITIM domain (TIGIT), lymphocyte activation gene-3 (LAG-3), and several others. This information implies that inhibiting one immune checkpoint could end up in compensated overexpression of additional checkpoint receptors within the tumour microenvironment (TME). This comparable compensating process involving TIM-3 and PD-1 has been described in lung carcinoma.

Programmed Cell Death Protein 1 (PD-1) Inhibitors

Programmed Cell Death Protein 1 (PD-1) is a sort of inhibitor receptor that modulates T-cell-mediated responses through programmed death signalling. PD-1 involvement may restrict cytokine production including IL-2, IFN-γ, and TNF-α, along with proliferation of cells, by interacting with the CD28-costimulatory signalling pathway. The production of PD-1 had been observed on active monocytes, dendritic cells (DCs), natural killer (NK) cells, T cells, and B cells inside the TME. Immunotherapies targeting the PD-1 pathway have been demonstrated to improve outcomes in a variety of cancers, including cancers of Merkel cells, melanoma, carcinoma of the head and neck squamous cells, and non-small-cell lung carcinoma (NSCLC). Table 1 shows a list of ICIs approved by the FDA which blocks PD-1 with the indication of type of cancer.

Table 1. List of ICIs Approved by FDA which blocks PD-1with the indication of type of cancer.

Drugs Name	Involved Targets	Date of Approval	Accredited Indications By FDA
Pembrolizumab	Programmed Cell Death	Oct-2016	Non squamous and squamous NSCLC
Nivolumab	Programmed Cell Death Protein 1 (PD-	Mar-15	Squamous NSCLC (Stage III-B or IV)
Cemiplimab	Programmed Cell Death Protein -	Sep-18	metastatic cutaneous squamous cell carcinoma

Programmed Cell Death Ligand 1 (PD-L1) Inhibitors

Programmed Cell Death Ligand 1 (PD-L1) and Programmed Cell Death Ligand 2 (PD-L2) are the two PD-1 ligands. Because PD-L1 can be produced by both tumor cells as well as immune system cells, it is a useful indicator to determine the reaction to anti-PD-1/PD-L1 antibody within certain individuals possessing cancer. Through interacting with negative controllers of T-cell stimulation including PD-1 and B7.1, PD-L1, additionally referred to as B7-H1 or CD274, assists in the suppression of the cancer-immunity cycle. As a result, PD-L1 ligation has been shown to inhibit T Lymphocytes migration as well as proliferation, hence reducing tumor cell killing. The US Food and Drug Administration has granted authorization for three PD-L1 inhibitors for use in solid cancers including NSCLC, HNSCC, melanoma, and MCC. These three authorized inhibitors are maintained in Table 2.

Table 2. List of ICIs which blocks PD-L1with the indication of type of cancer

Drugs Name	Involved Targets	Date Of Approval	Accredited Indications By FDA
Atezolizumab	Programmed Cell Death Ligand 1 (PD-L1)	Oct-16	nonsquamous and squamous NSCLC(Stage III-B or IV)
Durvalumab	Programmed Cell Death Ligand 1 (PD-L1)	Feb-16	non-small-cell lung cancer (NSCLC) (Stage-3)
Avelumab	Programmed Cell Death Ligand 1 (PD-L1)	Mar-17	Metastatic Merkel cell carcinoma

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4 Inhibitor)

CTLA-4 has been found as an immunoglobulin superfamily protein generated predominantly by stimulated T Lymphocytes within a cytotoxic T lymphocyte cDNA library. It can only be found on T Lymphocytes, and it determines the intensity of T cell stimulation in the initial stages of development. It predominantly suppresses the activity of a T lymphocyte co-stimulatory receptor, CD28. Although the simple fact that CTLA-4 interacts with the exact similar B7 ligand onto B cells as well as antigen-presenting cells (APCs) as

their homologous CD28, activation of CTLA-4 led to T cell-moderate inhibition of the production of antibodies and allograft rejection avoidance. CTLA-4 expression characteristics were found to deviate considerably from CD28 expression in the year 1994. Expression of CTLA-4 is enhanced for two to three days afterwards TCR/CD3-moderate activation of T lymphocytes, beginning approximately 24 hours following TCR activation, while CD28 upregulation is found on naive T cells. The results of this studies advocates that CTLA-4 plays a important role in controlling activity of activated T lymphocytes, since a lack of it leads to unregulated T cell proliferation. Researchers wanted to observe if suppressing CTLA-4 will boost antitumor immune reaction as an outcome of these fresh findings into CTLA-4's mechanistic activity.

Inhibiting CTLA-4 increases a series of immunological reactions which depends on helper T lymphocytes, while CTLA-4 interconnection onto Treg cells raises its suppressive action. Since CTLA-4 is a target gene of the forkhead transcription factor (FOXP3), the level of expression of this defines Treg cell lineage, Treg cells generate it continuously. Although the certitude that procedure through which CTLA-4 increases the immune suppression action of Treg cells is still not known, deletion and inhibition of Treg cell-specific CTLA-4 drastically diminishes their ability to control overall autoimmune as well as anticancer responses. As an outcome, enhanced effective CD4+ T cells functioning and reduced Treg cell-dependent suppression of immunity are most likely important components of CTLA-4 blockade's mechanistic activity.

Ipilimumab is a human immunoglobulin monoclonal antibody which has ability to block CTLA-4 activity and was authorized and suggested in 2011 for the management of melanoma. Ipilimumab is additionally employed to treat progressed renal cells cancer, MSI-H/dMMR advanced colorectal carcinoma, Non-Small Cell Lung carcinoma, and hepatic cell carcinoma in conjunction with nivolumab. FDA declared in 2020 the combined use of nivolumab along with ipilimumab (given as iv injections) possesses beneficial effects for adult individuals having inoperable MPM and NSCLC as a treatment of choice. Nonetheless, the CTLA-4 is implicated in the prevention of autoimmunity as an adverse regulator of T cell immunologic reactions; hence, inhibiting it with ipilimumab may result in immune-associated adverse reactions which include enterocolitis as well as colitis.

ICI therapy has recently emerged as a viable therapeutic approach with promising results in therapy due to its persistent anti-tumor effects. Although tumor-specific and acquired ICI resistance, combined with treatment-related toxic effects, restricts their therapeutic utility. As a result, numerous studies have demonstrated that combining ICIs with additional therapeutic strategies including chemotherapy, radiation, cancer vaccinations, as well as CXCR4 blocking treatment may successfully overcome tumor responses to ICI therapy. The combined use of Immune checkpoint inhibitors, vinorelbine along with cyclophosphamide inhibits Triple negative breast cancer development in vivo principally by increasing APC selection and activity. Furthermore, in breast cancer and colorectal mice models, CT LA-4 inhibitors solo therapy and combined therapy with either cyclophosphamide or gemcitabine demonstrated potential outcomes. A phase one clinical study amongst the fifteen individuals possessing resistant as well as advanced Head and neck squamous cell carcinomas (HNSCCs) discovered radiation treatment and cyclophosphamide combination along with granulocyte macrophage-colony-stimulating factor i.e.GM-CSF had a substantial medicinal impact. In a B16-F10 mouse melanomas tumor model, researchers discovered that utilizing CTLA-4 as well as PD-L1 inhibitors along with the combination of CSC-DC i.e. Cancer's

stem cell-pulsed dendritic cells enhanced T cell multiplication, blocked secretion of TGF, raised secretion of IFN, along with enhanced host-specified CD8+T lymphocyte response against cancer stem cells. In melanoma, prostate, and PDA mouse models, GMCSF i.e. Granulocyte macrophage colony-stimulating factor cell-associated vaccine in combination of a CTLA-4 inhibitors reduced tumor development as well as reestablished anticancer immunity. CTL-mediated immunity against tumors is activated when RT is combined along with PD-1/PD-L1 and/or CTLA-4 targets. Integrating PD-1 inhibition with brain-associated radiotherapy in glioma xenograft-enduring mice, for instance, leads to a 75% full pathological response along with enhanced Survival because of CTL as well as macrophage activation.

Drugs that disrupt those pathways are now utilized to treat a various malignancy and have shown long-term therapeutic effect on a subset of cancer individuals. Novel inhibitory methods have been studied as well as medications that inhibit, TIM-3, B7/H3, VISTA, or LAG-3. Because of their different method of activity as contrast to conventional anticancer medicines, next-generation immunological checkpoints have a interdependent effect when mixed with other treatments including chemotherapy or other Immune Checkpoint Inhibitors.

ADOPTIVE CELL THERAPY

Adoptive cell therapy is a sort of the immunotherapy that aids the immune system in combating cancer-related cells. T lymphocytes are utilized for cellular immunotherapy in various forms, primarily because of its intrinsic propensity of killing malignant cells. T cells are withdrawn from a cancer individual's blood or cancerous tissue, modified in the lab to better target cells with cancer, and then transferred to the individual with the cancer. T cells solely might not be enough to eradicate cancerous cells. Killer T cells as well, must be their pre-activated, and active at a considerable number of tumor sites unless the tumor has been entirely eradicated. TIL i.e. Tumor-Infiltrating Lymphocyte therapy represents one of the potential adoptive cell therapy strategies that attempts to meet all these criteria. T cells that had already penetrated a cancer patient's tumor tissue are extracted, expanded, then re-installed into the affected individual in hope of to supply adequate numbers. Despite its potential benefits, TIL therapy has some drawbacks. Unfortunately, even when T Lymphocytes are duplicated in vitro conditions, patients often do not have enough of them. In order to address these concerns, a genetically modified T cell receptor (TCR) therapy utilizing cells tissues in peripheral region was established. Not only does this technique activate and increase already existing anti-tumor T cells, but it also permits T cells to concentrate on antigens associated with cancer. TIL and TCR treatment strategies can only target cancerous cells that display antigens associated with them. T cells can detect cancer by presenting specialized antigens generated at the outermost layer of cancerous cells through MHC. In CAR-T i.e. chimeric antigen receptor strategy established towards addressing that limitation, T cells comprehend cancerous cells as major histocompatibility complex (MHC), independent. It serves as a case of customized medication in action, along with the CAR-T therapy medications Kymriah® and Yescarta® have also been licensed for application in lymphoma management by the FDA and EMA.

CANCER VACCINES

PREVENTIVE CANCER VACCINES

Vaccinations that target viral infections interlinked with cancer production are amongst the first to be beneficial in cancer prevention. The hepatitis B virus, also known as HBV, is prevalent reason of persistent liver illness that raises the

chance of developing liver cancer. The HBV vaccination is accessible since the early eighties, and the WHO i.e. World Health Organization recommends it immediately after birth of the children. Figure 1 shows T-Cell therapy process with tumor-

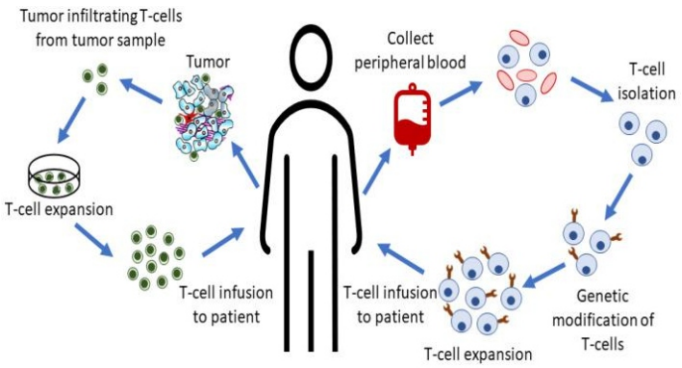

Figure.1: T-Cell therapy process with tumor-infiltrating and genetically modified T-Cells for cancer treatment

infiltrating and genetically modified T-Cells for cancer treatment Three injections of vaccine provide excellent long-term defense from chronic infection with HBV. This was the first preventive vaccine to be shown to decrease the rate of Hepatocellular carcinoma i.e. HCC in people who had been vaccinated. Taiwan became one among the very first countries to launch nationwide hepatitis B vaccination initiative, which started with neonates delivered to mothers with infection and was eventually expanded to involve all newborns in the country. Additional study discovered a substantial reduction in Hepatocellular prevalence in Taiwanese children vaccinated up to twenty years following the program's inception. Similar studies in Thailand, where a nationwide neonatal Hepatitis B vaccination program was launched in the late 1980s, discovered that babies who were vaccinated at birth had a significantly lower hepatocellular carcinoma (HCC) incidence. A more incredible story of achievement is found in the US, whereby compulsory neonatal immunization with HBV vaccine, begun within Alaska Natives in 1984, has resulted in the eradication of HCC amongst Alaska Natives children below the Twenty years of age. Human papillomavirus i.e. HPV a virus that transmits sexually and is associated with a variety of cancers, such as penile, vulvovaginal, anal, cervical, and oropharyngeal cancers. Vaccinations against HPV has been in the global market since 2006 and are recommended as a preventive vaccine to provide girls and boys above the age of eleven and prior to the start of sexual activities. There are Three vaccinations against HPV has been authorized to use in humans to prevent HPV-related illnesses. HPV vaccines give protection from HPV strains which are responsible to cause a high risk. The bivalent Cervarix vaccination, that safeguards from types of HPV sixteen and eighteen, the quadrivalent Gardasil-4 vaccine, that safeguards from HPV types six, eleven sixteen, and eighteen and the nonvalent Gardasil-9 vaccine, that safeguards from HPV types six, eleven sixteen, eighteen thirty-one thirty-three, forty-five, fifty-two, and fifty-eight, are among these vaccines. Vaccines against HPV are secure, extremely immunogenic in teens, and provide adults with long-term antibody responses and protection.

