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Role of Terpenoids Active Ingredients Targeting for Neuroprotective Agents

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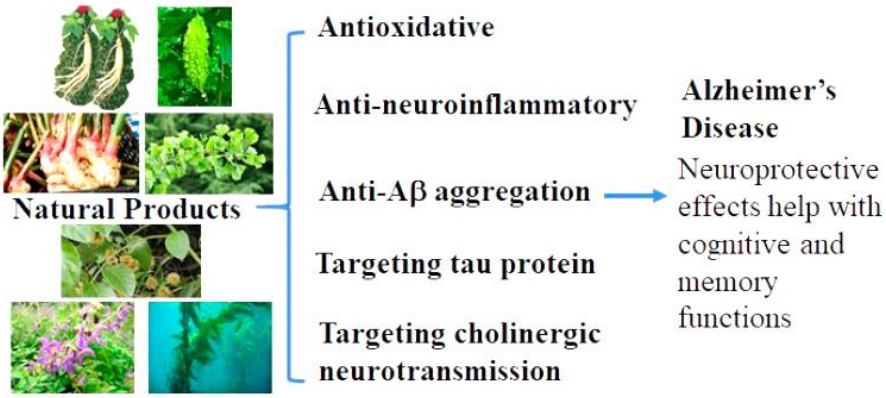
GRAPHICAL ABSTRACT



ABSTRACT

Neuroinflammation is a characteristic sign of a wide variety of neurodegenerative diseases, including Alzheimer's and Parkinson's, amongst others. Microglia, which are native immune cells found in the brain, become activated very quickly in response to a brain infection or injury. When microglia become overactivated, their production of pro-inflammatory and cytotoxic chemicals can become unregulated and uncontrolled, which is the primary cause of neuroinflammation. Microglia are principally responsible for neuroinflammation. As a result, the investigation of novel approaches to reduce neuroinflammatory reactions is an essential component of neurodegenerative disease treatment. In the research of brain inflammation, bacterial lipopolysaccharide is frequently used. This compound is responsible for the initiation of a number of significant cellular processes that significantly contribute to the pathophysiology of neuroinflammation.

Keywords- Neuroinflammation, Terpenoids, Neurodegenerative, Herbal Products.

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I. INTRODUCTION

The brain is amazing in that it has the ability to switch gears, to use a metaphor. During wakefulness, the brain is primarily focused on cognitive and behavioural activities, whereas during sleep, it shifts its attention to homeostatic functions[1]. The remarkable improvements in medical care and scientific research have led to a significant rise in the average longevity, which is projected to approach 120 years by the year 2050[2]. Along with the proportion of elderly people in the population, the prevalence of age-related ailments including neurological conditions is expected to skyrocket[3].

Alzheimer's disease (AD), the most common form of dementia, is responsible for between 50 and 60 percent of all instances of the disease. Alzheimer's disease (AD) affects approximately forty percent of the elderly population that is above the age of 85, and the prevalence rate of AD increases with age[4]. Patients who have Alzheimer's disease have a decline in their cognitive ability and a loss of short-term memory in the disease's early stages. As the disease progresses, patients have difficulty communicating and thinking coherently; in addition, they lose the ability to remember things that occurred in the distant past. Patients who have reached the late stage of the disease require care around the clock due to symptoms such as impaired language skills, depression, hostile attitude, and psychosis[5].

Alzheimer's disease is characterised pathologically by the presence of senile plaques, also known as SPs. Extracellular beta-amyloid (A) deposits can be found encircled by dystrophic neurites and microglia. -secretase and -secretase perform a step-by-step cleavage of amyloid precursor protein (APP), which results in the production of A [6]. Alzheimer's disease (AD) patients either have an increased production of A or a decreased clearance of A, both of which contribute to A accumulation in the brain. Patients with Alzheimer's disease who have mutations in the APP gene (also known as familiar AD) produce an abnormally high amount of the protein A. This is linked to an earlier onset of the disease (in the 30s). In the brain, the monomeric form of A that is soluble can self-aggregate into A oligomers, which can contain anywhere from two to six A peptides [7]. These A oligomers are more harmful to cells than the monomeric or fibrillar form [8]. According to the amyloid hypothesis [6, therefore], the fundamental source of the development of Alzheimer's disease is an excessive amount of toxic A. In particular, the quantities of A oligomers play an important part in the development of Alzheimer's disease [9], and are connected with the degree of cognitive impairment in people who have Alzheimer's disease. When A oligomers form, oxidative stress and inflammation are produced, both of which contribute to synaptic dysfunction [10]. A recent study concluded that A is responsible for the death of neurons because it binds to nuclear factor of activated T cells receptors (NGFRs) such as p75NTR and activates the c-Jun N-terminal kinase signal downstream of these receptors. In addition, stimulating the N-methyl-D-aspartate (NMDA)-type glutamate receptor (NMDAR) can cause oxidative stress and loss of synaptic connections [11]. However, A oligomers bind to and control these channels presynaptically at glutaminergic and gamma-aminobutyric acid-ergic synapses [12][13]. P/Q current is essential for neurotransmission and synaptic plasticity.

Inside neurons, hyperphosphorylated tau proteins can form paired helical filaments (PHFs), which are referred to as neurofibrillary tangles (NFTs) [14]. NFTs are yet another destructive component of Alzheimer's disease. By attaching to microtubules, the tau protein, which is typically located in neurons, is able to maintain the microtubules' stable state and contribute to their assembly. On the other hand, defects in tau hyperphosphorylation significantly reduce the protein's affinity for microtubules, which results in the buildup and creation of PHFs [15]. When Wnt signalling is downregulated as a result of binding to the Frizzled receptor, which is a Wnt protein acceptor [16], neurotoxic hyperphosphorylated tau proteins, also known as NFTs, are generated. The significance of NFTs in the aetiology of Alzheimer's disease is confirmed by a report that demonstrates a link between the amounts of hyperphosphorylated tau protein in cerebrospinal fluid (CSF) and the degree of cognitive impairment in people who have Alzheimer's disease. [17]. A is responsible for inducing both the phosphorylation of tau protein and the aggregation of tau into [18]. Both of these processes are critically crucial in neurodegenerative disorders. Tau phosphorylation is another factor that can decrease the death of A-induced cells [19]. The concept that tau phosphorylation is essential to the development of A-induced Alzheimer's disease is given more support by these findings.

