"NEUROPROTECTIVE ROLE OF FARNESOL IN ALZHEIMER'S DISEASE: TARGETING INFLAMMATION, OXIDATIVE STRESS, AND COGNITIVE DECLINE"

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuroinflammation, oxidative stress, and neuronal loss. Farnesol, a natural sesquiterpene alcohol found in various essential oils, has recently gained attention for its neuroprotective potential in AD. This review explores the multifaceted role of farnesol in combating key pathological features of Alzheimer's disease. Farnesol has been shown to attenuate oxidative stress by enhancing antioxidant defenses and reducing reactive oxygen species (ROS) production. It also exhibits strong anti-inflammatory properties by modulating microglial activation and downregulating pro-inflammatory cytokines, thus alleviating neuroinflammation. Additionally, farnesol may help preserve cognitive functions by protecting neuronal integrity and supporting synaptic plasticity. Preclinical studies suggest that farnesol not only mitigates amyloid-β-induced toxicity but also improves mitochondrial function and neuronal survival. Given its favorable safety profile and broad pharmacological activity, farnesol holds promise as a potential therapeutic agent for the prevention or management of Alzheimer's disease. Further clinical research is warranted to validate its efficacy and mechanisms in human subjects.

Keywords: Farnesol, Alzheimer's disease, Neuroprotection, Oxidative stress, Neuroinflammation, Cognitive decline, Amyloid-β, Antioxidant, Microglia, Mitochondrial dysfunction

INTRODUCTION

Cognitive decline, memory impairment, and behavioral abnormalities are the hallmarks of Alzheimer's Disease (AD), a progressive neurodegenerative illness that mainly affects the elderly. With 60–80% of cases occurring globally, it is the most prevalent type of dementia. Amyloid-β plaques and neurofibrillary tangles made of hyperphosphorylated tau protein build up in the pathophysiology of AD, causing synaptic dysfunction and neuronal loss, especially in the cortex and hippocampus. The precise etiology is still multifactorial despite much research, with lifestyle, environmental, and genetic factors all having a major impact. Alzheimer's disease is expected to become much more common as the world's population ages, which will present serious problems for both caregivers and healthcare systems. Over 55 million people worldwide suffer from dementia, with Alzheimer's being the most common cause, according to the World Alzheimer Report 2023 (Alzheimer's Disease International, 2023). This emphasizes how urgently effective early diagnosis, treatment, and support strategies for impacted individuals and their families are needed[1].

Alois Alzheimer, a German psychiatrist and neurologist, made the initial diagnosis of Alzheimer's disease (AD) in 1906. He recorded the case of Auguste Deter, a 51-year-old woman who displayed signs of erratic behavior, language problems, and memory loss. Alzheimer performed a postmortem examination after her death and found that she had severe cerebral atrophy, aberrant clusters (now called amyloid plaques), and tangled bundles of fibers (called neurofibrillary tangles) in her brain, all of which were indicators of what would eventually be called Alzheimer's disease[2]. Alzheimer's coworker Emil Kraepelin first used the term "Alzheimer's Disease" in 1910 when he included the illness in his psychiatry textbook[3]. At first, the illness was thought to be uncommon and mostly affected middle-aged people[4]. But as knowledge and diagnostic skills advanced over the course of the 20th century, it became clear that Alzheimer's was the most common type of dementia and that it also affected older adults[5]. Since then, research has progressed from purely clinical observations to molecular and genetic studies, which have resulted in the identification of important risk genes and biomarkers like APOE ε4[6]. Since Alzheimer's disease is now acknowledged as a significant worldwide health issue, efforts are being made to improve care strategies, diagnose the condition earlier, and develop potential disease-modifying treatments[7].

An estimated 60–80% of dementia cases worldwide are caused by Alzheimer's disease (AD), the most prevalent neurodegenerative illness. The rising life expectancy and global aging trends have made its prevalence a serious public health concern[8]. It is anticipated that the number of Alzheimer's disease patients will rise significantly during the

next few years as populations age, especially in low- and middle-income nations. According to Alzheimer's Disease International's (ADI) 2023 World Alzheimer Report, there were an estimated 55 million dementia sufferers globally in 2023[9]. Most of them are thought to have Alzheimer's disease. This number is expected to nearly double every 20 years, reaching 78 million in 2030 and 139 million in 2050, according to projections (Alzheimer's Disease International, 2023)[10]. Demographic changes, such as longer lifespans and fewer births, are primarily to blame for this quick growth.Age has a direct correlation with the prevalence of Alzheimer's disease. Before the age of 65, it is comparatively uncommon, but after that, it becomes more prevalent[11]. The risk of AD doubles roughly every five years in people 65 and older. Nearly one-third of those 85 and older are thought to be at risk for the illness[12]. Furthermore, there are gender differences; women make up almost two-thirds of all Alzheimer's patients. The longer average lifespan of women explains some of this imbalance, but new research also suggests that there may be biological and hormonal variations that increase a woman's vulnerability[13]. Prevalence differences by region are also significant. Because they have greater access to healthcare and greater awareness, high-income regions like Western Europe and North America report higher diagnostic rates[14]. In contrast, underdiagnosis is prevalent in many low- and middle-income nations, where health systems frequently lack the ability to adequately identify and treat dementia cases[15]. However, more than 60 percent of dementia patients currently reside in these areas, and as the world's population ages, this percentage is predicted to increase. Individuals, families, healthcare systems, and economies are all severely impacted by the rising incidence of Alzheimer's disease[16]. The estimated global cost of dementia was over USD 1.3 trillion in 2023, and by 2030, that amount is expected to double. In addition to the financial costs, AD causes a great deal of emotional and physical stress for those who provide the majority of care—often family members—when there is insufficient institutional support[17]. A complex and multifaceted etiology, Alzheimer's disease (AD) is caused by a dynamic interaction of lifestyle, environmental, and genetic factors. Significant developments in molecular biology and neuroscience have revealed a number of important mechanisms and risk factors that contribute to the onset and progression of the disease, even though the exact cause is still unknown[18].