Various phase II/III clinical studies have indicated that HPV vaccines are highly successful in lowering the incidence of HPV-a associated high-grade vulvar, cervical, lesions of vagina along with genital warts within females. A subsequent examination of Human papilloma virus vaccination programs throughout Australia as well as US involving girls from age of eleven to twenty-six found that vaccinated women had significantly fewer HPV-related cervix lesions and deformities than non-vaccinated women. Long-term HPV vaccination programs with high participation are projected to considerably reduce the rate of cancer associated with Human papilloma virus (HPV)in men as well as women.

There is no officially approved vaccine for non-viral cancers for human consumption. This is due,

in part, to a lack of tumor associated antigens as well as the possible self-molecules interactions on healthy tissues, leading in autoimmunity. Several tumor-associated antigens (TAAs), however, has recently been utilized satisfactorily within medicinal vaccination studies with no eliciting severe adverse reactions. Furthermore, the presence of antibody responses against TAAs have been linked with a more favorable outcome and possibly reduced cancer risk in cancer patients, meaning that activation of an anti-TAA reactions already i.e. When person is free from illness will effectively result in minimization of development of cancer. Furthermore, achievements in medical testing along with the imaging technologies have enhanced the diagnosis for pre-malignant lesions and malignancy, enabling the introduction of preventive vaccinations which induce cancer-fighting immunity in advance of disease manifestation.

THERAPEUTIC CANCER VACCINES

As an immunotherapeutic method, therapeutic cancer vaccines are utilized for the treatment of an active illness. There are just two licensed therapeutic vaccines for cancer immunotherapy. These involve the Bacillus Calmette-Guerin (BCG), used to treat initial-stage bladder carcinoma along with Sipuleucel-T i.e. Provenge, a DC i.e. dendritic cell - dependent immunization which is used to treat castration-resistant prostate carcinoma.

BCG-Bacillus Calmette-Guerin is a non-pathogenic *Mycobacterium bovis* bacterium that promotes an immune system response for tuberculosis triggered by *Mycobacterium tuberculosis*. It is presently the only tuberculosis vaccination that is commercially accessible. When it was established within the mid-late seventies that iv application of these bacteria might arrest the illness progression and relapse of NMIBC - non-muscle-invasive bladder cancer, BCG was approved for management of increased risk NMIBC. Although the BCG vaccine is now often used to treat NMIBC, the accurate mechanisms of this treatment in NMIBC still not known. Following tumor excision, the treatment includes a 6-week course of BCG instillation into the bladder. Patients can then proceed to the maintenance stage of treatment, which includes weekly BCG vaccination installation into their bladder over a period of three to six weeks every three months for a period of one to three years. BCG therapy has been linked to genitourinary side effects such bladder ulcerations, prostatitis, penile lesions, cystitis, and infections associated to kidney infection, along with requisite side effects like BCG sepsis, generalized infections, fever and so forth.

In individuals suffering from castration-resistant prostate cancer, the sipuleucel-T vaccine increases cellular immune reaction produced by T lymphocytes contrary to PAP i.e. Prostatic acid phosphatase. Dendritic cells (DCs) are cells that present antigen that generates an antigen-specialized stimulation along with triggering of T cells. They deliver antigenic peptide: HLA complexes to T lymphocytes by expressing of both class I and II HLA molecules. To generate DC stimulation, processing of prostatic acid phosphatase antigenic epitopes, as well as synthesis of the antigenic peptide: HLA complexes and costimulatory molecules, patient dendritic cells are given with a protein fusion containing Prostatic acid phosphatase coupled to GM-CSF which is granulocyte macrophage colony-stimulating factor. Following that, the patient is reinfused with activated DCs, which expose antigens as well as induce T lymphocytes responses to the PAP i.e. Prostatic acid phosphatase protein. After phase III studies revealed that patients acquiring the vaccine experienced significantly longer survival rates and a reduced chance of death corresponding to the group of individuals under the placebo-controlled studies, the vaccine was granted approval for the management of castration-

resistant prostate carcinoma. Every two weeks, three injections of roughly 50 million autologous DCs are administered. Most individuals had moderate side effects such as symptoms associated with the flu, back discomfort, pain in the joints, pain in the muscles, headaches nausea, loose stool, anemia, and feeling disoriented.

ONCOLYTIC VIRUSES

Oncolytic viruses are species capable of discover, affect, and destroy numerous cells in the cancerous surroundings, with a purpose of regulating and delaying tumor progression. They can present an inherent response to cells possessing cancer or be biologically directed towards identifying specified targets. Various Oncolytic Viruses are being studied in clinical studies as potential cancer treatments. In addition, Oncolytic viruses can trigger the immune system towards tumor cells, leading to a occurrence of anticancer response.

MODE OF ACTION

Oncolytic viruses may infect cells that aren't normal through specialized targets which include nuclear transcription factors like cyclooxygenase-2, prostate specific antigen, human telomerase reverse transcriptase, osteocalcin, as well as surface markers including folate receptor, prostate-specific membrane antigen, and endothelial growth factor receptor, these all are generated by cells possessing tumor. Pathogenic viral genes may also be removed in the lab to increase Oncolytic viruses' specificity to cancerous cells while lowering Oncolytic Virus harshness for healthy tissues.

How Oncolytic Viruses are delivered Is intrinsically tied to the category of tumors being treated, since the viral channel has a direct influence on the success of the treatment owing to virus presence on-site and the organism's innate antigen-fighting barrier. Subcutaneous, intrathecal, intertumoral, as well as Intraperitoneal distribution, that offers larger control of viral amount in the tumor surroundings with fewer side reactions, along with iv distribution, that is associated with the management of metastatic disease.

With regards to immune evasion processes cancer cells may alter how they express and activate of certain pathways, such as the interferon 1 and protein kinase R signaling pathways, which interact with responses to infection by viruses, programmed cell death, and inflamed cell development. Modifications in the antiviral responses, in combination with virus proteins with the ability of inhibiting cell death i.e. apoptosis, that enables Oncolytic Viruses to persist prolonged within cells, possessing tumor completing their lifespan and developing of the destructive stage.

Virus presence Pathogen-associated molecular patterns (PAMPs) are immune-related indications associated with virus structure that are detected in the human body and include proteins which are viral in nature and include DNA -Deoxyribonucleic acid, RNA-Ribonucleic Acid, as well as viral capsid. Dendritic cells promote development of antiviral inflammatory agents such as TNF-alpha which is tumor necrosis factor alpha, type 1 interferons, and cytokines including IL-2 i.e. interleukin 2 upon identification of PAMPs via TLRs i.e. toll-like receptors, that are receptors involved in recognition of pattern.

TNF-alpha is involved with the response to infection caused by virus i.e. viral infection, beneficially affecting the expression of class one major histocompatibility complex within membrane of cell and beneficially affecting caspase enzyme activation as well as death of the cell in certain cancers. Such interferon has the capacity to induce the death of cancer cells by the mechanisms which facilitates apoptosis and

necrosis, as well as to generate thrombotic events through its antiangiogenic activity, which may result in removal of certain blood vessels that are essential to the tumor's blood supply. Tumor necrosis factor alpha is also associated with the activation of helper T Lymphocytes cell type one i.e. Th1 responses, a rise in natural-killing cell cytotoxicity, and antigen-presenting cell maturation.

IL-2 has been associated with the triggering of T Lymphocytes responses, the promotion of cancer-causing lymphocytes, the evolution and multiplication of T Lymphocytes + CD8 i.e. TCD8 and naturally occurring killer cells, and the beneficial control of T lymphocytes+CD4 i.e. TCD4. Inter Leukin-2 can also modulate T regulatory lymphocyte activity as well as homeostasis, by occurrence of an inflammatory milieu that is conducive to tumor combat. In addition, the Th1 inflammatory appearance had been associated with a reduction in T regulatory cells, a rise in TCD4 and TCD8 effector cell levels, T lymphocyte promotion and distinction, and dendritic cell maturation, every one of that assists to the tumor's immunosuppressive state being reversed and promoting an inflammatory response. Aside from the harm caused by the inflammatory reaction, viral activity within the cell contributes to the breakdown and death of aberrant cells. Oncolytic viruses can cause organelle malfunction, like the lysosome, ER i.e. endoplasmic reticulum, or mitochondria, by compromising healthy activity of the cells. Furthermore, the virus may produce an oxidative stress by creating reactive nitrogen species, as well as endoplasmic reticulum stress, which is related with a rise in intracellular levels of calcium, which helps to stabilize and reduce tumors.

The application of cell checkpoint “inhibitors in combination with OVs is a crucial strategy for improving viral rate of survival within the body of humans, because it assists the beginning of inflammatory reaction towards the tumor's cells. The inhibition of PD-L1 allows the tumor to avoid detection by the immune system, blocking T cell development. In this manner, PD-L1 suppression was effective in eliciting a Th1 response, encouraging the development of TCD8 cells towards tumors, and increasing natural-killing cell function. Additionally, investigations demonstrated that giving OVs and monoclonal antibody therapy can inhibit the activity of lethal T lymphocyte-associated antigen four aided in improving immunotherapy effectiveness.

The mechanisms described above contributes to several kinds of tumor cell removal, including autophagic death of cells, necrosis, and apoptosis, resulting to formation of the immune related signs linked to cell damage, such as elevated mobility group box one protein and Adenosine Tri Phosphate. Damage-associated molecular patterns i.e. DAMPs stimulate dendritic cell development and help in the expression of antigens associated tumor w.r.t. immune cells through cross-expression of Damage-associated molecular patterns along with antigens associated tumor, that results in maintenance of inflammation procedure. As an outcome, cellular breakdown promotes virus expulsion in the cell's external surroundings and afterward infection to the another tumor cells, leading to tumor-fighting continuous reaction.

CONCLUSION:

Immunotherapy has revolutionized the field of cancer treatment, providing new hope for patients with previously untreatable malignancies. The advent of immune checkpoint inhibitor, adaptive cell therapy, oncolytic viruses and vaccines of cancer (cancer vaccines) has significantly expanded the therapeutic arsenal against cancer. Furthermore, emerging concepts, such as combination therapies and personalized

medicine, hold great promise for optimizing immunotherapeutic strategies. However, several challenges, including immune-related adverse events, manufacturing complexities, and cost implications, must be addressed to ensure wider accessibility and the realization of the full potential of immunotherapy. As research continues to advance, it's getting obvious that immunotherapy will serve a critical role in shaping the future of oncology, leading to improved patient outcomes and prolonged survival rates.

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POLYMERIC MICELLES: FUNDAMENTAL CONCEPTS AND EMERGING USES IN THERAPEUTICS

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ABSTRACT:
The clonal expansion of mature B lymphocytes is a common feature of small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL), two common neoplastic diseases. With a lifetime risk of about 0.57%, CLL is the most prevalent form of adult leukemia in the Western world. The condition usually manifests in men and is diagnosed in those between the ages of 70 and 72. The treatment landscape for sickle cell disease (CLL/SLL) has changed over time, bringing with it a variety of therapeutic alternatives such as immunotherapy, targeted medicines such BTK inhibitors, chemotherapy, and novel drug delivery techniques. A promising method for drug delivery that increases the solubility and bioavailability of anti-cancer drugs is the use of polymeric micelles. Due to the enhanced permeability and retention (EPR) effect in tumor tissues, which is caused by leaky blood vessels and impaired lymphatic drainage, these nanoscale structures—which are created by the self-assembly of amphiphilic block copolymers—allow targeted drug delivery. This paper discusses the fundamental concepts of polymeric micelles, their mechanisms of action, and their potential applications in improving therapeutic outcomes for CLL/SLL patients.