Acetylcholinesterase (AChE) inhibitors are the type of Alzheimer's disease medication that is currently available on the market the most frequently. The quantity of acetylcholine (ACh) that is present in the brains of Alzheimer's disease (AD) patients has been shown to have an inverse relationship with the severity of dementia that these people experience [20]. A number of AChE inhibitors, including tacrine, donepezil, rivastigmine, and galantamine, have all been the subject of research into their possible use as pharmacotherapies for Alzheimer's disease[21].AChE inhibitors are able to improve the quality of life for those who have Alzheimer's disease, but they do not slow or stop the progression of the disease. As a consequence of this, there is an urgent need for innovative therapeutic drugs that are capable of blocking the processes that cause

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disease [2 2].For the treatment of Alzheimer's disease (AD), the NMDA receptor antagonist memantine has been given approval by the Food and Drug Administration (FDA) of the United States [23]. Patients with Alzheimer's disease (AD) ranges from moderate to severe gain significantly from taking this medication in terms of their ability to operate linguistically and cognitively in general [24,25].

People have been seeking treatment for their health issues using natural therapies for a very long time. 63% of all medications were derived from natural sources between the years 1981 and 2006 [30], which can be attributed to the advances made in the processes of extracting and isolating natural substances as well as the efforts made to develop natural products as prospective therapeutics. There has been a significant amount of research conducted with the goal of locating and producing natural anti-AD agents [26].

Isolation of galantamine from both the bulbs and the blooms of snowdrops Because of the plant's inhibitory effect against AChE, the Food and medication Administration (FDA) has given Galanthus woronowii (Amaryllidaceae) approval as an anti-AD medication.[27]. Numerous studies have been conducted on Alzheimer's disease to investigate the anti-degenerative effects of ginsenosides and other terpenoids found in Panax ginseng (Araliaceae)[28]. It is more likely that one of these molecules will be found to have anti-AD activity if terpenoids are considered to be the natural product group that is both the largest and most diversified in terms of their composition[29-32] This article explores the possibility of using terpenoids, also known as terpenes, as therapeutic agents in the treatment of Alzheimer's disease[33]

1.1 Terpenoids

Terpenoids can be found in a wide variety of creatures, including plants, bacteria, fungus, mammals, marine life, sedimentary rocks, and oils [34]. These substances are natural chemicals that have been generated through the process of biosynthesis; they are structurally diverse and are frequently referred to as "terpenes." Terpenoids are compounds that have an integral number of C5 units and are formed from the basic branch C5 unit isoprene (2-methyl-1,3-butadiene) [35-36] The name "terpenoid" refers to a molecule that has an integral number of C5 units. Terpenoids are comprised of a wide variety of different structural subtypes, each of which confers a specific set of biological effects on the larger group of molecules that they belong to [37-38]. These effects include the creation of cell membranes, the transmission of signals, immunomodulation, the regulation of inflammation, antioxidation, and the inhibition of many enzymes[39-40]

Terpenoids and the semisynthetic derivatives of terpenoids have the potential to be useful neuroprotective medicines in the treatment of a variety of neurological and cognitive disorders. Celastrol, ginsenosides, oleanolic acid, ursolic acid, asiatic acid, erythrodiol, and several triterpenoid saponins have been investigated for years and have shown efficacy in protecting the brain against processes including neuroinflammation and oxidative stress [5,6]. Other triterpenoid saponins have also shown efficiency in protecting the brain against these processes. In recent years, there has been an increased level of interest in a variety of other compounds, such as lupeol, rosmarinic acid, resveratrol, betulinic acid, pomolic acid, maslinic acid, uvaol, tormentic acid, and erythrodiol [5].

These compounds can exist as free compounds, conjugates, or saponins (containing one or more sugar units) and can be found in higher plants, including common edible and nonedible plants. [5,7,8] These compounds can be found in higher plants. Memory and cognitive function have both been shown to be improved with the usage of these terpenoids, which have been utilised in traditional medicine for millennia. Some of them are now undergoing preclinical or clinical testing, while others are already authorised for use in human patients. Terpenoids have a wide variety of structures and activities, which has prompted interest in researching the commercial application of these molecules. This attention highlights the practical significance of terpenoids as alternative therapies for psychiatric diseases.

Psychiatric disorders are characterised by recurrent patterns of altered behaviour that are associated with considerable emotional suffering or functional deficits in daily life. This class of pathology can be distinguished from other neurological disorders due to the modifications in behaviour and mental state that are typical of those associated with malfunction and structural damage of the central nervous system. In this review, we made use of the references for some of the major types of illnesses that are detailed in the Diagnostic and Statistical Manual of Mental illnesses (DSM) [9], which is the most frequently used system for classifying psychiatric diseases and standardising the diagnostic criteria for them. Multiple pathophysiological factors, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, neuronal degeneration, and synaptic loss, have been linked to the development of psychiatric illnesses [10].

Octocorals, a subclass of sessile invertebrate animals that include soft corals, sea pens, and blue corals, are the most prolific source of terpenoids in marine ecosystems where plants do not exist. Octocorals produce terpenoids by a process known as octocorral terpenoids.

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Figure 1: Role of Terpenoids in Neuro disease

II. PHYTOCHEMICALS IN COSMETICS: TERPENOIDS

The complex pathogenic mechanisms of Alzheimer's disease (AD), which is a neurodegenerative illness that worsens with age and is responsible for the majority of instances of dementia, are not completely understood. In addition to the genetic and environmental factors that are thought to play a role in the aetiology of Alzheimer's disease (AD), researchers have put forward a number of hypotheses in an effort to explain this complex disorder. The hypotheses that have received the most attention are the A cascade hypothesis, the tau hypothesis, the inflammation hypothesis, the cholinergic hypothesis, and the oxidative hypothesis [21]. Because the extracellular deposition of A peptides as senile plaques (SP) and NFTs will result in neuron loss, vascular injury, and dementia [22], the A cascade hypothesis proposes that A peptides are the causative agent in Alzheimer's disease (AD). NFTs are primarily composed of tau protein, which is a microtubule-associated scaffold protein that is concentrated in the axons of neurons. They are regarded as another intracellular characteristic of Alzheimer's disease (AD). Aggregation of it causes damage to axons, which in turn leads to neurodegeneration [23]. In recent years, the inflammatory hypothesis has emerged as a leading candidate for the next major pathology associated with Alzheimer's disease (AD). This idea involves a prolonged immunological response in the brain. Continued activation of immune cells in the brain, such as microglia, leads to the creation and release of a large number of proinflammatory cytokines, which not only results in the death of neurons but also makes it easier for both amyloid beta and tau disorders to develop [24]. Damage to cholinergic neurons is a key pathogenic change that has been largely regarded as a correlation with cognitive impairment in people with Alzheimer's disease (AD). Therefore, according to the cholinergic hypothesis, a malfunction of cholinergic neurons in the brain is a significant contributor to the cognitive loss that occurs in Alzheimer's disease [25]. The fact that cholinesterase inhibitors are a therapy option for Alzheimer's disease lends credence to this notion. It has also been found that oxidative stress plays an important part in the aetiology of Alzheimer's disease. Direct supporting evidence has indicated that Alzheimer's disease is always accompanied by high cellular oxidative stress in the brain. This is caused by the increased generation of free radicals, increased lipid peroxidation and decreased polyunsaturated fatty acid, increased protein and DNA oxidation, as well as the accumulation and aggregation of A, which also induces oxidative stress [26]. Direct supporting evidence has indicated that this is always the case.