Genetic Factors: Alzheimer's disease development is significantly influenced by genetics, especially in familial forms of the disease that manifest early[19]. Early-onset AD, which usually appears before the age of 65 and is inherited in an autosomal dominant fashion, is directly associated with mutations in three specific genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2)[20]. On the other hand, the apolipoprotein E (APOE) gene, particularly the APOE ε4 allele, is strongly linked to late-onset AD, which is the more prevalent type. The risk of developing AD is two to three times higher for people with one copy of the ε4 allele, and up to twelve times higher for those with two copies[21]. Having the APOE ε4 allele, however, is neither required nor sufficient for AD development, suggesting that other factors are also important[22].

Amyloid Cascade Hypothesis: The amyloid cascade hypothesis, one of the most prominent theories elucidating the pathophysiology of AD, postulates that the build-up of amyloid-beta (Aβ) peptides, especially Aβ42, in the brain sets off a series of neurotoxic events, ultimately resulting in amyloid plaques outside cells that interfere with cell-to-cell transmission and trigger immunological reactions, ultimately causing neuroinflammation along with synaptic dysfunction[23].

Tau Pathology: The aberrant phosphorylation of the tau protein, which typically stabilizes microtubules in neurons, is another characteristic of AD[*24]. Tau gets hyperpho sphorylated in AD and creates neurofibrillary tangles inside neurons, which leads to cortical atrophy and cell death. Compared to amyloid plaques, the spread of tau pathology correlates more strongly with cognitive decline, indicating a crucial role in the course of the disease[25].

Neuroinflammation and Oxidative Stress: It is becoming more widely acknowledged that a major factor in AD pathology is chronic neuroinflammation [26]. In reaction to Aβ plaques and other cellular damage, activated microglia and astrocytes release reactive oxygen species (ROS) and pro-inflammatory cytokines, which causes oxidative stress, synaptic loss, and additional neuronal damage. The

development of disease may be accelerated if these immune responses are dysregulated[27].

Vascular and Lifestyle Factors: Emerging evidence suggests that vascular dysfunction and lifestyle factors significantly influence the onset and progression of AD[28]. Conditions such as hypertension, diabetes, obesity, smoking, and physical inactivity are associated with increased AD risk. Vascular damage can compromise the blood-brain barrier (BBB) and reduce cerebral blood flow, impairing the clearance of amyloid and other metabolic waste from the brain[29].

Environmental and Epigenetic Factors: AD risk may also be increased by environmental exposures, including chronic stress, low educational attainment, and traumatic brain injury (TBI)[30]. Moreover, epigenetic changes like DNA methylation and histone acetylation are being researched more and more for their potential to link environmental factors to molecular alterations in the brain by modifying gene expression linked to AD pathology[31].

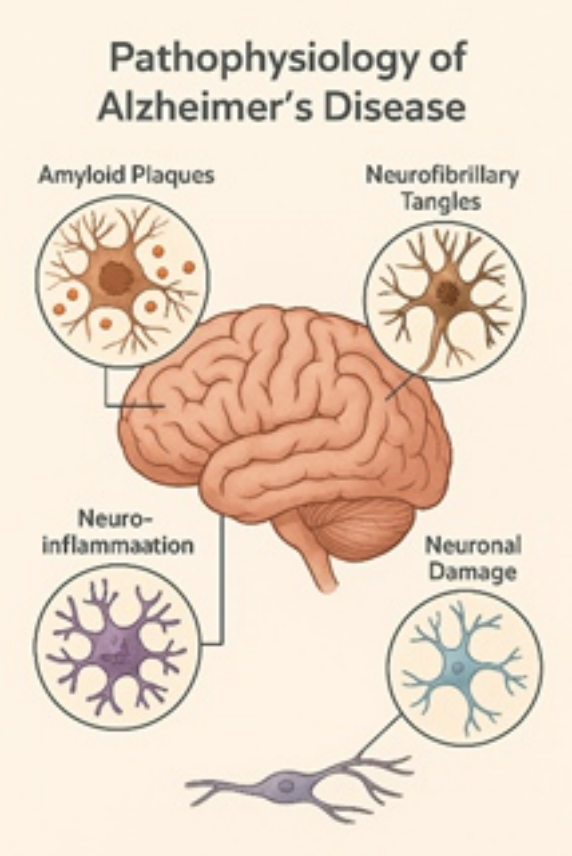

Fig.1: Pathophysiology of Alzheimer's Disease(AD).