Keywords: *Polymeric Micelles, Targeted Drug Delivery, Nanomedicine.*

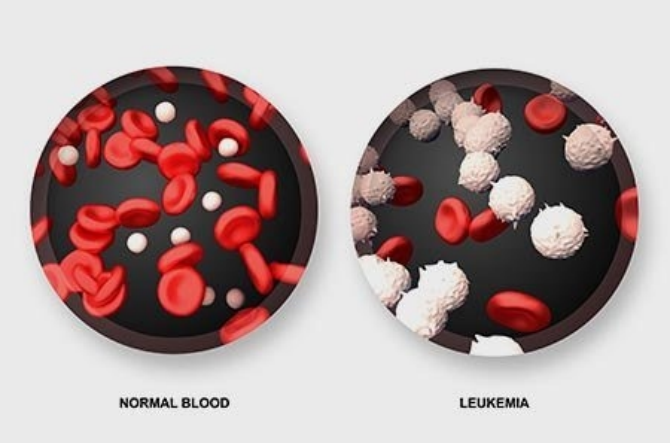
1.INTRODUCTION:

In the West, adult leukemia with Chronic Lymphocytic Leukemia (CLL) is the most common type; in Asia, however, it is less common and comparatively rare in Korea and Japan, even among Japanese visitors to the West. [1] For the general population, the lifetime risk of getting CLL is roughly 1 in 175 (0.57%). With roughly twice the risk of females, males have a slightly higher chance of developing CLL/SLL. The median age of diagnosis for CLL is between 70 and 72 years old, and the disease's risk rises with age. In adults under 40, CLL is infrequent and rare in children. The clonal expansion of mature B cells is a hallmark of small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL), two closely related neoplastic diseases [2]. These indolent malignancies are distinguished by the overproduction of dysfunctional B cells, often

leading to lymphadenopathy, splenomegaly, and cytopenias. [3] These malignancies are non-Hodgkin lymphoma (NHL) subtypes that target B lymphocytes, which are specific types of white blood cells [4] The spleen, lymph nodes, bone marrow, and peripheral blood are the main illness sites. There exist multiple therapeutic options, like as immunotherapy and chemotherapy, aimed at inhibiting the progression of CLL/SLL. CLL/SLL is a progressive, morbidity-causing disease if left untreated. as well as a rise in mortality [3].

For both systemic and local cancer therapy, oral drug delivery is the recommended method since it improves patient quality of life and lowers medical expenses [5]. Optimizing drug distribution to target cancer cells while reducing toxicity and off-target effects is a major problem in the treatment of CLL/SLL. The limited water solubility of several antineoplastic drugs limits their oral bioavailability [6,7]. Various approaches, such as size reduction, surfactant use, salt creation, pH adjustment, prodrug design, and integration into polymeric or lipid formulations, can be used to address issue and improve drug solubility and bioavailability. Drug solubility for CLL/SLL treatment can be effectively increased by formulation techniques like hydrogel-based forms, liposomes, cyclodextrins, polymeric/inorganic nanoparticles, lipid-based formulations, and nanoparticle encapsulation [8]

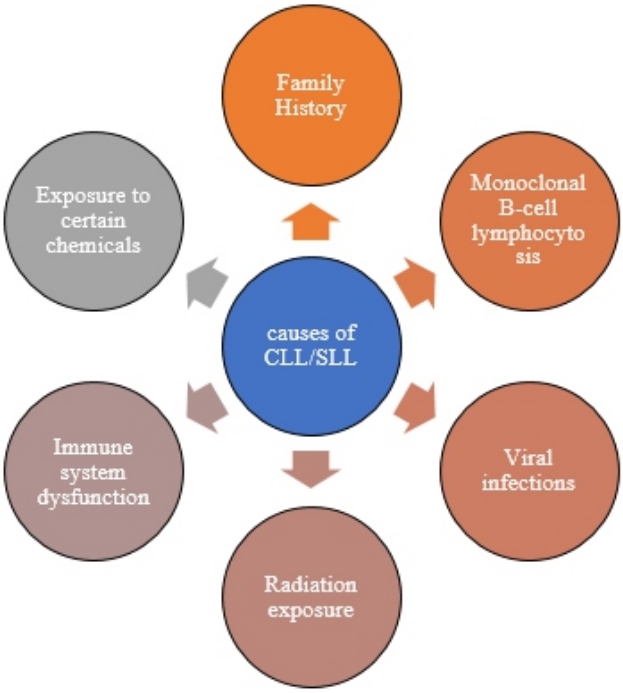
Figure : Comparison of (A) Normal blood (B) Patient having CLL/SLL Blood



2. CAUSES OF CLL/SLL:

Throughout a person's lifespan, specific chromosomes and genes might mutate or change, which can result in chronic lymphocytic leukemia. The precise origins of CLL are unknown, while some circumstances can induce the disease, and medical professionals are unsure of what causes these changes. raise the likelihood of getting the illness. Qualities that raise the risk include the following as follows in *Figure 2*:

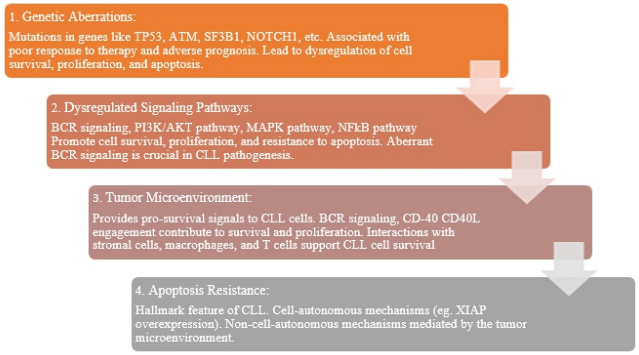
Figure: Causes of (CLL) / (SLL)



3. PATHOGENESIS OF CLL/SLL:

Mature CD5+ B cells accumulate in peripheral blood, bone marrow, and secondary lymphoid organs in chronic lymphocytic leukemia (CLL), a clonal lymphoproliferative disease. Leukemogenesis is facilitated by a complicated interaction between hereditary and non-genetic variables in the pathophysiology of CLL. The multistep mechanism of CLL development has been clarified by the identification of recurrent mutations and clonal evolution. The pathophysiology of CLL is largely determined by genetic anomalies, dysregulated signaling

pathways, and interactions with the tumor microenvironment. Apoptosis, NF-κB signaling, inflammatory pathways, RNA and ribosome processing, NOTCH1 signaling, BCR signaling, DNA damage response, genome/chromatin structure, and cell cycle regulation are some of these processes [9].



4. TREATMENT OF CLL/SLL:

For CLL/SLL, conventional therapies consist of surgery, radiation, chemotherapy, or a mix of these. Although parenteral administration is a common practice in traditional chemotherapy, Oral delivery of polymeric micelles has gained popularity because it can enhance patient compliance and address issue related to low bioavailability and short half-life as polymeric micelles have hydrophilic corona which makes it suitable candidate to eliminate the process of opsonization and hence it may lead to a greater bioavailability. Innovative dosage forms such as prodrugs, solid dispersions, microparticles, nanomicelles, nanodispersions, nanocapsules, and nanosuspensions offer intriguing ways to get around the drawbacks and improve the effectiveness of oral drug delivery in the treatment of CLL/SLL [10,11]. Significant progress has been made in the therapeutic landscape for CLL/SLL, offering patients a variety of treatment alternatives. Conventional methods encompass chemotherapy, targeted therapy (like BTK inhibitors), immunotherapy (like monoclonal antibodies), and stem cell transplantation for qualified patients. Chemotherapy is the process of targeting and killing cancer cells by administering anti-cancer medications parenterally or orally. Purine analogs, alkylating drugs, and corticosteroids are common chemotherapeutic treatments for CLL, with fludarabine typically being the first-line option. Through the use of laboratory-engineered immune components or by boosting the patient's own immune response, immunotherapy uses the immune system to fight cancer cells. Monoclonal antibodies such as ribauximab and obinutuzumab are utilized in CLL immunotherapy [3,12]. Biologically active substances known as "targeted therapies" specifically target particular molecular changes in cancer cells to encourage the proliferation of those cells. Targeted therapies, as opposed to traditional chemotherapeutic medications, aim to interfere with one or more particular proteins implicated in the etiology of chronic lymphocytic leukemia (CLL). Certain CLL cells require a protein called Bruton's tyrosine kinase (BTK) in order to proliferate and survive. BTK inhibitors are a type of targeted treatments that are frequently used as a first-line treatment for CLL. Furthermore, cutting-edge therapies including chimeric antigen receptor (CAR) T-cell therapy have shown promise in the treatment of CLL/SLL [12,13].

5. MODERN PHARMACOLOGIC THERAPIES FOR CHRONIC LYMPHOCYTIC LEUKEMIA:

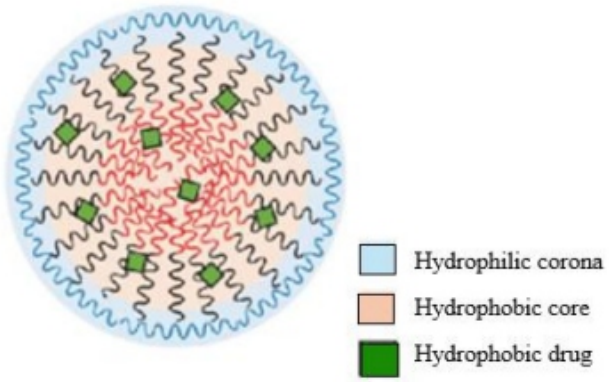
Table 1: Modern pharmacologic therapies for Chronic Lymphocytic Leukemia

Sr No.	Classification	Drug Name	Mechanism of Action
1.	Chemotherapy		
	Alkylating Agents	Bendamustine	Inhibits the expression of genes involved in DNA repair
		Chlorambucil	DNA replication and RNA transcription inhibitor
		Cyclophosphamide	DNA synthesis inhibitor

	Purine Analogs	Fludarabine	DNA polymerase and ribonucleotide reductase inhibitor
		Pentostatin	adenosine deaminase inhibitor
		Cladribine	DNA synthesis inhibitor
	Monoclonal antibodies	rituximab	Anti-CD20 Monoclonal Antibodies
		ofatumumab	
		Obinutuzumab	
		Alemtuzumab	
2.	**Targeted Therapy Drugs**		
	Bruton's tyrosine kinase (BTK) inhibitor	Ibrutinib	Bruton's tyrosine kinase (BTK) inhibitor
		Acalabrutinib	BTK inhibitor
		Zanubrutinib	
		Pirtobrutinib	
	PI3K inhibitors	Idelalisib	phosphatidylinositol 3-kinase inhibitor
		Duvelisib	
3.	B-cell lymphoma 2 inhibitor	Venetoclax	BCL-2 Inhibitor

6. POLYMERIC MICELLES:

Polymeric micelles are nanoscale structures composed of a core-shell architecture formed by the spontaneous assembly of amphiphilic block copolymers in aqueous solutions. Amphiphilic copolymers possess both hydrophobic and hydrophilic segments within the same molecule, which, when present at or above the critical micelle concentration (CMC), self-assemble into a dynamic micellar structure with a core-shell morphology. Because of its unique features, which include nanoscale dimensions, ease of synthesis, superior solubilization qualities, biocompatibility, low toxicity, core-shell architecture, micellar association, form, and relative stability, polymeric micelles are used in drug administration. The hydrophobic core of polymeric micelles encloses and shields the drug, while the hydrophilic shell provides stability and support for the drug in the aqueous medium. This facilitates drug administration and increases the polymers' solubility in water. Polymeric micelles are useful in medicine for many reasons, such as improving drug solubility and safeguarding encapsulated medications [15,16].

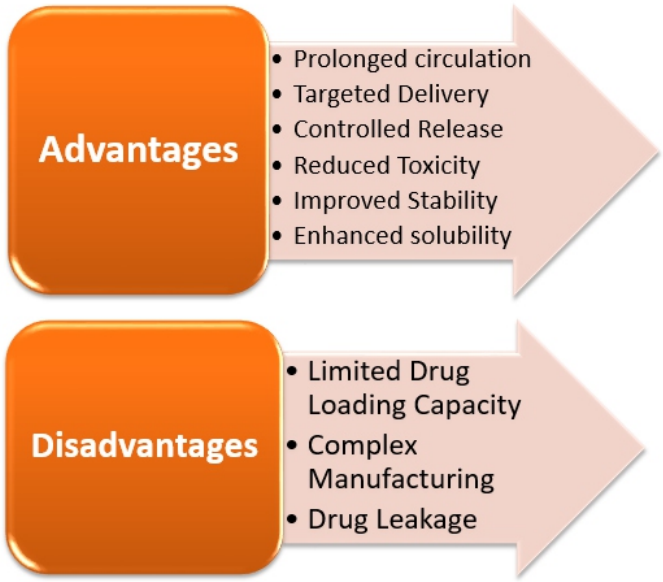


6.1. The Mechanism of Polymeric Micelle Permeation:

Polymeric micelles penetrate tissues through both passive and active processes, which are carefully adjusted to promote therapeutic effects. Passively, their nanoscale size take advantage of the enhanced permeability and retention (EPR) effect, which is particularly strong in tumor tissues and inflamed areas with irregular, highly permeable vasculature, allowing for preferential accumulation. The hydrophilic outer layer of micelles provides steric stability, reduces opsonization, and increases circulation time.

Active micelle penetration into cells is required for subcellular drug delivery, which is predominantly accomplished by endocytosis. Micelles engage with the cell membrane to start this process, which is then internalized and translocated by endosomes into the cytoplasm. Micelles may deconstruct at the plasma membrane or degrade in lysosomes upon entry, resulting in drug release within or outside of cells, as well as drug accumulation at the plasma membrane or in other cellular compartments. Micelles are gaining popularity due to their capacity to circumvent ATP-dependent efflux pumps via endocytosis, which aids in the fight against drug and multidrug resistance. This effect is frequently generated by unimers causing increased membrane fluidity below the critical micelle concentration (CMC), resulting in ATP depletion and lower ATPase activity, which enhances efflux pump inhibition [16].