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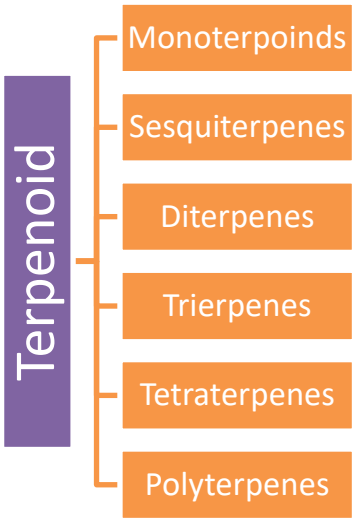

Figure 2: Types of Bioactive

2.1 Terpenoids Compounds

2.1.1 Neuroprotective Strategies for AD

Because there is a significant body of evidence demonstrating that the buildup of AD is the fundamental causal factor in the pathogenesis of Alzheimer's disease [27], reducing A has become the primary strategy in the development of new therapies for Alzheimer's disease [28]. However, it is possible that effective Alzheimer's disease therapy regimens will require the concurrent application of more than one neuroprotective drug. Several molecular targets that are mediating the pathophysiological processes that are occurring in Alzheimer's disease have been identified as a result of meticulous investigation of these processes. These targets could be used as a guide in the creation of neuroprotective techniques that have the potential to provide significant yields [29]. Possible neuroprotective strategies concentrate on the regulation of detrimental intraneuronal mechanisms that are induced by A and other toxic stimuli. This is accomplished by specialised interaction with a variety of neuronal targets [30]. The discovery of small molecules that can block A interactions with its extracellular and intracellular targets [31], minimise stress kinase signalling cascades [32], prevent caspase activation [33] and pro-apoptotic protein expression [34], inhibit excessive tau protein phosphorylation [35], counteract cholinergic function loss [36], promote the trophic state and neuron plasticity [37], and hinder reacquaintance [38] are all examples of practical neuroprotective approaches It is important to note that the neuroprotective agents demonstrate their effects in more than one way, which is the case with some of the agents. This is especially relevant when considering combinations and extracts of natural items that contain more than one bioactive ingredient. Therefore, the neuroprotective effects that can be obtained from combinations and extracts of natural products are always multidimensional, and they offer an advantage for the treatment of AD in comparison to the use of a single ingredient. Additionally, the additive or synergistic action of crude extracts or mixtures can eliminate some of the side effects associated with the predominance of a single xenobiotic compound, providing a more comprehensive spectrum of activity and minimising the chances of pathogens developing resistance [41]. This action can be accomplished by combining the effects of multiple xenobiotic compounds.

2.1.2 Neuroprotective Effects from Natural Products

It has been demonstrated that natural products can perform neuroprotective effects through virtually all of the many molecular mechanisms described in the previous paragraph[42]. The observed neuroprotective effects, when focusing on the mixtures and extracts of natural products, have typically been recognised as being obtained through anti-oxidative or anti-neuroinflammatory activities, preventing the aggregation of A and tau protein, as well as enhancing cholinergic signalling[43]. In addition, it has been found that these effects can be obtained by enhancing cholinergic signalling. There is sufficient evidence to support the hypothesis that the start and course of Alzheimer's disease (AD) could be slowed down or possibly avoided by using natural ingredients[44].

2.2.1.1 Monoterpenes

Monoterpenes are compounds that have several beneficial properties, including the ability to inhibit the growth of cancer cells and fight bacteria[45]. Effects that are antifungal5 and antinociceptive4 (which mean they reduce sensitivity and pain) are also included among its attributes. You most likely already have some experience with monoterpenes derived from essential oils. These are light hydrocarbons that are soluble in alcohol or an oil. Their structure consists of two units of isoprene (C10H16), thus they aren't very dense. Essential oils that have been pressed or distilled frequently contain monoterpenes[46].

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The most well-known examples are linalool (a monoterpenol) from lavender essential oil and geraniol (a monoterpenol) from rose or geranium essential oils. Both of these examples come from essential oils[47].

2.2.1.2 Sesquiterpenes

Three isoprene units make up sesquiterpenes (C15H24). Still sufficiently light to be distilled into the essential oils, the molecules are. The most prominent members are beta-bisabolene (basil and oregano) and farnesol (jasmine, rose, ylang-ylang)[48].

Antifungal, antibacterial, anaesthetic[6], antioxidant, anti-inflammatory[7], and deodorant characteristics are all possessed by sesquiterpenes[49].

2.2.1.3 Diterpenes

Diterpenes are made up of four C20H32 isoprene units. The molecule is too heavy to be distilled, and when they are present at all, diterpenes are typically found in resinoid essential oils. Ginkgolides are diterpenes taken from the leaves of Ginkgo biloba[8]. They are used in pharmacies in cardiovascular treatments medications for the treatment of migraines, and medications for the prevention of dementia and Alzheimer's disease. Diterpenes from coffee called cafestol and kahweol have anticancer effects[50].

2.2.1.4 Triterpenes

They are made up of 6 C30H48 Isoprene units. Triterpenes are the source of steroids, and saponins (plant-based surfactants) can be classified as triterpene or steroid derivatives[51].

The most notable member of this category is squalene. Since squalene has a poor shelf life and a high Iodine value, it is hydrogenated to create squalene, a highly popular emollient that most of you use in your cosmetics[52]. Squalene can be made from whale liver oil, amaranth, wheat germ, or olive oil. This group includes all those great phytosterols found in plant oils and extracts. They have anti-inflammatory, anti-aging, and antioxidant effects. The most notable members of this category are stigmasterol, campesterol, and stigmasterol. They can be found in unprocessed plant oils such olive oil, macadamia oil, soybean oil, wheat germ oil, and rice bran oil[53].