Diagnosis of Alzheimer's Disease (AD)

Diagnosing Alzheimer's disease (AD) requires a complete clinical assessment, which includes medical history, cognitive tests, neurological examination, brain imaging, and biomarker tests. An early and accurate diagnosis helps in better management, future care planning, and understanding the likely course of the disease. In the past, a definite diagnosis was only possible through examining brain tissue after death, but today, imaging and biomarker advances allow doctors to detect key features of AD in living individuals (in vivo) [51].

In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) updated the diagnostic guidelines to include both clinical symptoms and biomarker evidence [51]. Diagnosis involves checking for memory complaints either reported by the patient or their relatives, confirming memory and learning problems through tests, observing whether these problems affect daily functioning, and excluding other conditions like vitamin deficiencies, depression, or stroke [52].

Alzheimer's disease typically progresses through stages: preclinical AD (where biological changes are present but symptoms are not), mild cognitive impairment due to AD

(MCI-AD), and full AD dementia, where memory loss and functional decline interfere with daily life [53].

Cognitive and neuropsychological tests are vital tools for evaluating mental function. Standard tests include the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), Clock Drawing Test, Trail Making Test, and the Wechsler Memory Scale. These tools help assess memory, attention, executive function, language, and visuospatial abilities. A decline in episodic memory is particularly common in the early stages of AD [54].

Neuroimaging techniques help support the diagnosis by showing brain changes typical of AD and by ruling out other causes. MRI scans can reveal shrinkage in the hippocampus and thinning in specific brain regions. CT scans are helpful in detecting tumors or bleeding. PET scans using FDG can show reduced brain activity in the posterior cingulate cortex and temporoparietal areas, which is suggestive of AD. Amyloid-PET and Tau-PET can even detect the buildup of amyloid plaques and tau tangles in the brain [55,56].

Cerebrospinal fluid (CSF) biomarkers offer biochemical proof of AD. In AD, levels of Aβ42 protein are reduced due to its buildup in brain plaques, while levels of total tau (t-tau) and phosphorylated tau (p-tau) are increased, indicating damage and tangle formation in brain cells. A typical AD biomarker profile includes low Aβ42 and high t-tau and p-tau levels [57].

Recent research has also focused on blood-based biomarkers as a less invasive and more cost-effective alternative. Promising markers include the Aβ42/40 ratio in plasma, phosphorylated tau proteins (p-tau181 and p-tau217), and neurofilament light chain (NfL), which signals nerve cell damage. These blood tests may eventually be used routinely alongside or instead of CSF testing [58].

Genetic testing is sometimes recommended, especially for early-onset or familial Alzheimer's. The presence of the APOE ε4 gene increases the risk of AD, though it is not enough to confirm the disease. For inherited forms of Alzheimer's, doctors test for mutations in the Presenilin 1, Presenilin 2, and APP genes [59].

Since other conditions can cause similar symptoms, it is important to rule out other types of dementia. These include vascular dementia, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), normal pressure hydrocephalus (NPH), and depression-related cognitive issues (pseudodementia). Neuroimaging and biomarker testing help distinguish AD from these other conditions [60].

Treatment of Alzheimer's Disease (AD):

Alzheimer's disease (AD) is a neurodegenerative condition that worsens over time and has no known treatment. The main goals of current treatment approaches are to control symptoms, delay cognitive aging, and enhance quality of life. These interventions can be broadly classified into pharmacological and non-pharmacological approaches[61]. The cholinergic and glutamatergic systems are the targets of the most often prescribed drugs. Usually used in mild to moderate stages, cholinesterase inhibitors (such as galantamine, rivastigmine, and donepezil) function by raising the brain's acetylcholine levels[62]. In moderate to severe AD, memantine, an NMDA receptor antagonist, is frequently used to control glutamate activity and avoid excitotoxicity[63]. Disease-modifying treatments, or DMTs, have just become popular. Interestingly, monoclonal antibodies like lecanemab and aducanumab target amyloid-beta plaques, which are a defining feature of AD pathology[64]. Although there is potential for these treatments, their clinical benefits are still being studied, and they frequently come with risks like amyloid-related imaging abnormalities (ARIA)[65].

Holistic management requires non-pharmacological therapies. To treat mood disorders, these include behavioral therapy, dietary interventions (like the MIND or Mediterranean diets), physical exercise, and cognitive stimulation therapy. In order to manage the psychosocial burden of the disease, caregiver support and education are also essential[66].

Molecular Mechanisms involved in Farnesol:

A naturally occurring sesquiterpene alcohol, farnesol ($C_{15}H_{24}O$), is a precursor to farnesylated proteins and other compounds of biological importance. It is present in essential oils made from plants, including gardenia, ginger, lemongrass, and roses, and it is crucial for a number of physiological and biochemical functions[67]. Because of its many biological actions, such as its antibacterial, anti-inflammatory, antioxidant, and maybe neuroprotective properties, farnesol has been the focus of research.