6.2. Advantage and Disadvantage of Polymeric Micelles:



6.3. COMPOSITION OF POLYMERIC MICELLES:

Table 2:Composition of Polymeric Micelles

Amphiphilics block polymer	Organic Solvents	Aqueous Solvents	Surfactants
Pluoronic (poloxamer)	Acetonitrile	Phosphate buffer	Tween 80
PEG-PLGA	Chloroform	saline	Sodium Dodecyl Sulfate
PEG-PCL	Acetone	water	
PEG-PLA	Dichloromethane		

6.4. Preparation Methods of Polymeric Micelles:

6.4.1. Thin Film Hydration Method

The medication and polymer are dissolved in an organic solvent using this approach. A rotary vacuum evaporator is then used to extract the solvent at a regulated temperature. To guarantee that all solvent remains are completely eliminated, vacuum drying is next performed. This technique produces a thin vesicular film, which is subsequently hydrated with saline phosphate buffer or Milli-Q water by rotating the flask in the evaporator at a predetermined temperature. Micelles are created and kept for future research. The medicine is integrated according to its solubility in organic or aqueous solution [18].

6.4.2. Direct Dissolution Method

This is the most common technique for micelle production. It uses block copolymers with great aqueous solubility. To help the drug load into the micelle, the drug and polymer are dissolved in water, stirred, and heated. Micelle production happens as the core-forming blocks are dehydrated. This process involves dissolving the polymer and medication separately in aqueous solutions, which are then mixed in the proper ratio to generate micelles [18].

6.4.3. Dialysis Method

This method dissolves the hydrophilic and hydrophobic segments of the drug and polymer by dissolving them in a water-miscible solvent. Water can enter the dialysis bag when the solution is dialyzed against it, which starts the block copolymer's self-assembly into micelles. The dialysis bag's semipermeable membrane allows free medication to be released while preserving the micelles inside [19].

6.4.4. Emulsion Method

This approach uses water-insoluble solvents, including acetone, chloroform, or tetrahydrofuran, to dissolve the medication and polymer. Water is gradually mixed with the solution while being vigorously stirred. This creates an emulsion in which the water is the continuous phase and the organic solvent is the internal phase. The solvent is progressively removed by lyophilization or evaporation, which encourages the block copolymers to spontaneously self-assemble into micelles [18].

6.4.5. Drug-Encapsulation Method by Agitation

To make sure homogeneous dispersion, water is added to the drug and block copolymer residue

that remains after the solvent is removed, and the mixture is agitated at temperatures lower than 30°C. This approach creates micelles with over 73% encapsulation effectiveness and can be sterilized using a 0.22 µm filter [18].

6.5. APPLICATION OF POLYMERIC MICELLES:

The various applications of Polymeric micelles are listed in Table 3 [19,20].

Table 3: Application of Polymeric micelles in different diseases

Sr.no.	Name of disease	Application
1	Cancer	**Chemotherapy:** Enhances solubility and provides targeted delivery of hydrophobic anticancer drugs like paclitaxel and doxorubicin, minimizing systemic toxicity.
		Photodynamic Therapy (PDT): Improves efficacy by delivering photosensitizers directly to tumors.
2	Cardiovascular Diseases	**Atherosclerosis:** Targets delivery of anti-inflammatory or cholesterol-lowering drugs to atherosclerotic plaques, improving treatment and reducing systemic side effects.
		Heart Failure: Facilitates delivery of cardioprotective drugs to heart tissue, potentially improving function and reducing damage post-myocardial infarction.
3	Infectious Diseases	**Antibiotic Delivery:** Enhances antibiotic delivery to infected tissues, improving effectiveness against resistant bacterial strains and minimizing side effects.
		Antiviral Therapy: Directly delivers antiviral drugs to infected cells, increasing concentration at the infection site and reducing systemic toxicity.
4	Neurological Disorders	**Alzheimer's Disease:** Improves drug delivery across the blood-brain barrier, targeting brain tissues for better treatment of neurodegenerative diseases.
		Parkinson's Disease: Delivers neuroprotective agents or dopamine precursors to the brain, potentially slowing disease progression and improving symptoms.
5	Dermatological Conditions	**Psoriasis and Eczema:** Targets delivery of anti-inflammatory drugs to the skin, enhancing therapeutic outcomes and reducing systemic drug exposure.
6	Eye Diseases	**Macular Degeneration:** Provides targeted drug delivery to the retina for treating age-related macular degeneration.
		Glaucoma: Delivers drugs to lower intraocular pressure, increasing effectiveness and reducing side effects.
7	Autoimmune Diseases	Rheumatoid Arthritis: Targets delivery of anti-inflammatory drugs to inflamed joints, improving therapy and minimizing systemic immunosuppression.

7. Conclusion:

The utilization of polymeric micelles in the treatment of CLL/SLL represents a significant advancement in drug delivery systems. Their distinct core-shell structure improves oral bioavailability and therapeutic efficacy by making poorly water-soluble medications more soluble. The ability of micelles to bypass ATP-dependent efflux pumps through endocytosis addresses the challenge of drug resistance, a common issue in cancer therapy. Furthermore, the passive and active permeation mechanisms of polymeric micelles enable targeted delivery to tumor sites, maximizing therapeutic effects while minimizing systemic toxicity. As research progresses, the integration of polymeric micelles with existing treatment modalities, including CAR T-cell therapy and targeted therapies, holds promise for improving patient outcomes in CLL/SLL. To get over the present barriers to cancer treatment and enhance patient quality of life, more research into these novel drug delivery methods is essential. The results highlight the importance of creating sophisticated formulations that can successfully handle the difficulties of cancer treatment and provide fresh approaches to therapeutic intervention.

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PERMEATION ENHANCERS FOR TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT
The use of topical drug delivery methods is appealing because they offer easy administration, bypass the initial metabolic process, and utilize the extensive skin surface area. Drug molecules can penetrate the skin surface via two pathways: transcellular and intercellular. Permeation enhancers temporarily increase skin permeability, facilitating drug absorption. This article explores various classifications of permeation enhancers, including physical, chemical, and natural agents.

Keyword: *SC- Stratum corneum, TDDS- Transdermal drug delivery system, OTC- Over the counter, DMF- dimethyl formamide, DMAC- dimethyl acetamide*

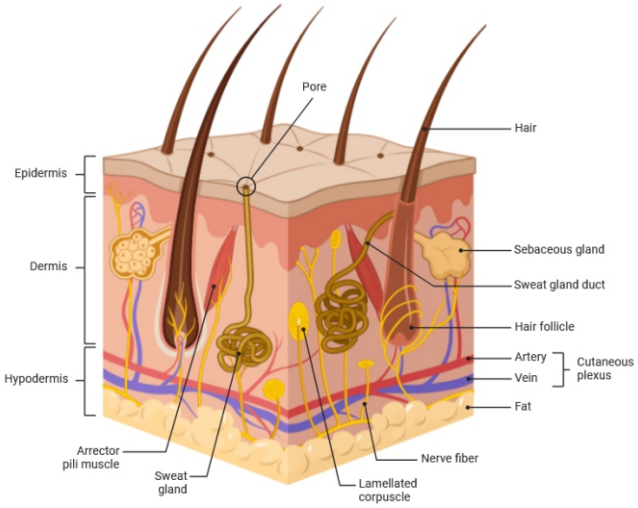
INTRODUCTION

While oral administration remains widely used for delivering medications, it suffers from drawbacks such as first-pass metabolism, expense, and the need for repeated doses. To address these challenges, a new drug delivery approach is needed to enhance therapeutic efficacy, stability, and pharmaceutical protection.[3] Stoughton's foresight in 1965 anticipated percutaneous drug absorption, laying the groundwork for topical/transdermal drug administration systems.[3] These systems offer several advantages over traditional methods, including improved efficacy, safety, avoidance of first-pass metabolism, enhanced convenience, and better patient adherence.[1] TDDS-based medications offer a broad range of administration options for various formulations, including single or multiple active ingredients. When applied to the skin, these formulations can disperse throughout the body or exert their effects locally at the application site, thanks to the extensive and versatile epidermis. The formulation of TDD is essential for treating the stratum corneum, known as the skin's uppermost layer, which is keratinized and extremely impenetrable.[3] Although the stratum corneum serves to protect underlying tissues, its barrier function often limits the passive penetration of medications. Permeation enhancers temporarily increase skin permeability, facilitating medication absorption through the skin.[2]Agents capable of altering the skin's barrier to penetration are known as

Penetration Enhancers, or substances that temporarily reduce the resistance of the stratum corneum (SC) barrier without causing harm to living cells. Numerous compounds have been examined for their ability to enhance penetration, including sulphoxides (such as DMSO), azoles (like laurocapram), pyrrolidines (such as 2-pyrrolidone), alcohols and alkanols, glycols(such as propylene glycol, PG, commonly found in topically applied dosage forms), surfactants, and terpenes. Skin penetration enhancers offer a diverse range of potential sites and mechanisms of action.[5]

STRUCTURE OF SKIN

The skin may be a significant obstacle to topical medicine administration; however, it may also be highly valued for its protective and self-healing properties.[6]



1. Epidermis:

The stratum corneum, the uppermost layer of the epidermis, is made up of three layers: stratum granulosum, stratum spinosum, and stratum germinativum. A layer of intercellular lipids separates the keratinized corneocytes, forming the approximately 15 µm-thick stratum corneum. This intercellular lipid domain, comprising neutral lipids, ceramides, triglycerides, and free fatty acids, serves as a structural framework for the epidermis. Additionally, phospholipids glycosphingolipids, and cholesterol play essential roles in the desquamation process. The lipid-protein matrix resembles a brick wall, with corneocytes arranged in clusters. The lipid-protein matrix acts as the mortar, while the corneocytes serve as the bricks. Corneodesmosomes bind the closely packed corneocytes together, and a varied intercellular lipid matrix envelops them. This matrix plays a crucial role in creating permeability barriers for hydrophilic molecules with molecular weights exceeding 200–350 Da, contributing to the tightness and impermeability of intact skin.[1]

2. Dermis:

The dermis, typically ≥1 mm thick, is responsible for the skin's strength and suppleness. The bulk of the material is made up of fibroblasts embedded in a matrix that is extracellular mostly composed of cellular structural proteins like both elastin and collagen. Furthermore, the dermis is home to a range of cells related to immunity, including as macrophages and dermal dendritic cells. The upper papillary dermis and lower reticular dermis are two dermal subtypes distinguished microscopically by looser and thinner collagen fiber packing in the corpus papillare. The dermo-epidermal junction is where papillae of the corpus papillare join with the basal layer of the epidermis. The dermis contains structures such as hair follicles, sebaceous glands, sweat glands, sensory nerve endings, lymphatic veins, and blood capillaries, which extend to the dermal side of the dermo-epidermal junction. This arrangement allows for the elimination of waste items and the transfer of nutrients to the avascular epidermis via diffusion across the dermo-epidermal interface. [7]

3. Hypo epidermis:

Within the skin, the deepest layer is referred to as the hypodermis or subcutaneous layer. This layer provides insulation and serves as a cushion to

absorb any shocks directed at the body. Comprising various cell types such as fibroblasts, blood vessels, macrophages, connective tissue, and adipose tissue (fat cells), the hypodermis contributes to the skin's structure and function. Huge numbers of fat cells make up the elastic subcutis layer, which acts as a shock absorber for blood arteries and nerve terminals. This layer ranges in thickness from 4 to 9 mm on average. But the real thickness varies from person to person and also based on the area of the body12.[8]

MECHANISM OF SKIN PERMEATION

When drug molecules encounter the skin's surface, they have three potential pathways for entry: through sweat ducts, hair follicles, and sebaceous glands, or directly across the stratum corneum. [9] Several investigations have been undertaken to assess how topical chemicals penetrate the skin. Medication permeability through the skin necessitates the drug to diffuse through the stratum corneum. Additionally, human skin includes sweat glands and hair follicles, which create pathways through the intact epidermis, accounting for approximately 0.1 percent of the total skin surface area. The stratum corneum regulates medication entry through the skin. Drugs can overcome this full barrier via two main pathways: transcellular and intercellular. [3]

The mechanisms by which drugs enter the skin (illustrated by the stratum corneum) comprise the appendageal pathway, the transcellular pathway, and the convoluted extracellular pathway. The trans epidermal pathway consists of both transcellular and intercellular pathways. The ceramide lipid component and dead keratinocytes that make up the stratum corneum (SC) combine to form a thick structure that is frequently compared to a "brick-and-mortar" layout. [13] Keratin, a protein produced by keratinocytes, serves as the 'brick' in the stratum corneum (SC), while lipids act as the 'mortar'. Glycoprotein desmosomes, also known as Corneodesmosomes, link keratinocytes.[14]. The trans-epidermal pathway is the primary and most frequently utilized absorption route. [13] The trans epidermal route can be further classified into two pathways: transcellular and intercellular in the absorption process. In the transcellular route the drugs penetrate through the SC. Drugs must therefore pass through lipid bilayer-based membranes. [15] Another route is intercellular, in which medications must pass through the lipid layer of the SC keratinocytes' intercellular gap. [16] The second route of medication penetration from the skin is trans appendageal. [13]

Table no. 1 Transdermal permeation pathways

Type of pathway	Route
Transdermal	Through the Stratum corneum
Inter-cellular	Passing through the protective barrier of the skin and the air-associated cavities of hair.
Trans-appendage	roots, sebaceous glands, tiny muscles, sweat glands.