***2.2.1.5* Tetraterpenes**

Carotenes stand in for these. Tetraterpenes (C40H64) are made up of 8 isoprene units. These molecules are large and prominently coloured. Tetraterpenes include lycopene (found in tomatoes) and crocin (found in saffron). They have photoprotective[13], antioxidant[14], and anti-inflammatory activities in skin care[54][55]

2.2.1.6 Polyterpenes

Many isoprene units make up Polyterpenes. The most noticeable member of this group is natural rubber. Another Polyterpenes is latex, which is produced in the vesicles of laticifers (plants that produce latex)[56] These do not matter for our needs. Only when using specific plant oils (like avocado oil) in your formulations should you be concerned about potential latex allergies[57].

III. PLANTS WHICH CONTAIN TERPENOIDS

All plants create a wide variety of terpenoid compounds, which can act as phytohormones, instruments for protein modification, antioxidants, and a variety of other functions. There are several hundred different terpenoids[58][59].

The synthesis of terpenes requires a number of different building blocks, the most important of which are the isopentenyl diphosphate (IPP) unit and its isomer, dimethylallyl diphosphate (DMAPP)[60].Terpenes are found in high concentrations in the leaves, flowers, stems, and roots of higher plants such as citrus, conifers, and eucalyptus. These terpenes have antimicrobial and antifungal properties[61].

Figure 3: Terpenoids extract from different herbs for medicament of Neuroprotective agent Cannabis

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IV. CANNABINOIDS & ENDOCANNABINOIDS SYSTEMS

Since ancient times, humans have been aware of both the recreational and pharmacological benefits associated with marijuana. The first source that provides evidence of the beneficial effects of marijuana for medical purposes is a Chinese medical manual that dates back to about 2700 B.C. [62]. In the most recent decades, the scientific community has increased its examination of the chemical properties of the major actives in marijuana extract; however, in recent years, the attention has been concentrated on understanding the biological mechanism involved in their myriad effects [63]. Marijuana, also known as Cannabis sativa, includes around 500 unique chemicals, 120 of which are classed as phytocannabinoids and have a variety of chemical structures as well as pharmacological effects [64]. Cannabinol (CBN) and cannabidiol (CBD) were the first compounds to be isolated from marijuana extract in the year 1940 [65]. This was followed by the isolation of the primary psychoactive component of marijuana ()-trans-9-tetrahydrocannabinol (9-THC or THC) in the year 1964 [66]. The discovery of the endocannabinoid system in the early 1990s [67] is regarded as a watershed moment in the more recent annals of medical marijuana's application as a treatment for a variety of conditions. A number of years later, the isolating, cloning, and expression of the CB1 receptor was followed by the characterisation of the CB2 receptor [68]. Both of these receptors are connected to the pathway for signal transduction that is mediated by Gi/o proteins[69]. In recent years, several other receptors have been associated as part of the endocannabinoidergic system. These receptors were able to modulate the effect of phyto- and synthetic cannabinoids and endogenous ligands. These receptors include the orphan G protein-coupled receptors GPR3, GPR6, GPR12, and GPR55 and the nuclear hormone peroxisome proliferator-activated receptors (PPARs) [70,71]. Both the peripheral and the central nervous systems contain an expression of the CB1 receptor, which can be found in a presynaptic location the majority of the time. Cannabinoids are known to have a number of physiological effects, some of which include an impairment in the formation of short-term memory, altered motor activity, and anxiety [72]. The distribution of CB1 in the brain is consistent with these effects. The hippocampus, areas of the cortex, and the cerebellum have all been found to contain a significant amount of CB1 receptors. Only lately have studies shown the presence of CB1 receptors in astrocytes [73][74]. These investigations found that activation of CB1 receptors was associated with an increase in calcium uptake and release of glutamate. On the other hand, the CB2 receptor is mostly expressed in the cells and tissues of the peripheral immune system. CB2 has been found in the neurons of the ventral tegmental area and the hippocampus region of the brain [75]. However, its presence in the brain is extremely scarce in comparison to that of CB1. Nevertheless, it appears that CB2 plays a significant part in the functions of macrophages and microglia [76,77]. When microglia are activated, there is a significant rise in the expression of CB2, and activation of CB2 leads to a reduction in the synthesis of chemicals that promote inflammation [78]. The discovery of endogenous substances that were able to modify cannabinoid receptors was yet another significant step in the process of elucidating the brain's cannabinoidergic system. The arachidonic acid derivatives have received the greatest research and have been the most thoroughly characterised. N-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG) [79]. Endocannabinoids are distinguished from other cannabinoids in that they are not stored in vesicles and instead are generated postsynaptically on demand [80]. Endocannabinoids are released in the synaptic cleft from the postsynaptic neurons, as shown in figure, which reported a schematic picture of the endocannabinoidergic system at the neuronal level[81]. They do this by interacting with the cannabinoid receptors that are found on the presynaptic neurons and so negatively influencing the release of GABA and glutamate [82]. The half-lives of anandamide and 2-AG are exceptionally short. Following their production in the synaptic cleft, these chemicals undergo re-uptake and are hydrolytically inactivated by the integral membrane enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase, respectively (MAGL) [83][84]. Memory, memory acquisition, and memory consolidation processes like long-term potentiation are all affected by the release of anandamide and 2-AG in the brain [85]. This is an extremely remarkable finding[86].

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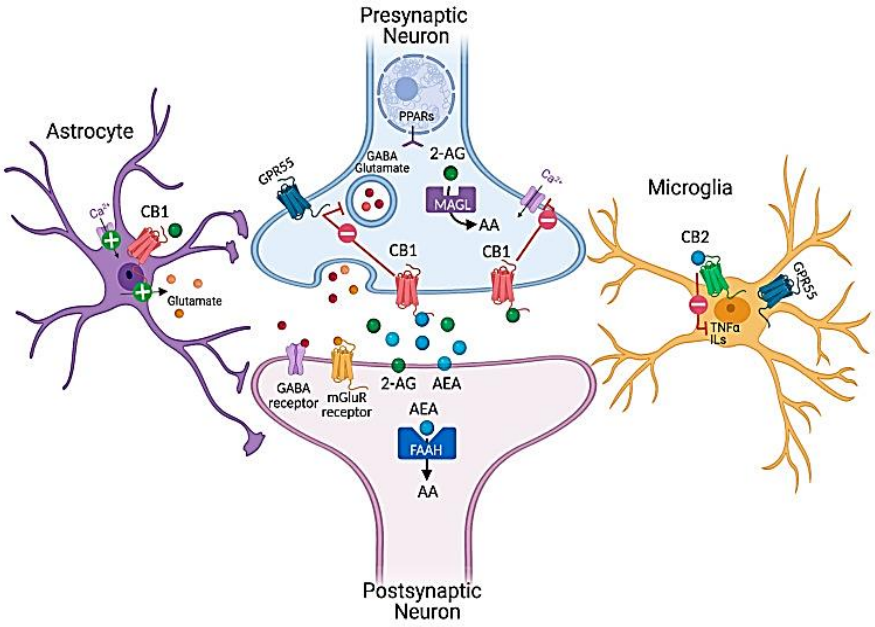