Depending on the organism, either the methylerythritol phosphate or mevalonate pathways are used to produce farnesol[68-69]. It participates in the prenylation process, which modifies proteins and is essential for biological processes like signal transmission, cell division, and protein stability. Farnesol is significant in the context of neurobiology and neurodegenerative diseases because of its role in these processes[70].

Chemical Structure and Biosynthesis:

With 15 carbon atoms, three double bonds, and a single hydroxyl group (OH) at the end, farnesol (C15H24O) is a sesquiterpene alcohol. It is produced by either the bacterial methylerythritol phosphate (MEP) pathway and plants or mevalonate route in mammals and fungi. Geranylgeranyl pyrophosphate (GGPP), the precursor in this process, is reduced to produce farnesol[71].

The production of farnesylated proteins, which are essential for the operation of several physiological functions such as cell signaling, membrane attachment, and protein-protein interactions, depends on the farnesol biosynthesis pathway. Because it affects proteins involved in cell proliferation, differentiation, and survival, farnesylation is a post-translational modification that is particularly significant in neuronal function[72].

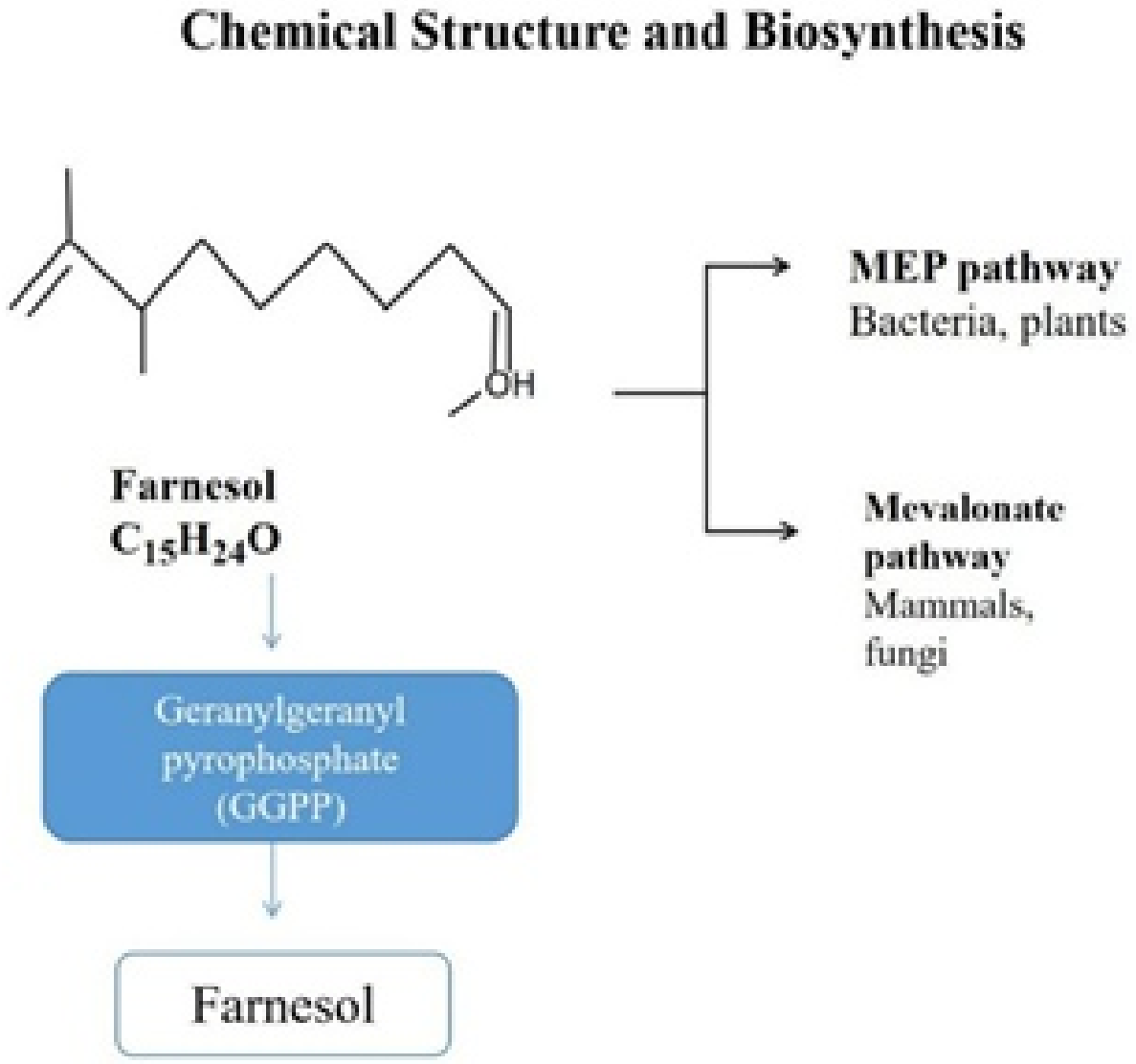

Fig.2: Chemical Structure and Biosynthesis.