PHYSIOCHEMICAL PROPERTIES OF DRUG MOLECULE RESPONSIBLE FOR ITS PENETRATION

The physicochemical properties of a drug molecule play a crucial role in determining its ability to penetrate biological barriers, such as cell membranes, tissues, and the blood-brain barrier. These properties influence the drug's absorption, distribution, and overall pharmacokinetic behaviour.

Table no.2 Physiochemical properties of drug molecule responsible for its penetration

Sr. No.	Characteristics the drug	Description	Referenc
1	Molecular weigh and size	• Molecules which are small size enable easy penetration rapidly passing through th epithelial barrier and mainta strong contact with the strat corneum.	[10,11]
		• The majority of pharmacol compounds utilised in transd routes have molecular weight than 500 Dalton.	

2	Lipophilicity	• Partitioning the drug molecule's free energy between two immiscible phases is strongly • The key determinant of a drug's penetrability across the SC is its lipid or water partition coefficient. • Drug molecules with a low molecular weight and a low partition coefficient readily • As an illustration, liposomal amphotericin is less harmful to skin than traditional forms and has good penetration.	[10]
3	Hydrogen–Bonding groups	• The main factor influencing its spread throughout the stratum corneum. • Mono- or di-substituted drug molecules containing hydrogen bonding groups have the most significant impact on the magnitude of the diffusion coefficient.	[10]
4	Solubility	• Dependent in part on molecule surface characteristics and the partition coefficient • Substances that are molecularly soluble in water and lipids penetrate more readily than those that only exhibit high solubility in one of the two media.	[10]
5	Ionization of drug molecule	• Depends on the solution's pH, which changes a drug's ionisation state and, in turn, its hydrophilicity or lipophilicity when it crosses a membrane and eventually influences skin penetration.	[12,10]
6	Stereochemistry and steric interaction	• It has an impact on a drug's solubility and, eventually, how well it penetrates skin. The steric hindrance caused by hydroxyl groups influences water solubility, which in turn affects the ability of a medication molecule to penetrate the skin.	[10]

THE DISTINCTION BETWEEN TRANSDERMAL AND TOPICAL MEDICATION ADMINISTRATION

For a wide range of illnesses, topical medicines are frequently utilized as prescription or over-the-counter (OTC) therapies. The distinction between topical and transdermal products is often unclear, despite their widespread use among the general population and certain medical experts. All topical and transdermal medications are administered topically; However, only transdermal formulations are meant to work on deeper or more distant tissues by penetrating the skin's outer layer. [18] Topical medications are applied directly to the skin's surface and work by diffusing passively into the skin to produce a localized effect. On the other hand, transdermal medications are also applied topically but contain substances or technologies that enhance skin penetration. These enhancements allow a larger amount of the drug to traverse the skin barrier, often leading to systemic absorption, where the drug can enter the bloodstream and exert effects beyond the site of application. [18]

PERMEATION ENHANCERS

Penetration enhancers alter the integrity of the epithelial cell layer and facilitate the passage of medications past the corneal barrier. [1] Permeation enhancers are substances that increase the skin's penetrability for a brief period of time to facilitate medication absorption via the skin. They are utilized to pass both impermeable drugs (such as heparin) and ionizable drugs, to sustain blood drug levels, to administer higher doses of less potent drugs (for instance, oxymorphone), to reduce the lag time of transdermal drug delivery systems and to administer high molecular weight hormones and peptides. [19,20]

The perfect attributes of penetration enhancers are:

1. These substances ought to be biocompatible. They shouldn't irritate skin or trigger allergies over the long term. It shouldn't cause toxicity.
2. It ought to work well with the medication being administered.
3. It shouldn't have any negative pharmacological effects on the body.
4. It must be both physically and chemically stable.
5. It shouldn't result in the unidirectional flow of endogenous materials and bodily fluids, and the skin should instantly return to its natural barrier qualities after these materials are eliminated. [2]

CLASSIFICATION OF PERMEATION ENHANCERS: [21]

1. PHYSICAL PERMEATION ENHANCERS:

To improve topical application's skin penetration, a variety of physical methods can be used either before or after. These can be classified into groups based on how they affect the skin. [22] The SC thickness is decreased by mechanical techniques such skin abrasion and tape stripping, whereas the barrier is often weakened by flexing, stretching, or massage. The SC barrier is circumvented via direct injection techniques, such as jet propulsion and microneedles. With relative or cavitation procedures, energy (thermal, ultrasonic, radiofrequency, and others) is applied directly to the skin to create pores at preciseplaces.

Lastly, methods like non-cavitational ultrasonography, magnetophoresis, and iontophoresis strengthen the penetrant molecule's driving power. As will be seen, every technique includes drawbacks in addition to benefits that may make it more appropriate for particular uses. Promising tactics that are probably going to be used more frequently are combinations of optimal formulation and physical enhancement, including the use of chemical enhancers. [22]

Sr no.	Physical	Principle Enhancers	Characteristics	Reference
1	Sonophoresis	Sonophoresis is the process of temporarily increasing skin permeability by means of ultrasonic radiation.	Sonophoresis enhances skin permeability by operating at frequencies between 20 kHz and 16 MHz.	[23,24]
2	Iontophoresis	Iontophoresis involves applying a small electric current to enhance drug delivery by placing an anode and a cathode on a surface like the skin.	Iontophoresis utilizes an electric current of approximately 0.5 A/cm, allowing drug permeation through passive diffusion, electroosmosis, or electromigration.	[24]
3	Electroporation	Electroporation enhances the flow of ions and macromolecules through the skin by applying strong electrical field pulses to the cell membrane, creating nanosized pores.	Both reversible and irreversible electroporation is possible.	[24,25]
4	Direct injection with microneedles	Administer drugs using a transdermal patch with the same effectiveness as a needle.	Vaccinations targeting the West Nile virus, herpes simplex virus, human papillomavirus, influenza, and Chikungunya virus.	[22]
5	Radiofrequency	One easy, safe, and efficient treatment for chronic radiation proctopathy is radiofrequency ablation (RF).	The range of the frequency is 10 kHz to 900 MHz.	[26,24]
6	Dermaportation or magnetophoresis	Delivery with either a constant or varying magnetic field.	Benzoic acid, naltrexone, 5-ALA, terbutaline sulphate, and Ala-Trp (dipeptide).	[24]

2. CHEMICAL PERMEATION ENHANCER:

Chemical enhancers are inert substances that interact with the components of SC by diffusing and partitioning into the skin. They are thought to be safe in general. [27, 28] Through the intracellular pathway's interaction, engaging with the intercellular pathway, and altering the solubility or partition of the SC, chemical enhancers improve the penetration of medicines. The solute may interact with the polar head group in both the lipid and aqueous regions of intercellular bilayers during the intercellular pathway. [28] Chemical penetration enhancers have the potential to function through three primary ways. [31]

1. Disruption of the highly organized structure of the stratum corneum lipids.

2 Interaction with a protein found inside cells.

3. Enhanced medication, coenhancer, or solvent distribution into the SC.

Table no. 4: Types of chemical penetration enhancers

Sr. no.	Chemical enhancer	Compounds	Principle	Reference
1	Water	Water	It seems that transdermal distribution of both lipophilic and hydrophilic	[30,32]
2	Alcohols	Caprylic alcohol, ethanol, polyglycols, glycols, and glycerol.	Ethanol permeates human skin rapidly, akin to water, exhibiting a steady-state flux	[30,32]
3	Amides	Pyrrolidone (1-dodecylazacycloheptan-2 one)) urea, pyrrolidone (N-methyl-2-pyrrolidone, 2 pyrrolidon) azones.	These have the ability to alter the membrane's solvent structure within the tissue.	[30,29]
4	Esters	Isopropyl myristate	Monoglycerides had an impact on the partition,	[30,34]
5	Acids	Among the fatty acids are oleic and undecanoic acids.	Permeability flaws in the bilayers allow hydrophilic substances to pass through	[30,34]
6	Amines	Amines that are primary, secondary, tertiary, cyclic, and acyclic.	-	[30]
7	Pyrrolidones	Two pyrrolidones (2P) and N-methyl-2-pyrrolidone (NMP)	These chemicals cause the polar head group to form a solvation shell, which	[29,30,37]
8	Sulphoxides	The compounds dimethyl and dodecyl methyl sulfoxides.	Subsequently, sulphur dioxide displaces the protein-water and disrupts the protein's natural structure	[30,31]
9	Surfactants	Dodecyl dimethyl ammoniopropane sulphate, polysorbate 80, cetyltrimethyl ammonium bromide, sorbitan monolaurate, and sodium lauryl sulphate.	Anionic surfactant, or SLS, causes the SC to swell. The swollen keratin can absorb more water and aid in the drug's penetration. SLS also Cationic surfactants disrupt the cellular-lipid matrix by Non-ionic surfactants exhibit their capacity to improve penetration by inducing the	[30,35]
10	Terpenes, terpenoids and essential oils	Menthol, limonene	These are lipophilic substances that primarily affect the SC's lipid pathway. Both polar and non-polar	[30,34]

3. NATURAL PERMEATION ENHANCERS:

Within the pharmaceutical industry, natural permeation enhancers (NPEs) represent a recent category of penetration enhancers. Additional research is needed to know about a reliable transdermal formulation using NPEs (Non-Phospholipid Penetration Enhancers), enabling commercial scalability owing to their benefits, including cost-effectiveness and improved safety profile. [39,40]

PAPAIN:

Carica papaya is extracted to obtain papain an endocytic cysteine protease found in plants Papain, a proteolytic enzyme, was investigated for its ability to facilitate the penetration of low-molecular-weight heparin (LMWH) in both laboratory experiments and live subjects.It was discovered that administering LMWH and papain together was a novel way to increase the absorption of heparin taken orally and, consequently, its bioavailability [42].

PIPERINE

Ripe fruits of Piper nigrum and Piper longum are utilized for the production of piperine. [43]The impact of piperine on the in vitro penetration of aceclofenac through human cadaver skin was investigated, revealing that piperine enhances aceclofenac's transdermal permeation through a biphasic process that involves partial removal of SC lipids and interaction with SC keratin. Fourier transform infrared technology was employed to validate this potential mechanism. [44]

TERPENES:

Terpenes are widely known to improve medication penetration through human skin, and the pharmaceutical industry is showing a lot of interest in using them for this purpose. [45] Terpenes are a popular option in studies on transdermal medication delivery. There is a wide variety of people in this class. The effect on the skin is influenced by the physicochemical characteristics of a particular terpene, particularly its lipophilicity. Smaller terpenes with nonpolar groups, on the other hand, are thought to improve skin penetration more effectively. By modifying the lipid layers of the skin, terpenes have been demonstrated to enhance the diffusion and distribution of medications into the skin. [46, 47] They serve as safe enhancers for both hydrophilic and lipophilic drugs. [48]

CAPSAICIN:

Terpenes are mostly known to increase drug permeation. One of the main capsaicinoids, capsaicin is only found in the fruits of the genus Capsicum, which is a member of the Solanaceae family. [49]

MYRISTICA FRAGRANS:

Diclofenac sodium served as the focal medication in a transdermal gel formulation, with M. fragrans assessed as a penetration enhancer. Unlike the synthetic enhancer Triton X, extracts of M. fragrans in methanol, chloroform, and n-hexane were employed as penetration enhancers. Results indicated that the methanol and chloroform extracts exhibited higher percentage cumulative release (%) in both laboratory and animal studies, suggesting enhanced penetration compared to the artificial enhancer. [50]

ESSENTIAL OIL:

Essential oils consist of volatile aromatic compounds, primarily terpenes, terpenoids, and phenylpropanoids, which are naturally sourced from aromatic plants. (As described in Table no.5) [51] Because of their promising penetration-enhancing effect, they can be considered a natural substitute for synthetic skin permeation enhancers. [52] A penetration enhancer distributes into the stratum corneum (SC) without harming

underlying skin cells, connecting to tissue components to lower barrier characteristics. Both D-limonene and eucalyptol have been demonstrated to alter permeant diffusivity by disrupting stratum corneum lipid composition. [53]

FARNESOL:

Farnesol, identified as a sesquiterpene alcohol, is present in several essential oils such as citronella, neroli, cyclamen, lemongrass, tuberose, balsam, and tolu. Research suggests that farnesol (0.25%) demonstrates superior permeation enhancement of diclofenac sodium compared to other terpenes, with the ranking as follows: farnesol > carvone > nerolidol > menthone > limonenoxide. [65]