Figure 4: The endocannabinoidergic system in the brain is depicted below in a schematic form foryour viewing pleasure. A possible distribution of endocannabinoid receptors across the neurological and glial systems is presented here. Both pre- and postsynaptic neurons have been found to have enzymes that are involved in the manufacture and breakdown of endocannabinoids.In GABAergic neurons and glutamatergic neurons, respectively, activation of presynaptic CB1 receptors has the effect of negatively modulating cell calcium influx as well as the release of GABA and glutamate neurotransmitters. Instead, activation of CB1 receptors in astroglia results in a positive modulation of calcium influx as well as glutamate release. In microglia, activation of the CB2 receptor has a suppressive effect on the production of TNF and ILs. AA stands for arachidonic acid, 2-AG for 2-acylglycerol, AEA for anandamide, PPARs for peroxisome proliferator-activated receptors, FAAH for fatty acid amide hydrolase, MAGL for monoacylglycerol lipase, mGluR for metabotropic glutamate receptors, ILs for interleukins, and TNF- for tumour necrosis factor alpha.

4.1 Turmeric

The poor bioavailability of curcumin is a key critique [86], despite the fact that it has various positive effects on health. Low absorption, quick metabolism, chemical instability, and swift clearance from the system are some of the possible explanations that have been suggested [87]. According to the findings of a number of research conducted on animals, around 90% of ingested curcumin is removed in the faeces. In an effort to find a solution to this issue, numerous approaches have been explored and tested to increase the bioavailability of curcumin. A few examples of adjuvants include piperine, liposomal curcumin, curcumin nanoparticles, phospholipid complexes, and structural analogues of curcumin such as turmeric oil [88]. As a direct consequence of these efforts, higher blood concentrations have been spotted. On the other hand, substantial human clinical tests contrasting the therapeutic potencies and pharmacodynamic responses of these more bioavailable versions to those of traditional curcumin have not yet been carried out. In addition, the serum concentrations that are necessary to achieve a certain clinical or biological effect have not yet been discovered. This is something that needs to be done. It is the piperine component of black pepper that is responsible for its pungent flavour. Piperine is an alkaloid that is mostly found in the Piper nigrum plant. It has been demonstrated that piperine can boost the bioavailability of curcumin [89]. Piperine inhibits the activity of the enzyme UDP-glucuronyl transferase in the liver, which in turn reduces the quantity of curcumin that is glucuronidated. In addition, due to the action of this system, curcumin can be consumed by the body [90]. Animals and mice were given an oral dosage of 2 g/kg curcumin together with 20 mg/kg piperine at the same time during an in vivo experiment [91]. The relative bioavailability of curcumin was increased by a factor of 1.54 in rats and by a factor of 20 in healthy individuals. Although the increase in curcumin bioavailability was greater in humans than in rats, the amount of curcumin that was consumed by rats was significantly larger than that which was consumed by humans. In a different clinical trial, healthy human volunteers were given daily doses of 2 grammes of curcumin and 5 milligrammes of

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piperine. According to the findings of the study [92], absorption was increased by a factor of two hundred percent when piperine was combined with curcumin during administration. In the study conducted by Zeng et al. [93], the authors investigated the effect of piperine pre-administration on the oral bioavailability of curcumin. For the purpose of this study, rats were given 20 mg/kg piperine first, followed by 200 mg/kg curcumin at intervals ranging from 0.5 to 8 hours following the piperine treatment. The rats that received piperine before the curcumin displayed a statistically large increase in the curcumin oral bioavailability, particularly at 6 h following the administration of piperine, with AUC0-t increasing 97-fold [94]. This was in comparison to the rats that received pure curcumin as their treatment. According to the findings of the aforementioned investigations, it has been discovered that administering natural chemicals like piperine, quercetin, resveratrol, and silibinin in conjunction with curcumin results in an increase in the amount of curcumin that is absorbed by the body. This is a potentially cost-effective method for increasing the oral bioavailability of curcumin and further exploring its potential use in the development of innovative drug delivery systems [95].

The distribution of curcumin by means of nanocarriers is one of the most effective methods for increasing curcumin's solubility and bioavailability while simultaneously shielding it from the hydrolysis-induced inactivation that can occur otherwise. The long-term retention and circulation in the body was a primary priority for some nanocarriers, whereas the intracellular release mechanisms and cellular delivery was the primary focus for others. In these conditions, curcumin is made more soluble by becoming entrapped in hydrophobic pockets, the primary mechanism for this occurring being hydrophobic interactions.[96] Because the fluorescence of curcumin is increased when it is solubilized in any of these systems, determining how well it binds may be accomplished with relative ease. Because of their biocompatibility, these systems may be successfully examined for anticancer activity in cancer cells and in vivo systems. It has been observed that increased curcumin bioavailability leads to significant increases in anticancer activity. It has been demonstrated that curcumin liposomal formulations are the most effective method for boosting curcumin bioavailability in cells [97], and products that are based on liposomal formulations are currently in the process of being commercialised. The size, surface area, charge, and hydrophobic nature of the nanocurcumin particles contribute to its efficacy, making it superior to native curcumin [98] and regarded as an acceptable target for employment as a medication in comparison to normal curcumin. This characteristic is particularly important in the battle against infectious diseases that are brought on by intracellular infections [99].