Farnesol as a Modulator of Cholinergic Function:

A variety of physiological and cognitive functions, such as learning, memory, attention, and neuromuscular function, depend on the cholinergic system, which is mainly controlled by the neurotransmitter acetylcholine (ACh). A substantial loss of cholinergic neurons in the basal forebrain is correlated with cognitive deterioration in Alzheimer's disease (AD), one of the neurodegenerative illnesses most closely linked to cholinergic dysfunction. The essential oils of a number of plants, including citronella, rose, and lemongrass, contain farnesol, a naturally occurring acyclic sesquiterpene alcohol. It has long been known for its industrial uses and smell, but new research has revealed that it may also have biological functions, especially in the neurological system. Farnesol's antioxidant, anti-inflammatory, and neuroprotective qualities, as well as its capacity to penetrate the blood-brain barrier (BBB), make it a viable option for cholinergic function modulation.

Biochemical Properties of Farnesol:

A lipophilic substance produced by the mevalonate route, farnesol ($C_{15}H_{26}O$) serves as a bridge in the production of cholesterol, steroids, and other isoprenoids. It can interact directly with neural tissues because of its hydrophobic nature, which makes it easier for it to diffuse across cell membranes, including the BBB. Furthermore, farnesol has the ability to incorporate into lipid bilayers, which may have an impact on membrane-bound proteins such as neurotransmission-related enzymes and receptors.

Farnesol's Effects on Cholinergic Neurotransmission:

Acetylcholinesterase Inhibition: Inhibiting acetylchol inesterase (AChE), the enzyme that hydrolyzes acetylcholine, is one of the main ways to improve cholinergic function. In vitro tests have demonstrated that farnesol has AChE inhibitory action. Because of this impact, acetylcholine levels in the synaptic cleft are raised, which improves cholinergic transmission. AChE activity has been shown to be dose-dependently inhibited in experiments where farnesol is administered to experimental models. Farnesol's multifunctional qualities offer a distinct benefit, despite its limited inhibitory potential when compared to traditional cholinesterase inhibitors like donepezil or rivastigmine.

Modulation of Cholinergic Receptors: Despite the paucity of direct binding experiments, there is growing evidence that farnesol may affect the activity of cholinergic receptors, especially muscarinic acetylcholine receptors (mAChRs). By altering receptor shape and membrane fluidity, farnesol may function as a positive modulator, increasing receptor sensitivity to acetylcholine. Indirect regulation via anti-inflammatory pathways can also maintain the expression and integrity of receptors.

Neuroprotective Mechanisms Supporting Cholinergic Function:

One of the main causes of cholinergic neuron degeneration is oxidative stress. By scavenging reactive oxygen species (ROS) and upregulating endogenous antioxidant enzymes, including catalase and superoxide dismutase (SOD), farnesol has strong antioxidant activity. Farnesol prevents cholinergic neurons from degenerating by reducing oxidative damage. Cholinergic dysfunction can also be caused by chronic neuroinflammation. It has been demonstrated that farnesol downregulates the NF-κB signaling pathway and inhibitsTNF-α, IL-1β, and IL-6 are examples of pro-inflammatory cytokines that are expressed. Cholinergic neurons' both functionality and survival are supported by the **neuroprotective environment this produces.**

Cholinergic neuron loss has been linked to mitochondrial malfunction. By preserving membrane potential, lowering lipid peroxidation, and boosting ATP synthesis, farnesol improves mitochondrial function and supports the cellular energy needs for neurotransmission.

Experimental and Preclinical Evidence:

Farnesol has been shown in vitro to improve cell survival, raise acetylcholine levels, and lower oxidative stress indicators in PC12 cells and primary neuronal cultures. In neurotoxic settings, farnesol therapy also resulted in reduced AChE activity and maintained synaptic integrity. Additional evidence for farnesol's neuromodulatory properties has come from experiments conducted on animals. Farnesol treatment markedly enhanced memory and learning performance in rodent models of scopolamine-induced amnesia (e.g., Morris water maze, passive avoidance test). Alongside these cognitive advantages, the hippocampus's acetylcholine level rose while AChE activity fell.

Furthermore, farnesol therapy decreased amyloid load,

decreased neuroinflammation, and maintained cholinergic neuron density in the basal forebrain in models of Alzheimer's disease caused by β-amyloid peptide injection.

Clinical Implications and Future Directions: The preclinical data indicates that farnesol may be a novel medication or adjunct in the treatment of cholinergic impairments, especially in Alzheimer's disease and age-related cognitive decline, despite the existing paucity of human research. To enhance results, use adjunct therapy in addition to current cholinesterase

inhibitors. Because of its neuroprotective properties, preventative supplements are used in at-risk groups. Formulation to improve CNS availability in targeted administration systems like liposomes or intranasal sprays.Carrying out human pharmacokinetic and pharmacodynamic investigations.Assessing tolerance and safety over the long term.Examining potential synergistic effects with additional neuroprotective drugs[73].

Experimental Evidence on Farnesol in Alzheimer's Models:

Farnesol, a sesquiterpene alcohol of natural origin, has shown great promise as a neuroprotective drug in experimental models of Alzheimer's disease. Its action has been thoroughly investigated in vivo and in vitro models that replicate the pathological characteristics of AD.