MENTHOL:

Methyl alcohol, extracted from the blossoms of Mentha piperita, is acknowledged for its efficacy as a penetration enhancer. The synergy between menthol and limonene exemplifies the potential of terpenes in enhancing permeation. [65]

EUCALYPTOL:

Eucalyptol, also referred to as 1,8-cine, cajeputol, and cineole, is a cyclic ether and a monoterpenoid with various synonyms. It finds applications in the cosmetic, fragrance, and flavouring industries due to its spicy aroma and taste. Additionally, eucalyptol has been employed for facilitating the percutaneous permeation of numerous lipophilic drugs through hairless mouse skin. [66]

EUGENOL:

Eugenol was evaluated for its potential to improve the permeation of lornoxicam. In vitro tests were conducted on lornoxicam transdermal patches using rat skin in a Franz diffusion cell. The findings demonstrated that eugenol effectively boosts the permeation of lornoxicam across rat skin. [66]

BORNEOL:

Borneol increases the transdermal permeation of 5 model drugs: 5-fluorouracil, antipyrine, aspirin, salicylic acid, and ibuprofen. Borneol effectively facilitated the transdermal permeation of these model drugs.[66]

Table no. 5: Classification of permeation enhancers

Penetration Enhancers	Mode of Action	Examples
Physical enhancer	Increasing the permeation by physical, magnetic, and ultrasonic separation are some examples of these sorts.	Thermophoresis, sonophoresis, electroporation, iontophoresis, Needless injection
Chemical enhancers	They act via multiple mechanisms 1. disturbing SC's well-organized structure. 2. via intercellular (interaction with the proteins). 3. through intercellular (protein-interaction) communication.	sulphoxides and chemicals like dimethyl sulphoxide (DMSO), dimethyl formamide (DMF), oxizolidinones, pyyolidones, azones,
Biochemical	Carried out by converting chemicals into suitable form.	co-adminisration of metabolite inhibitor of skin. Synthesis of bio-convertible pro drug
Drug vehicle Based	Interaction of the enhancers with the stratum corneum.	complex coacervates and Ion pairs
Natural penetration enhancers	Act via altering Diffusion coefficient, partition coefficient and solubility of drug	Basil oil, Neem Oil, limonene, linalool
Miscellaneous enhancers	Act via varied mechanisms	Lipid synthesis inhibitors, phospholipids and clofibric acid

CONCLUSION

Many medications today require injection-based administration, which can be uncomfortable, unappealing, and, in some cases, risky. As a result, skin-based drug delivery—commonly known as the topical drug delivery system—has emerged as a preferred alternative. Topical medications are applied directly to the skin, relying on passive

diffusion to exert a local effect. However, they must first overcome the skin's natural barrier, the stratum corneum, which poses a significant challenge to drug permeation. To address this, permeation enhancers play a crucial role in facilitating drug absorption through the skin. This field is rapidly evolving, presenting numerous opportunities for innovation. Extensive research has demonstrated the effectiveness of various absorption enhancers, which can be categorized into physical, chemical, and natural methods. These approaches show great promise in improving drug delivery through the skin.

CONFLICT OF INTEREST:

There is no conflict of interest.

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A CASE OF SCRUB TYPHUS IN A 18 YEAR OLD ASIAN GIRL.

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ABSTRACT:

Objective: Scrub typhus is an acute infectious disease caused by Orientia tsutsugamushi, also known as Rickettisia, which is a mite borne gram negative bacterium. According to WHO, Scrub typhus is one of the under-diagnosed and under-reported febrile illnesses in the Asia-Pacific region. The incidence of scrub typhus infections depends majorly on the climate, temperature and degree of rainfall. In India, increased humidity favors hatching of mite eggs into chiggers which leads to transmission of Scrub typhus

Case Summary: In this report, we present a case of an 18-year-old Asian girl who developed Scrub Typhus infection after being exposed to the causative organism.

Conclusion: The report emphasizes the public health burden of the disease in India, the importance of evidence-based use of antibiotics, coupled with patient centric inter-professional care which could bring about reduction in symptoms and better outcomes.

Keywords: *Scrub Typhus, Orientia tsutsugamushi, maculopapular rash, doxycycline.*

I. BACKGROUND:

The acute infectious disease scrub typhus, which is brought on by Orientia tsutsugamushi, formerly known as Rickettisa, was initially identified in Japan in 1899. The term “Scrub” refers to the type of vegetation that harbors the vector. The Greek word typhus, which implies fever with stupor, is where the name "Typhus" first appeared [1]. Gram-negative O. tsutsugamushi bacteria are carried by mites. O. tsutsugamushi is typically found in small rodents, although it can also be propagated via transovarial transfer within mite colonies. The inoculation occurs at the larval stage followed by an incubation period of 6 to 10 days. The disease is characterized by the presence of red and a black scab also known as eschar, found at the area of bite. Nonspecific symptoms such as headache, fever, rash, stupor, myalgia, and regional lymphadenopathy make diagnosing this fever typically challenging. If untreated, the infection progresses to more severe complications like pneumonia, jaundice, haemorrhage, multi organ failure, paralysis and death [1,2].

The World Health Organization states that "scrub typhus is probably one of the most underdiagnosed and under-reported febrile illnesses requiring hospitalization," [3]. It is a life-threatening community health problem in the Asia-Pacific region with the occurrence of over one million new scrub typhus cases every year. A study from Thailand had documented 59.5% scrub typhus positivity, whereas in Bangladesh, Indonesia, Malaysia, Papua New Guinea, and Sri Lanka, the seroprevalence was found to be 23.7%, 9.3%, 17.9%, 27.9%, and 26.3%, respectively [4] and the risk of infection is projected to be around 1 billion. About 23% of all febrile episodes in India are caused by scrub typhus, and this incidence rises throughout the winter and rainy seasons. Increased humidity in India encourages mite eggs to hatch into chiggers, which spreads scrub typhus [3]. In the past 10 years, outbreaks of scrub typhus have started to appear in India. Andhra Pradesh recorded 39% seroprevalence, However, a recent Tamil Nadu study found 31.8% seropositivity. The case of an 18-year-old female patient with scrub typhus who had no co-morbidities is presented in this paper.

II. CASE REPORT:

A female patient, age 18, was brought to the general medicine department with serious complaints of fever in the past 10 days which was high grade, intermittent, evening raise of temperature associated with chills and rigor along with headache at the time of admission with no other known co-morbidities. She was treated for the same symptomatically at an outside setting with IV antibiotics and other medications. On examination she was conscious, oriented and febrile and pale with normal cardiac, respiratory and neurological functions. The vital signs assessed at the time of admission showed that temperature was 103° F, blood pressure was 90/60 mmHg, Pulse was 144 bpm and SpO2 was 98%. The laboratory investigations showed that the patient tested negative for Covid-19. The investigations done at the outside setting showed hemoglobin and total leukocyte count was 8.5 g/dL and 5100 cells/cu.mm respectively, platelets was 1.8 L, the patient tested negative for WIDAL and dengue specific antibodies. The urine analysis showed mild fluctuations. On admission, patients had elevated levels of D dimer-1340 ng/ml, and blood culture was sterile. She was negative for malarial parasite, ANA and comb's test. She had elevated levels of procalcitonin 0.62ng/ml, which was managed with injection meropenem 500 mg every 6 hours. The CT scan of thorax showed mild pleural effusion, which was managed with monteleukast tablet. The next day, the patient had complaints of ear pain which was occult for which an ear drops was given, backache and fever spike in the evening. The liver function tests showed elevated levels of globulin 3.6 g/dL, ALP 130 U/L, SGOT 75 U/L, GGT 117 U/L, for which liver protectants like silymarin and ursodeoxycholic acid was given orally twice daily. On the sixth day, serum analysis showed that she was positive for tsutsugamushi antibody and she was confirmed with Scrub typhus infection and eschar was found in the armpit. She was put on a doxycycline 100 mg regimen for 14 days twice daily orally. She had recurrent fever spikes with temperature ranging between 100° and 102° F, headache and vomiting. Multiple fever spikes were noted on the next day for which she was given with parenteral and oral paracetamol, anti-emetics. The liver function tests repeated on the 9th day showed abnormality, same treatment regimen was followed. On day 10, she was afebrile for 24 hours and had complaints of severe ulcer of mouth and entire food pipe, she also had epigastric pain, dysphagia and abdominal pain. Ultrasound sound of abdomen showed that she had mild spleenomegaly, edematous thickening of gall bladder, mild to moderate ascites, right periephric fluid present and right pleural effusion. She had multiple episodes of loose stools greenish in colour, anti-motility drugs

and ORS was given for the same. On the 12th day her liver function tests were repeated which was normal, stool culture, blood culture and urine culture were normal. The patient was symptomatically improving without fever spikes and loose stools. Her peripheral smear tests showed that she had normocytic normochromic anaemia with mild neutropenia and thrombocytopenia, she was given with oral iron supplements for the same. On the day before discharge, she had no complaints of fever and bleeding gums, she was clinically better but had occasional cough. The doxycycline regimen was completed, and she was discharged with liver protectants, antibiotics, pre-probiotics, anti-leukotrienes, iron supplements, anti-tussive and antacids.

III. DISCUSSION AND CONLUSION:

Scrub typhus is transmitted to humans by a Rickettsial mite borne arthropod vector, Orientia tsutsugamushi belonging to the Trombiculidae family which is more common in India and many other Southeast Asian countries predominant in mite infested areas, rice fields and mite islands. The arthropod feeds on ground feeding birds or small mammals, generally human beings get infected due to accidental exposure. Human to human transmission of infection is yet to be reported. As stated above, Scrub typhus is an acute febrile illness with an onset of fever, myalgia as the initial symptoms. Five to eight days after the infection, there occurs the development of maculopapular rashes on the trunk, and it may extend further to legs and arms. Lymphadenopathy and splenomegaly are more commonly encountered in physical examinations and the same was manifested in the above reported case. The systemic symptoms appear by the end of 14 days which manifests as diffuse or focal mononuclear cellular infiltration of the leptomeningis, encephalomyelitis, and other central nervous system symptoms, brain haemorrhage), abdominopelvic system (Splenomegaly, splenic infarct and ascites, hepatic congestion, lymphedema) cardiovascular system(Cardiomegaly, cellular infiltration in endocardium and pericardium) renal system (Acute renal failure), respiratory system (pleural effusion, acute respitratory distress syndrome)[1,5]. The exact mechanism remains unclear, One of the most dangerous side effects of a scrub typhus infection is Acute Respiratory Distress Syndrome. Septic shock, hypo-albuminemia, high lymphocyte counts which can be attributed to endothelial cells dysfunction and invasion by inflammatory cascades are also seen [6]. Rational and targeted use of antibiotics can prevent the progression of complications. The guidelines laid down by DHR-ICMR in 2015 for the diagnosis and management of rickettsial diseases states that, the specific investigation for Scrub typhus include IgG and IgM ELISA, Polymerase Chain Reaction (PCR) & Immuno Fluorescence Assay(IFA) and the standard management provided at primary care setting involves initially Recognizing disease severity. When scrub typhus is thought to be possible, the following medications should be given to adults: 200 mg of doxycycline every day, divided into two doses, for seven days if the patient weighs more than 45 kg. It is recommended that patients take 500 mg of azithromycin orally once for five days. It is advised that children under 45 kg receive either two separate doses of 4.5 mg/kg body weight/day of doxycycline or a single dose of 10 mg/kg body weight for five days. A single 500 mg dosage of azithromycin should be administered to pregnant women for five days. Since pregnant women should not take doxycycline. To complete the 7–15-day regimen, oral medication should be administered after an infusion of 100 mg of doxycycline twice a day in 100 ml of normal saline that lasts for 30 minutes. Likewise, intravenous chloramphenicol 50–100 mg/kg/d or intravenous azithromycin 500 mg IV in 250 ml normal saline

given once daily for 1–2 days, followed by oral medication to complete the 5-day course Initially, six-hourly dosages should be given as an infusion over one hour, and thereafter oral medication should be used to complete the seven to fifteen days of treatment. Individual complications should be managed in accordance with current procedures. There have been reports of doxycycline and/or chloramphenicol-resistant strains from South-East Asia. These strains are sensitive to azithromycin [7]. In our case report patient had lung involved complication, pleural effusion which was confirmed by CT scan of thorax. The pathophysiology of pleural effusion associated with scrub typhus is due to widespread vasculitis and perivasculitis [8]. The progression of pleural effusion into pneumonia in this patient was prevented by appropriate antibiotic and anti-leukotrienes. Patient centric inter-professional care could play an important role in early detection of the condition with proper immunofluorescence techniques and could aid in better management of the condition. Evidence based choice of antibiotics and other adjuvant medications like anti- allergic, multivitamin and protein supplements, mouth paints, fluid replacement, can be made use of for reduction in symptoms and better outcomes.

CONSENT: The study's purpose was explained to the patient, and their informed consent was acquired.

COMPETING INTERESTS: The authors declare that they have no competing interests.