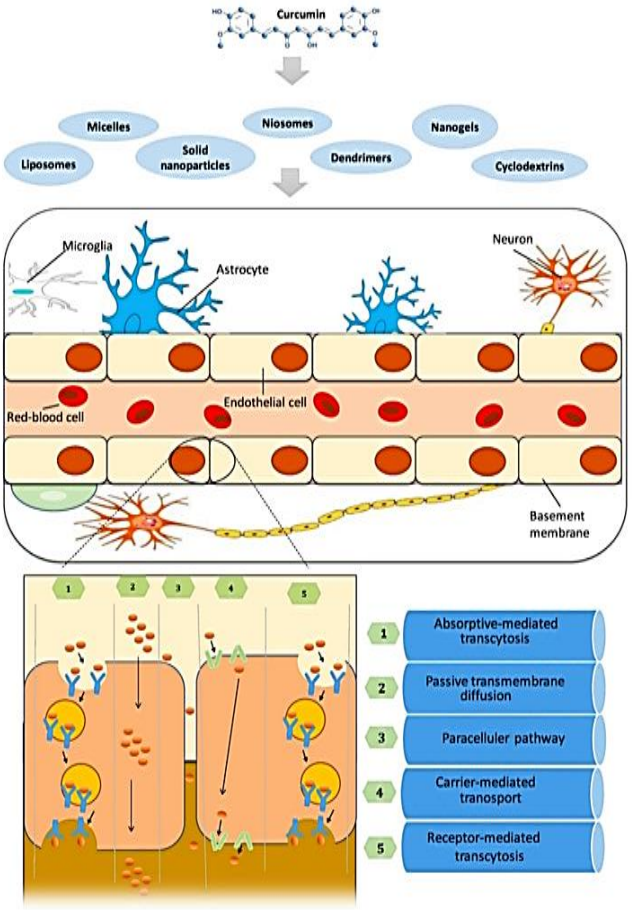

Figure 5: The most common kinds of curcumin nanocarriers, the structure of the blood–brain barrier (BBB), and the process that allows substances to pass the BBB.

4.2 Citrus Plant

Alzheimer's disease (AD) is one of the prevalent neurodegenerative diseases that is primarily characterised by cognitive impairment and gradual memory regression. This is driven by the regression in cholinergic neurotransmitter levels, specifically acetylcholine (Ach), as well as the accumulation of amyloid beta (A) and neurofibrillary tangles (NFTs) [100]. As a result, increasing the levels of Ach and preventing the aggregation of proteinaceous deposits have emerged as the two most important factors in the fight against the symptoms associated with Alzheimer's disease (AD). Targeting and blocking the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are responsible for Ach breakdown, is the fundamental mechanism for this effect[101].

As a result, limonene was examined for its efficacy against both acetylcholinesterase and

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butyrylcholinesterase (BChE)[102] Research found that limonene had anti-AChE and anti-BChE activity at a rate of 10 and 12%, respectively. Amyloid plaques are a pathological hallmark of Alzheimer's disease that contribute to poor synaptic plasticity and cognitive function [103]. They are created as a result of the buildup of amyloid beta, which is a protein. A fruit fly model of Alzheimer's disease known as drosophila was used in a recent study to determine whether or not limonene is effective against A42-induced neurotoxicity[104]. According to the findings of the study, limonene inhibited the death of neuronal cells caused by A42 and reduced the levels of reactive oxygen species (ROS), which are known to have a detrimental effect on ERK phosphorylation. The researchers came to the conclusion that although limonene did not directly inhibit ERK, the antioxidant characteristic of the compound did prevent ERK activation. The rough eye phenotype (REP), which is induced by A42, is one way in which the severity of neurotoxicity and the presence of Alzheimer's disease can be determined [105]. The results of the inquiry into REP suggested that flies fed with limonene had eased REP in a manner that was comparable to that of donepezil, which had been employed as the positive control because it was likewise effective in relieving REP. Limonene was shown to have anti-inflammatory properties when it was examined, and the results showed a significant reduction in the number of activated glial cells and nitric oxide (NO) expression in the heads of flies that were treated with limonene [106].

In vitro biological experiments were used to examine the anti-inflammatory and antioxidant effects of Citrus sinensis (orange) byproducts to determine whether or not they had a neuroprotective effect. It was demonstrated there is a high correlation between the antioxidant potential of monoterpenes such as limonene and their ability to protect neurons [107].

In addition, it was discovered that Citrus medica L., which has limonene as its most abundant ingredient (15.20%), has anti-AChE action. This discovery was made after it was discovered that the plant contains limonene. This activity was discovered to be connected to the existence of a hydrocarbon skeleton in limonene, which is known to be a hydrophobic ligand and has the potential to contribute to the interaction with the hydrophobic active site of AChE. The same study that established the plant's antioxidant capability based on in vitro experiments [108] also looked at the plant.

Limonene also had a good effect on scopolamine-induced amnesia, where it improved the alterations generated by scopolamine in short-term memory that were found in several cognitive abilities scrutinising tests[109]. This effect was observed in limonene's ability to ameliorate scopolamine's impact on short-term memory. This finding is in line with an attenuation of AChE activity that was observed to be elevated in the brains of rats that had been given scopolamine[110]. In the microtiter assay, the percentage of enzyme inhibition was found to be 24.97% for AChE and 69.12% for BChE correspondingly. This is in addition to the emphasis that has been placed on limonene's potential to decrease oxidative stress biomarkers such as protein carbonyls and malondialdehyde (MDA), and to increase superoxide dismutase (SOD), catalase, and glutathione (GSH) [111].