Farnesol in In Vivo and In Vitro Models of Alzheimer's Disease

Farnesol has been widely studied for its neuroprotective effects in both in vivo and in vitro models of Alzheimer's disease (AD). In in vivo studies, one common model involves the administration of streptozotocin (STZ) in rats. STZ induces insulin-resistant conditions in the brain, which closely resemble the pathology of sporadic Alzheimer's disease. In these experiments, rats received intracerebroventricular (ICV) injections of STZ to impair cognitive function, followed by oral administration of farnesol over a period typically ranging from 14 to 21 days. Results from these models demonstrated significant improvements in spatial learning and memory, assessed using behavioral tests such as the Morris Water Maze and Y-Maze. Rats treated with farnesol showed better cognitive performance compared to controls. Furthermore, farnesol reduced oxidative stress markers, including malondialdehyde (MDA), while increasing the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT). In addition, it suppressed the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, and reduced neuronal loss in hippocampal regions CA1 and CA3, indicating substantial histological improvements [74].

Another widely used in vivo model involves the induction of neurotoxicity by injecting amyloid-beta (Aβ1–42) oligomers into mice. This model simulates amyloid plaque accumulation and associated neurodegeneration. In these studies, farnesol treatment led to a marked reduction in amyloid burden in the hippocampus and cortex. The compound also attenuated neuroinflammation by inhibiting microglial activation and downregulating the expression of inflammatory markers such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and nuclear factor kappa B (NF-κB). Neuroprotective benefits were further highlighted by increased levels of synaptic proteins, including postsynaptic density protein 95 (PSD-95) and synaptophysin, which play essential roles in maintaining synaptic function and plasticity [74].

In in vitro studies, farnesol's protective effects have been evaluated using SH-SY5Y human neuroblastoma cells exposed to Aβ1–42, which causes cytotoxicity. Co-treatment with farnesol significantly improved cell viability in a dose-dependent manner. It helped maintain mitochondrial membrane potential (MMP), thereby reducing apoptosis. Additionally, farnesol reduced the accumulation of reactive oxygen species (ROS) and restored antioxidant balance, showing a clear reduction in oxidative stress [74].

At the molecular level, farnesol exerts its neuroprotective action through multiple signaling pathways. One key mechanism involves the inhibition of the NF-κB pathway, which leads to decreased transcription of genes involved in inflammation. Farnesol also modulates the MAPK/PI3K-Akt pathways, enhancing neuronal survival and synaptic function. It contributes to apoptosis regulation by increasing the Bcl-2/Bax ratio, thereby favoring cell survival. Additionally, farnesol blocks the activation of caspase-3, a critical executor of apoptosis, thus protecting neurons from cell death [74].

Table 1: Neuroprotective Effects of Farnesol on Alzheimer's Disease-Related Parameters.

Parameter	Farnesol effect
Cognitive function	Enhanced memory and learning
Oxidative stress	↓ MDA, ↓ ROS; ↑ SOD, ↑ CAT, ↑ GSH
Inflammation	↓ IL-1β, ↓ TNF-α, ↓ NF-κB
Amyloid pathology	↓ Aβ plaques and oligomers
Apoptosis	↓ Caspase-3, ↑ Bcl-2
Synaptic function	↑ Synaptophysin, ↑ PSD-95
Mitochondrial integrity	Maintained MMP

Synergistic Effects of Farnesol with Other Therapeutic Agents in Alzheimer's Disease

Farnesol has shown promising potential in combination therapies for Alzheimer's disease due to its antioxidant, anti-inflammatory, and neuroprotective properties. When combined with curcumin, the active compound in turmeric, the two agents may work synergistically to target multiple AD pathologies. Curcumin is known for its ability to promote amyloid plaque clearance and enhance blood-brain barrier (BBB) permeability, which may also facilitate greater brain access for farnesol. Both compounds contribute to reducing oxidative stress and inflammation, and their combination may further suppress Aβ plaque formation and tau hyperphosphorylation, key pathological features of AD.

In combination with donepezil, a cholinesterase inhibitor widely used to improve cholinergic neurotransmission in AD, farnesol offers complementary benefits. While donepezil primarily improves synaptic transmission, it has little effect on neuroinflammation or oxidative stress. Farnesol fills this gap by reducing these non-cholinergic pathologies. This combination may enhance the overall therapeutic effect, slow cognitive decline more effectively than monotherapy, and even allow for a reduced dose of donepezil, potentially minimizing its side effects.

The combination of farnesol and resveratrol, a polyphenol known for activating SIRT1, AMPK, and autophagy pathways, also holds promise. Farnesol regulates NF-κBsignaling and apoptotic pathways, making this duo effective in improving mitochondrial protection, reducing neuroinflammation, and supporting synaptic plasticity. Their combined action may help recover energy metabolism and support neuronal survival in Alzheimer's disease models.