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EVOLVING STRATEGIES IN BREAST CANCER TREATMENT: A FOCUS ON SOLID LIPID NANOPARTICLES

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ABSTRACT

Breast cancer continues to pose a significant global health burden, characterized by its heterogeneous nature and complex pathophysiology. Standard treatment modalities encompass surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapies. Despite these therapies leading to improved survival rates, they are associated with significant side effects, including nausea, alopecia, fatigue, and cardiotoxicity, which adversely impact patient quality of life and treatment adherence. Multiple challenges persist in effectively managing breast cancer, including the development of resistance to chemotherapy agents. Although chemotherapy is the first line of treatment for breast cancer, it has many challenges and limitations. These include drug resistance, high toxicity, tumor heterogeneity, and non-specificity of the chemotherapeutic agents, thereby increasing the need for more targeted and effective therapeutic strategies. Nanoparticles, liposomes, micelles and polymer-based carriers are some of the drug delivery systems that have been designed to enhance targeting specificity for therapeutic agents. Solid lipid nanoparticles are an example of such colloidal drug delivery systems. They are advantageous over their conventional drug delivery systems such as better stability, controlled release profile and an increased biocompatibility. The lipid matrix of SLNs could protect the encapsulated drugs from degradation and assists in efficiently delivery to target tissues hence increasing therapeutic efficacy with less dosing intervals.

Key Words: *solid lipid nanoparticles; breast cancer; chemotherapy, nano drug delivery systems, Solid lipid nanoparticles.*

I. Prevalence and Epidemiology

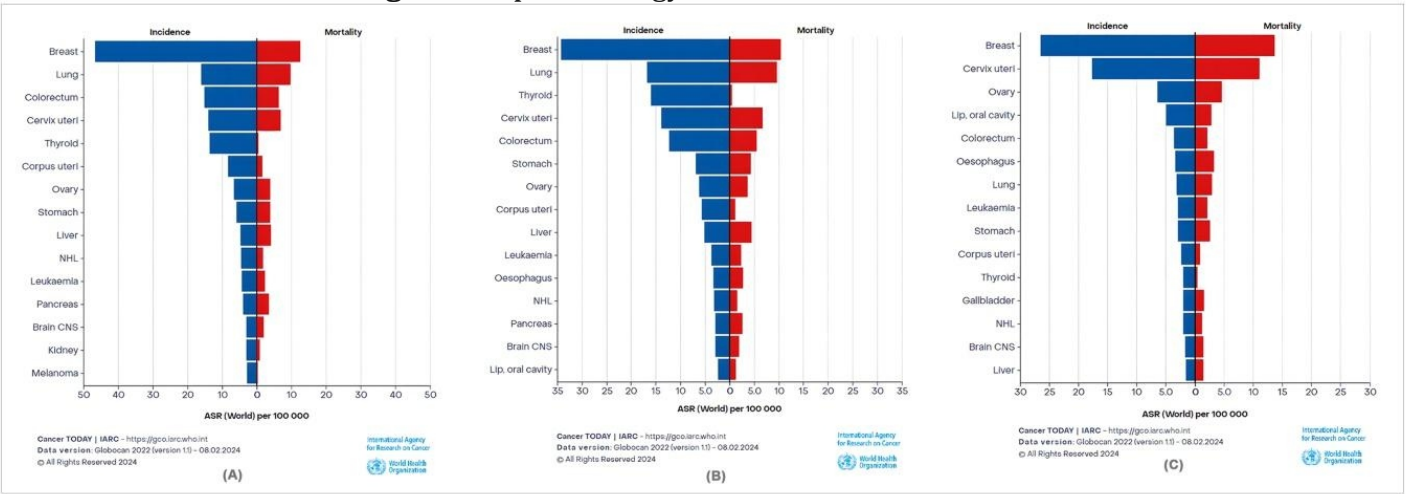
Breast cancer is the most prevalent cancer among females worldwide and a leading cause of cancer related mortality. The incidence and mortality rates vary across regions, influenced by genetic predisposition, environmental factors, and lifestyle choices (Figure 1). Despite advances in early detection and treatment, challenges persist in achieving optimal outcomes due to disease heterogeneity and treatment resistance[2].

While breast cancer remains a significant health concern worldwide, improvements have afforded some patients longer lives. In 2020, one in eight new cancer cases was breast cancer, with global diagnoses estimated at over two million. Incidence rates differ noticeably between regions, with higher occurrences in many Asian nations.

II. Pathophysiology

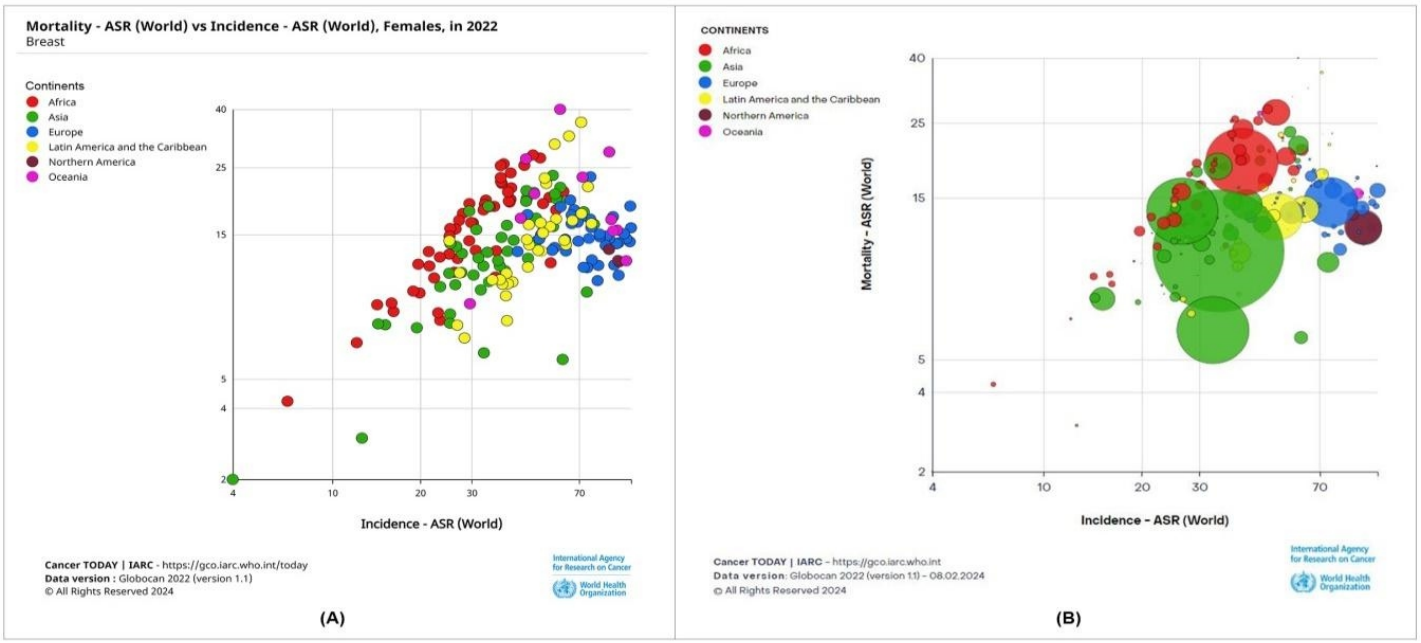
Breast cancer arises from the unchecked growth and multiplication of abnormal cells within breast tissue, fueled by genetic changes and disrupted signaling pathways. It comprises numerous molecular subtypes, such as hormone receptor-positive, and triple-negative breast cancers, which exhibit distinct biological behaviors and clinical consequences.The disease progression is

Figure 1: Epidemiology of cancer across the world



influenced by critical pathways, including irregular cell cycle regulation, resistance to programmed cell death, blood vessel formation, and the development of metastases.

Figure 2: Prevalence of breast cancer worldwide (Incidence Vs. Mortality).
(B) Prevalence of breast cancer worldwide comparing the population size (Incidence Vs. Mortality).



III. Current Treatment Modalities, Challenges faced and Their Limitations

Breast cancer management necessitates a multimodal approach tailored to the specific tumor subtype, stage, and patient factors[6]. Standard treatment modalities encompass surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapies, such as monoclonal antibodies and tyrosine kinase inhibitors[6]. Despite these therapies leading to improved survival rates, they are associated with significant side effects, including nausea, alopecia, fatigue, and cardiotoxicity, which adversely impact patient quality of life and treatment adherence. Multiple challenges persist in effectively managing breast cancer, including the development of resistance to chemotherapy agents, such as taxanes like docetaxel trihydrate & paclitaxel[4]. Resistance mechanisms involve alterations in drug metabolism, efflux pump activation, and molecular pathways involved in cell survival and proliferation, which contribute to treatment failure and disease recurrence[1,2]. Moreover, the heterogeneity of breast tumors underscores the need for personalized treatment approaches to optimize therapeutic outcomes[3'5].

Although chemotherapy remains a fundamental treatment for breast cancer, its systemic toxicity poses significant challenges for patients. Common adverse effects include myelosuppression, gastrointestinal disturbances, peripheral neuropathy, and immunosuppression, which can compromise treatment efficacy and patient well-being. Minimizing these side effects while maximizing therapeutic efficacy is a crucial objective in oncology research. Chemotherapy employs cytotoxic drugs that target rapidly dividing cancer cells, aiming to reduce tumor burden, prevent metastasis, and improve survival rates[5].

IV. Types of Chemotherapeutic Drugs

Chemotherapeutic agents used in breast cancer treatment can be broadly categorized based on their mechanisms of action:

1. Antimetabolites

Antimetabolites mimic natural substances within the cell, interfering with DNA and RNA synthesis. A notable example is Methotrexate, which inhibits dihydrofolate reductase, thus reducing the synthesis of nucleotides necessary for DNA replication. Another key antimetabolite is 5-Fluorouracil, which inhibits thymidylate synthase, disrupting DNA synthesis and function[7.]

2. Alkylating Agents

Alkylating agents introduce alkyl groups into DNA, leading to cross-linking and strand breaks that inhibit DNA replication and transcription. Cyclophosphamide, for instance, causes DNA cross-linking, leading to apoptosis in rapidly dividing cells. Ifosfamide, like cyclophosphamide, works through a different metabolic activation pathway[8].

3. Anthracyclines

Anthracyclines intercalate into DNA, inhibiting topoisomerase II and generating free radicals that cause DNA damage. Doxorubicin is a key anthracycline used in breast cancer treatment; it interferes with DNA replication and transcription, inducing apoptosis. Epirubicin, like doxorubicin, has a slightly different toxicity profile[6].

4. Taxanes

Taxanes prevent the depolymerization of microtubules, thereby inhibiting cell division. Paclitaxel prevents cell division at the metaphase-anaphase transition by stabilizing microtubules with bound tubulin. Docetaxel trihydrate is a semisynthetic analogue of paclitaxel but has

enhanced water solubility and different pharmacokinetics[9].

5. Antimicrotubule Agents

Antimicrotubule agents are a type of antineoplastic drug that interferes with the function of microtubules implicated in cell division. Vinblastine inhibits the assembly of microtubules; thus, causing cell cycle arrest followed by apoptosis. Vinorelbine is a semisynthetic vinca alkaloid that shares the same mechanism of action as vinblastine[10].

V. Challenges Faced During Chemotherapy

Despite the efficacy of chemotherapeutic agents, several challenges complicate their use in breast cancer treatment:

1. Drug Resistance

One of the most significant challenges in cancer treatment is the development of resistance to chemotherapeutic drugs. Resistance to chemotherapy is inclusive of intrinsic and acquired factors. Main mechanisms include overexpression of efflux pumps, the most notable being of the ABC transporter type, and among these, the best characterized is P-glycoprotein, which actively pumps drugs out from the cell, preceding a decline in intracellular drug concentration. Changes in the drug-metabolizing enzymes can result in increased inactivation or degradation of chemotherapeutic drugs. Diminished concentrations of drugs reaching their target due to changes in absorption, distribution, and metabolism lead to drug resistance. High DNA repair activity of cancer cells counterbalances the DNA damage given by chemotherapy. Finally, mutations in the apoptotic pathways, such as those involving p53 and Bcl-2 family proteins, allow cancer cells to bypass or minimize apoptosis and thereby survive despite the chemotherapeutic treatment[11].

2. Toxicity and Side Effects

Chemotherapeutic agents lack specificity, affecting both cancerous and normal rapidly dividing cells. This nonspecificity contributes to a range of adverse effects, including myelosuppression, leading to bone marrow toxicity, anemia, neutropenia, and thrombocytopenia. This increases the risk of infections and bleeding. The gastrointestinal toxicity manifests as nausea, vomiting, diarrhea, and mucositis due to its effect on the rapidly dividing cells in the gastrointestinal tract. Anthracyclines, mainly Doxorubicin, are generally linked to cardiotoxicity, which causes irreversible damage to the heart. The main agents responsible for neurotoxicity are taxanes and vinca alkaloids, leading to peripheral neuropathy that is responsible for a significant decrease in quality of life[11].