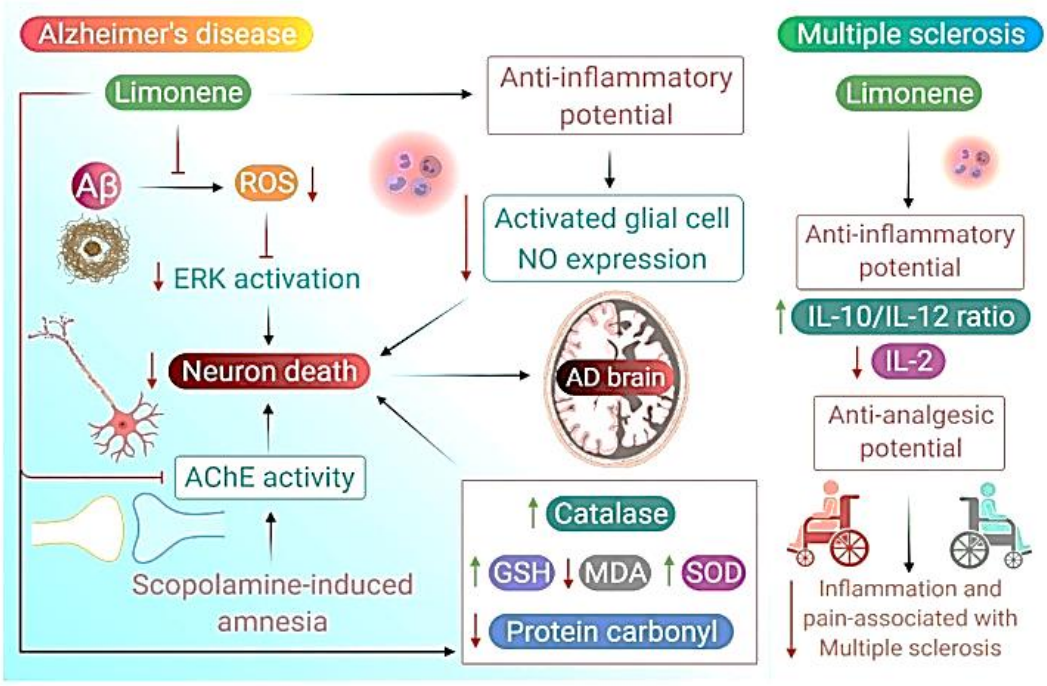

Figure 6: Neuroprotective mechanism of limonene in alzheimer's disease

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Zhou et al. investigated the effect that limonene has on monoamine neurotransmitters in both the striatum and the hippocampus, two areas of the brain that play critical roles in the processing of memories[112]. This study provides supporting evidence. As a result, it was discovered that the concentration of dopamine in the group that was given scopolamine was significantly lower when compared to the group that was given limonene. On the other hand, the concentration of DOPAC, which is a metabolite of dopamine, was shown to be greater in the scopolamine group as compared to the limonene group [113]. In addition, the memory errors that occurred in A1-42-administered groups that were recorded in multiple testing mazes were mitigated by the inhalation of T. articulata that contained 7.34% limonene [114].

In addition, Aloysia citrodora, which contains up to 20.1% limonene, was found to demonstrate neuroprotective properties against the neurotoxicity caused by beta-amyloid [115]. Black pepper oil was shown to contain a high anti-AChE activity using a microplate test, in addition to a -amyloid aggregation inhibitory action. This was discovered by the AChE inhibitory activity[116]. Limonene, which showed a significant inhibitory activity (with an IC50 value of 3.77 g/mL), is thought to be the active ingredient responsible for the action of black pepper oil in this assay [117]. This is based on the fact that limonene possessed a strong inhibitory activity[118].

Overall, this elucidates how limonene plays an important part in the pathological cascade of Alzheimer's disease (AD), as well as how its therapeutic role might be advantageously used in targeting AD-related dysfunction, whether via its antioxidant or neuroprotective capabilities. Mechanisms of pharmacological action and consequences of limonene in Alzheimer's disease[119].

V. TERPENOID CHEMICAL CONSTITUENTS USED AS PARKINSON DISEASE

Carlos R Rieder et.al 2020 A widespread and intricate neurological condition, Parkinson's disease (PD) includes a variety of clinical, epidemiological, and genetic subgroups. The primary mechanism causing the hallmark motor characteristics of PD15 is the loss of dopaminergic neurons in the substantia nigra, which results in striatal dopamine depletion. Although the most noticeable neurotransmitter alteration in Parkinson's disease (PD) is dopamine depletion, other neurochemical changes also take place and affect PD symptoms. In addition to the basal ganglia, many other parts of the neurological system are also involved in PD. Numerous routes and mechanisms, including -synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport, and neuroinflammation, are involved in the underlying molecular aetiology[120]. PD is linked with several non-motor symptoms that can be just as disabling as or even more so than the motor symptoms, even though clinical diagnosis depends on the presence of key motor aspects. The principal treatment for motor symptoms continues to be medication that raises intracerebral dopamine levels or activates dopamine receptors[121]. No existing therapies have demonstrated neuroprotective or disease-modifying properties. Particularly during the early stages of the disease, dopaminergic medications are beneficial. However, PD always advances, and long-term treatment with these drugs may result in decreased therapeutic efficacy and the emergence of comorbidities such as dyskinesias and motor fluctuations[123].

Anhita Torkaman-Boutorabi et.al 2022 Parkinson's disease (PD) is a multifactorial movement illness that affects patients' capacity to move. It is caused by the nigrostriatal system's gradual degradation[126]. The aetiology and pathogenesis of Parkinson's disease have been discovered to be impacted by oxidative stress. One of the most vital nutritional components in thyme species is the monoterpenic phenol thymol. It has some qualities that have been employed in conventional medicine, such as antioxidant, free radical scavenger, and anti-inflammatory. The purpose of this study was to examine the possible neuroprotective benefits of thymol in PD models through in vitro and in vivo investigations[127].

Mohona Islam Mitu et.al 2022 Neurodegenerative diseases (NDs) have traditionally been treated with natural medicines derived from plants. A ND is Parkinson's disease (PD). This trait distinguishes the decline and consequent cognitive deficits of the midbrain nigral dopaminergic neurons[128]. Despite the fact that the cause is unknown, numerous pathogenic pathways and essential elements have been identified, including protein aggregation, iron accumulation, mitochondrial dysfunction, neuroinflammation, and oxidative stress. In the current therapy paradigm, dopamine (DA) is replaced with anti-Parkinson medications such as levodopa, carbidopa, monoamine oxidase type B inhibitors, and anticholinergics. In situations where medication therapy is unsuccessful, surgery is indicated[129].

Unfortunately, the current traditional treatments for PD are expensive and come with a lot of negative side effects. Therefore, it is necessary to address innovative treatment approaches that regulate the processes that lead to neuronal death and dysfunction. Natural resources have traditionally been a good place to find potential cures. A number of natural remedies derived from healing fruits, vegetables, and herbs can be used to treat PD. These natural substances also limit iron accumulation, protein misfolding, the maintenance of proteasomal breakdown, mitochondrial homeostasis, and other neuroprotective activities in addition to their well-known anti-oxidative and anti-inflammatory properties.

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The objective of this study is to systematically describe the therapeutic effects of the Parkinson's drugs now on the market, which target a variety of pathways. We examined the plants that can be utilised as medicines to treat Parkinson's disease. There has been an increase in the use of natural treatments, particularly those made from plants, to treat PD. This article looks at the underlying traits of medicinal plants and the bioactive components that may be used to treat Parkinson's disease (PD).

Sajad Fakhir et.al 2021 One of the most common and disabling neurodegenerative diseases, Parkinson's disease (PD), is currently on the rise. The pathophysiology of PD is mediated by multiple dysregulated pathways, although the crucial targets are yet unknown. Therefore, it is crucial to identify the main dysregulated pathways in PD. The role of mitochondrial and cross-talked mediators in neurological diseases, genetic alterations, and related difficulties of PD has been underlined in several research. The need for discovering novel alternative agents is driven by the numerous pathophysiological causes of PD as well as the ineffectiveness and adverse effects of existing neuroprotective therapy[130]. The use of plant secondary metabolites (such as flavonoids/phenolic chemicals, alkaloids, and terpenoids) in the control of PD-associated symptoms by targeting mitochondria has received a lot of interest recently. The combined regulation of reactive oxygen species and mitochondrial apoptosis has been demonstrated to be a promising application for plant secondary metabolites. This review focused on how plant-derived secondary metabolites affect mitochondria and several dysregulated pathways in PD.