Similarly, co-administration of farnesol with omega-3 fatty acids, particularly docosahexaenoic acid (DHA), may result in enhanced cognitive benefits. Omega-3 fatty acids are known to reduce inflammation and improve neuronal membrane fluidity. Farnesol, with its role in antioxidant defense and lipid metabolism, may further stabilize neuronal membranes and inhibit amyloid aggregation. This combination supports neuronal health and may boost lipid-derived signaling mechanisms crucial for neuroprotection.

Finally, the combination of farnesol with natural antioxidants such as vitamin E and N-acetylcysteine (NAC) could significantly enhance antioxidant capacity. Farnesol increases the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH), while vitamin E and NAC function as exogenous antioxidants that protect lipid membranes and restore glutathione levels. Together, they can amplify reactive oxygen species (ROS) scavenging, preserve neuronal integrity, and reduce excitotoxicity and synaptic loss [75].

Biological and Pharmacological Properties:

- **Antioxidant Activity:** Research has shown that farnesol possesses antioxidant qualities that may shield cells from oxidative damage, a factor linked to the development of a number of illnesses, including neurological conditions like Alzheimer's.
- **Neuroprotective Effects:** Research has examined farnesol's potential to affect the neurological system and has found that it may shield neurons from inflammation and oxidative stress. It is a molecule of interest in neurobiology because of its function in neurogenesis and neuronal survival under stress.
- **Anti-inflammatory Properties:** By

modifyingmechanisms like NF-κB, which are involved within the synthesiscytokines that promote inflammation, farnesol has shown anti-inflammatory benefits. These characteristics imply that it may be used to treat chronic inflammatory illnesses, such as neurodegenerative diseases.

- **Antimicrobial Activity:** Farnesol's antimicrobial qualities, which include antibacterial, antifungal, and antiviral actions, make it effective against a range of infections, including those brought on by Staphylococcus aureus and Candida albicans.
- **Anti-cancer Potential:** By encouraging apoptosis and preventing tumor growth, farnesol may have anti-cancer benefits, according to research. It alters a number of pathways that are essential for cancer cell survival, such as PI3K/Akt and MAPK/ERK.
- **Role in Steroid and Hormone Synthesis:** Farnesol contributes to the creation of cholesterol and steroid hormones, which are necessary for regular cellular function, as a precursor in the synthesis of bile acids and sterols[76].

Farnesol in the Nervous System:

Because farnesol plays a role in protein prenylation, its effects on the nervous system are especially remarkable. Learning, memory, and the general health of neurons depend on proteins that control neuronal function, synaptic plasticity, and signal transmission, all of which are impacted by farnesylation. According to studies, farnesol may have neuroprotective effects by reducing inflammation and oxidative stress, two major factors in neurodegenerative illnesses including Parkinson's and Alzheimer's[77].