3. Tumor Heterogeneity

Breast cancer is a heterogeneous disease with multiple subtypes characterized by distinct molecular and genetic profiles. This heterogeneity complicates treatment as different subtypes respond differently to chemotherapy. For example, hormone receptor-positive breast cancer generally responds well to hormone therapy but may exhibit resistance to certain chemotherapeutic agents. HER2-positive breast cancer is often treated with targeted therapies in combination with chemotherapy, but resistance to HER2-targeted agents can develop. Triple-negative breast cancer lacks estrogen, progesterone, and HER2 receptors, making it less responsive to targeted therapies and more reliant on chemotherapy, with a higher propensity for resistance[11].

VI. Limitations of Chemotherapy

While chemotherapy remains a critical component of breast cancer treatment, its

limitations underscore the need for improved therapeutic strategies:

1. Non-Specificity: Chemotherapeutic drugs target the normal rapidly dividing cells as well along with the cancer cells leading to significant toxicity and adverse effects. This non-specificity limits the maximum tolerable dose and can compromise treatment efficacy.

2. Short Duration of Response: Novel vehicles for optimized drug delivery and sustained bioavailability could potentially alter the disease trajectory over time, improving quality of life during continued therapy.

3. Quality of Life: The severe side effects associated with chemotherapy, including fatigue, hair loss, gastrointestinal issues, and cognitive impairment (often referred to as "chemo brain"), can severely impact patients' quality of life. Managing these side effects requires a multidisciplinary approach and can necessitate dose reductions or treatment interruptions.

4. Financial Burden: While chemotherapy shows potential for combating cancer, its cost demands considering patients' economic wellness alongside physical health. Exorbitant drug prices combined with expenses from supportive medications and hospital stays for side effects create substantial financial stress on individuals and medical infrastructure. This weighty monetary strain risks treatment compliance and prognoses.

5. Immunosuppression: Chemotherapy-induced myelosuppression weakens the immune system, increasing the risk of infections. This require close clinical monitoring and management to avert critical health consequences. This immunosuppressive effect can be life-threatening and careful surveillance is important for patients already battling with cancer.

Although chemotherapy is the first line of treatment for breast cancer, it has many challenges and limitations. These include drug resistance, high toxicity, tumor heterogeneity, and non-specificity of the chemotherapeutic agents, thereby increasing the need for more targeted and effective therapeutic strategies. Advances in molecular biology and cancer genomics are paving new approaches for personalized medicine that aim to provide treatment based on the individual patient's tumour profile. In addition, integrating novel drug delivery systems, such as solid lipid nanoparticles, holds promise for enhancing the therapeutic efficacy of chemotherapeutic agents like docetaxel trihydrate while minimizing adverse effects[12].

Understanding the mechanisms underlying chemotherapy resistance is essential for developing strategies to overcome treatment failure in breast cancer. Mechanisms include alterations in drug targets, activation of survival pathways (e.g., PI3K/Akt/mTOR), and interactions within the tumor microenvironment that promote resistance and disease progression. Targeted therapies aimed at overcoming these resistance mechanisms are under investigation to improve treatment outcomes and prolong survival in patients with advanced disease.

Despite significant advancements in breast cancer treatment, several knowledge gaps exist regarding the optimal delivery of these drugs and integrating alternative therapies to enhance their outcomes. The response and effect of drugs comes in question due to their varied side effects, majorly, developing resistance, low bioavailability, and weakened immune system. This needs a robust delivery system that can increase their shelf life and deliver the drug directly to the affected area. Exploring efficient drug delivery systems such as solid lipid nanoparticles and increasing their efficiency is a target of the ongoing treatment modalities that can lead to

improved and targeted therapeutics for breast cancer.

VII. Need for Targeted and Effective Therapies

The complexity of breast cancer underscores the urgent need for targeted therapies that deliver therapeutic agents specifically to tumor cells while sparing normal tissues. Targeted therapies exploit molecular vulnerabilities within cancer cells, offering the potential for enhanced efficacy and reduced toxicity compared to conventional treatments. However, challenges remain in identifying effective targets and overcoming mechanisms of resistance to these targeted agents.

VIII. Importance of Advanced Drug Delivery Systems

Recent advances in precision drug delivery can greatly enhance pharmacokinetics, biodistribution and therapeutic efficacy of anti-cancer drugs. These systems also offer controlled drug release, long circulation time, tumor-targeting capabilities leading to higher bioavailability of the drugs and reduced side effects as a result. Solid lipid nanoparticles are one such system that have emerged as potential drug carriers for anticancer drugs, being biocompatible in nature and providing great stability to the formulation besides ability of encapsulating both hydrophilic and lipophilic drugs.

Drug delivery systems that have been engineered to improve the therapeutic performance of pharmaceutical products. By participating in targeted drug delivery, these systems provide the potential for more efficacy and less systemic toxicity. The development of innovative drug delivery systems is crucial for addressing the limitations of conventional drug formulations and improving patient compliance and treatment outcomes in oncology and other therapeutic areas.

Nanoparticles, liposomes, micelles and polymer-based carriers are some of the drug delivery systems that have been designed to enhance targeting specificity for therapeutic agents. Each system offers unique advantages for drug encapsulation, release kinetics, and targeting capabilities, depending on the physicochemical properties of the drug and the desired therapeutic outcome[13]. Nano-carriers, such as SLNs have attracted increasing attentions in tumor therapy because of their potential to overcome physiological barriers and deliver the drug specifically at tumour site.

IX. Overview of Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are an example of such colloidal drug delivery systems. They are advantageous over their conventional drug delivery systems such as better stability, controlled release profile and an increased biocompatibility. The lipid matrix of SLNs could protect the encapsulated drugs from degradation and assists in efficiently delivery to target tissues hence increasing therapeutic efficacy with less dosing intervals[13].

I. Composition and Structure of SLNs

SLNs are compositions of lipids (e.g., triglycerides, phospholipids and waxes) that solidify into a matrix for entrapment therapeutic molecules. SLN surface modification with surfactants or polymers help in stabilizing and improving them biocompatibility, which is important for cellular uptake targeting. Due to the structural integrity of SLNs, smart drug release and prolonged blood circulation leads to increased bioavailability as well as therapeutic efficacy.

ii. Advantages over Traditional Delivery Systems

SLNs have definite advantages over other

conventional drug delivery systems such as polymeric nanoparticles, liposomes, and emulsions. SLNs offer continuous drug release kinetics and improved biocompatibility with low stability, unlike polymeric nanoparticles showing rapid burst release profiles guarded by cell damage. Whereas liposomes and micelles are plagued by low drug loading capacity and batch-to-batch variability, SLNs can offer reproducible encapsulation efficiency of just about all drugs as well as tunable release kinetics.

iii. Mechanisms of Drug Release from SLNs

The mechanisms governing drug release from SLNs are influenced by lipid composition, particle size, and surface characteristics. Drug release may occur through diffusion from the lipid matrix, erosion of the lipid core, or a combination of both mechanisms, depending on the physicochemical properties of the encapsulated drug and the lipid matrix. These mechanisms can be tailored to achieve desired release profiles, ranging from sustained release over an extended period to rapid release in response to specific stimuli.

iv. Efficiency of SLNs Compared to Other Delivery Systems

The formulation efficiency is influenced by lipid composition, particle size and surface characteristics that effects on drug release mechanism from SLN. For instance, SLNs have been shown to enhance the bioavailability of poorly water-soluble drugs, such as docetaxel trihydrate, by improving their solubility and cellular uptake. Comparative studies have highlighted the ability of SLNs to achieve higher drug concentrations at the target site while minimizing systemic exposure, thereby reducing the risk of off-target effects, and improving therapeutic outcomes.

v. Comparison with Polymeric Nanoparticles, Liposomes, and Micelles

Solid lipid nanoparticles have several advantages over polymeric nanoparticles, liposomes, and micelles due to higher stability, biocompatibility, and drug loading capacity. Table 1 compares each of these with different features to understand why SLNs should be preferred. SLNs, on the other hand, have demonstrated slow drug release kinetics and improved stability (as compared to polymeric nanoparticles) which make them more suitable for delivery both in vitro and in vivo. Liposomes and micelles also experience a restricted drug loading capacity, as well variety between batch to batch for their SLNs instead of the reproducibility in entrapment efficiency & controlled released kinetics.

vi. Stability and Biocompatibility of SLNs

The stability and biocompatibility of SLNs are important concerns in their application as cancer drug delivery systems. SLNs hold good stability under physiological conditions making the sustenance of premature release and long circulation times in blood stream. Because of biocompatible lipid components used in the preparation, SLNs were found to have low immunogenicity and toxicity rendering them a suitable system for parenteral administration as well as targeted drug delivery applications. In addition to, the biocompatibility and specificity of SLNs can be enhanced by functionalizing with suitable polymers or target ligands for efficient cell- as well tumor specific uptake14.

Table 1: Comparison of different types of delivery systems with various important features.

Feature	Solid Lipid Nanoparticles (SLNs)	Polymeric Nanoparticles	Liposomes	Micelles
Stability	High stability with sustained drug release profiles	May exhibit burst release kinetics and poor stability	Moderate stability, sensitive to environmental conditions	Moderate stability, potential for aggregation
Biocompatibility	Enhanced biocompatibility	Variable biocompatibility, dependent on polymer type	High biocompatibility, well-tolerated in the body	High biocompatibility, well-tolerated in the body
Drug Loading Capacity	High, with reproducible drug encapsulation	Variable, can be lower due to polymer characteristics	Limited drug loading efficiency	Limited drug loading efficiency
Release Kinetics	Controlled release kinetics	Burst release followed by sustained release	Initial burst release followed by sustained release	Initial burst release followed by sustained release
Batch-to-Batch Variability	Low, offers reproducible drug encapsulation and release kinetics	Moderate to high variability depending on synthesis process	High variability, sensitive to preparation methods	High variability, sensitive to preparation methods
Production Complexity	Moderate, scalable for industrial production	High, often requires complex synthesis and purification processes	High, complex preparation methods and stability issues	Moderate to high, requires careful control of surfactant concentration
Cost of Production	Moderate	High, due to complex materials and processes	High, due to liposome synthesis and stability requirements	Moderate to high, dependent on surfactant and stabilizer costs
Application Versatility	Suitable for a wide range of drugs and delivery routes	Suitable for specific drugs and delivery routes	Suitable for hydrophilic drugs, limited for hydrophobic drugs	Suitable for hydrophobic drugs, limited for hydrophilic drugs

vii. Targeting Capabilities and Drug Loading Capacity of SLNs

Solid lipid nanoparticles can be engineered to target specific tissues or cells through surface modification with ligands or antibodies that recognize overexpressed receptors on cancer cells. Accelerating the uptake of tumor-targeting nanoparticles by cells is an effective way to increase drug accumulation at the site where it needs to be and minimize systemic exposure, which causes off-target toxicity. Formulation adjustments like the selection of lipid composition, particle size and drug to lipid ratio are reported by researchers for obtaining highest therapeutic efficiency through optimal drug loading capacity of SLNs. Given their versatility, SLNs have the potential to serve as delivery vehicles for a broad array of therapeutic agents - including chemotherapeutics and biologics - across oncology and other disease indications[11].

viii. Role of SLNs in Breast Cancer Treatment

In breast cancer, SLNs loaded with docetaxel trihydrate offer several advantages over conventional formulations. They enhance drug accumulation in tumor tissues while minimizing systemic exposure, thereby reducing the risk of adverse effects associated with high-dose chemotherapy. SLNs can passively target tumors through the enhanced permeability and retention effect, where nanoparticles accumulate in tumor vasculature due to leaky blood vessels and impaired lymphatic drainage. This targeted delivery approach improves the therapeutic efficacy of docetaxel trihydrate by increasing its concentration specifically within cancerous tissues. Innovations in drug delivery, such as encapsulating docetaxel trihydrate in solid lipid nanoparticles are being explored to further improve its therapeutic index and reduce side effects. These advanced formulations aim to enhance drug stability, target specificity, and reduce systemic toxicity, making docetaxel trihydrate an even more attractive option in cancer therapy[13].

Conclusion

Breast cancer remains a major global health

challenge, with significant variability in incidence, treatment responses, and patient outcomes. While conventional chemotherapeutic approaches have improved survival rates, they are often limited by drug resistance, systemic toxicity, and tumor heterogeneity. The emergence of advanced drug delivery systems, particularly solid lipid nanoparticles (SLNs), offers promising avenues to overcome these limitations. By enhancing drug stability, improving bioavailability, and facilitating targeted delivery, SLNs have the potential to revolutionize breast cancer therapy.

Further research into personalized treatment strategies, novel drug formulations, and innovative delivery mechanisms is essential to optimize therapeutic efficacy while minimizing adverse effects. The integration of SLNs with targeted therapies represents a significant step toward precision medicine in oncology, ultimately improving patient quality of life and treatment outcomes. Continued advancements in nanotechnology and molecular oncology will be instrumental in shaping the future of breast cancer management, providing more effective and less invasive treatment options.

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