Tamanna Jahan Mony et.al 2022 Terpenoids are abundant in nature, particularly in the kingdom of plants, and they display a variety of pharmacological actions. Recent screening has uncovered numerous novel terpenoids that are effective in treating various psychiatric conditions. This review summarised the most recent preclinical research on terpenoid usage in psychiatric diseases that has been published[131]. In order to provide empirical evidence regarding the neuropharmacological effects of the large group of terpenoids in translational models of psychiatric disorders, their relevant mechanisms of action, and treatment regimens with evidence of the safety and psychotropic efficacy, this review was thoroughly investigated. As a result, we used nine (9) electronic databases and manually searched them all. The current articles' published data were searched for the pertinent information. In our search, we entered "terpenoids" or "terpenes" and "psychiatric disorders" (as opposed to "psychiatric diseases" or "neuropsychiatric disorders" or "psychosis" or "psychiatric symptoms")[132] Preclinical animal research showed the effectiveness of terpenoids or biosynthetic substances in the terpenoid group. In multiple preclinical trials of psychosis, ginsenosides, bacosides, oleanolic acid, Asiatic acid, boswellic acid, mono- and diterpenes, and other kinds of saponins and triterpenoids were discovered to be significant bioactive substances. When taken as a whole, the review's findings show that natural terpenoids and their derivatives have the potential to be a highly effective alternative therapy for treating the primary or secondary behavioural symptoms of psychiatric diseases.

Liting Hang et.al 2016 The most prevalent neurological movement condition in the world, Parkinson's disease (PD), is currently treated with pharmacological methods that are mostly symptomatic and frequently have unfavourable side effects. Despite this, they continue to be the standard treatment for PD because there aren't any better options. Nutraceuticals are substances obtained from whole-food sources that have therapeutic value. Their development has made it possible to use alternative methods to treat neurodegenerative disorders like Parkinson's disease[133]. Due to the fact that nutraceuticals are made from naturally occurring substances and may consequently have less adverse effects, they are able to market themselves as a "safer" option. We will look at some of the significant efforts made to better understand the role of nutraceuticals in PD in this study. These substances, generally speaking, carry out their beneficial effects via altering signalling pathways, reducing oxidative stress, inflammation, and apoptosis, as well as controlling mitochondrial homoeostasis. We will also point out how the green tea compound epigallocatechin-3-gallate (EGCG) imparts neuroprotection in Parkinson's disease (PD) via activating AMP kinase and explain how its positive effects in PD may be brought on by improving mitochondrial quality control[134].

Taejoon Kim et.al 2020 The majority of biogenic volatile organic compounds (BVOCs) come from forest trees. The primary BVOCs in forest aerosols are terpenes and terpenoids. These substances exhibit a wide spectrum of biological activities that have been demonstrated in numerous human illness models, suggesting that forest aerosols containing these substances may be connected to the health benefits of forest bathing. In this review, we looked at publications analysing BVOCs and chose the 23 terpenes and terpenoids that were most frequently released in Northern Hemisphere forests and were said to have anti-inflammatory properties. We divided the anti-inflammatory actions of these drugs into six groups and listed their underlying molecular mechanisms[135]. Last but not least, out of the important 23 compounds, we looked at the therapeutic potentials of 12 compounds that are known to be helpful against various inflammatory illnesses such neuroinflammation, atopic dermatitis, pulmonary inflammation, and arthritis. In conclusion, the current findings suggest that forest aerosols may be used as chemo preventive and therapeutic agents for treating a variety of inflammatory disorders in addition to supporting their positive effects.

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Zahra Shahpiri et.al 2016 The second most prevalent kind of chronic neurodegenerative illness that impairs both motor and cognitive function is Parkinson's disease (PD). The standard therapeutic strategies for the management of PD only effectively treat symptoms. Numerous present investigations are centred on searching for new compounds that can aid PD patients therapeutically. The current study's goal is to thoroughly review phytochemicals with therapeutic or preventive effects on PD with an emphasis on their neuropsychopharmacology processes[136]. The most prevalent classes of phytochemicals with known antiparkinsonian actions include terpenes and various subgroups of polyphenols (flavonoids, phenolic acids, stilbenes, and lignanes). Alkaloids, cinnamates, carbohydrates, amino acids, and fatty acid amides are a few more phytochemical categories containing representatives that have beneficial effects in PD. Numerous mechanisms of action are used by phytochemicals to exert their antiparkinsonian effects, including the suppression of apoptosis (by lowering levels of Bax/Bcl-2, caspase-3, -8, and -9, and -synuclein accumulation), reduction of dopaminergic neuronal loss and dopamine depletion, downregulation of proinflammatory cytokines (such as prostaglandin E2, interleukin-6, interle[137]. To increase their efficacy and lessen their psychological side effects in the management of PD, plant-derived natural products might be thought of as either future pharmaceutical medications or adjuvant therapy with conventional therapeutic procedures. To assess the preventive and therapeutic advantages of phytochemicals as potential future treatments for neurodegenerative disorders, well-designed clinical trials are essential[138].

VI. CONCLUSION

Natural products are desirable sources for the development of anti-AD medicines because of their ability to provide a variety of structural properties in addition to their biological activities. Regrettably, the Food and Drug Administration (FDA) has only given its blessing to some AChE inhibitors and NMDA receptor antagonists as treatments for Alzheimer's disease (AD). As a result, this study focused on the discussion of a few natural compounds and their respective molecular targets, mainly terpenoids, which have the potential to be transformed into anti-AD medicines. In in vitro experiments, the neuroprotective effects of other substances such as cornel iridoid glycoside, oleanolic acid, tenuifolin, cryptotanshinone, and ursolic acid are exceptionally strong. These chemicals are capable of exerting favourable effects on the central nervous system either directly by acting on central nervous system targets or indirectly by acting on peripheral nervous system targets. Therefore, in order to develop terpenoids as anti-AD medicines, it is necessary to take into consideration the ways that can effectively deliver the bioactive components to the brain. In addition, the availability of large quantities of biologically active molecules is crucial for the development of biologically active compounds that are produced from natural products for use as therapeutic agents. A combination of two or three bioactive chemicals that work together in a synergistic manner could be employed as an alternative to a single agent in order to circumvent the limitations imposed by this restriction. In addition, it is anticipated that the identification of anti-AD therapeutic agents derived from natural sources will come about as a result of an ongoing search for bioactive molecules like as terpenoids.

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