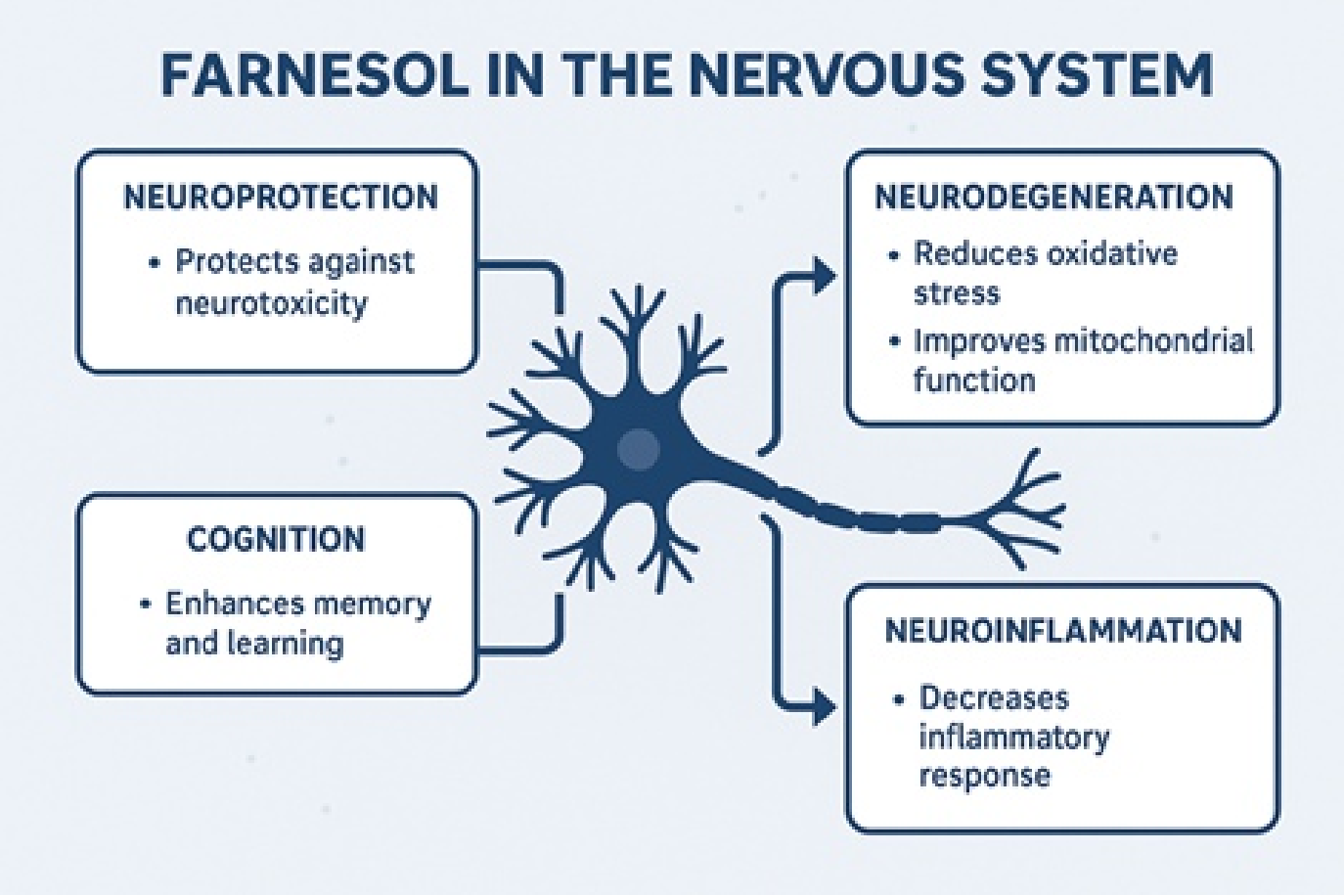

Fig.3: Farnesol in the Nervous System.

MECHANISMS OF FARNESOL IN AD

Antioxidant Activity and Oxidative Stress Regulation:

Pathway Involved: It has been demonstrated that farnesol has antioxidant qualities, mainly through lowering reactive oxygen species (ROS) levels. Since ROS can harm lipids, proteins, and DNA within cells, oxidative stress is a key component of brain degeneration in AD. By scavenging ROS, farnesol may lessen oxidative stress and shield neurons from harm.

Mechanism: The body's antioxidant defense system includes enzymes like glutathione peroxidase and superoxide dismutase (SOD), which may be modulated by farnesol. Farnesol may help preserve cellular integrity by preventing oxidative damage to neurons by lowering ROS levels[78].

Anti-inflammatory Effects via NF-κB Pathway:

By blocking the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway, farnesol has been demonstrated to have anti-inflammatory properties. This circuit is essential for controlling the brain's inflammatory response. Pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, are released when NF-κB is chronically activated, and these cytokines are linked to the pathophysiology of Alzheimer's disease.

The NF-κB pathway may be suppressed by farnesol, which would lower the synthesis of inflammatory cytokines. By stopping the activation of microglia and astrocytes, which release inflammatory mediators that lead to neuronal damage, this activity can help reduce neuroinflammation, a defining feature of Alzheimer's pathogenesis[79].

Alterations in Tau and Amyloid-β (Aβ) Pathology:

Accumulation of amyloid-β (Aβ) plaques and the hyperphosphorylation of tau protein are key pathological features of Alzheimer's disease. Farnesol has been suggested to modulate Aβ toxicity, possibly by reducing the aggregation of amyloid-β peptides or enhancing their clearance from the brain. Farnesol may regulate the expression or activity of enzymes involved in the breakdown of amyloid plaques, such as neprilysin and insulin-degrading enzyme (IDE). Additionally, farnesol may impact tau phosphorylation and reduce tau tangles by modulating the activity of kinases involved in tau hyperphosphorylation, like GSK-3β (glycogen synthase kinase-3 beta)[80].

Protein Prenylation and Neuronal Signaling:

Farnesol plays a critical role in protein prenylation, particularly through the farnesylation process, where farnesyl groups are attached to proteins like Ras, Rho, and Rab, which are important for neuronal signaling, growth, and survival. In Alzheimer's disease, disruptions in protein prenylation can affect synaptic function and neuronal health. Farnesol may enhance proper protein prenylation, which can improve the function of neuroprotective proteins involved in maintaining synaptic function and neuronal plasticity. Proper prenylation is crucial for the survival of neurons and may help reverse some of the cellular dysfunctions seen in Alzheimer's[81].

CONCLUSION

The research shows that protein farnesylation is an important facet of regulating synaptic plasticity and cognition in the hippocampus. We have shown that protein farnesylation, which is mediated by farnesyltransferase (FT), is essential for the signaling process in the neurons and the maintenance of synaptic functions. Ultimately, our discovery that protein farnesylation can be impaired and lead to synaptic dysfunction and cognitive deficits sheds light on the pathological role of farnesylation in the context of the cognitive deficits resulting from Alzheimer's disease. It is significant to note that reduction of FT, via genetic means, can ameliorate synaptic and cognitive deficits in transgenic mouse models of Alzheimer's disease. This is especially relevant in determining the role that protein farnesylation pathways can have to therapeutically target the impairment of cognitive functions and neuroprotection in Alzheimer's disease. The conclusion of the study points to the promotion or restoration of proper protein farnesylation may be an effective method of neuroprotection and cognitive preservationin neurodegenerative conditions like Alzheimer's, but additional research will be needed to completely explore the therapeutic potential and mechanisms that are engaged in modulating farnesylation in the context of neurological conditions.

Conflict of Interest

None

Funding

None

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