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MULTITARGET MECHANISMS AND TOXICOLOGICAL EVALUATION OF FARNESOL IN ALZHEIMER'S DISEASE: A NETWORK PHARMACOLOGY APPROACH

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by oxidative stress, neuroinflammation, amyloid-beta accumulation, and neuronal apoptosis. The present study investigated the therapeutic potential of farnesol against AD using a network pharmacology and in silico toxicity approach. Potential targets of farnesol and AD-associated genes were retrieved from public databases, and overlapping targets were subjected to protein–protein interaction, Gene Ontology (GO), and KEGG pathway enrichment analyses.

Farnesol-associated targets were significantly involved in oxidative stress regulation, inflammatory signaling, apoptosis, and neuroactive ligand-receptor interaction pathways, as confirmed by the results. In addition, toxicity prediction was assessed by using ProTox-3.0, which showed a favorable safety profile and low probabilities for carcinogenicity, mutagenicity, hepatotoxicity, and cardiotoxicity, along with high blood–brain barrier permeability.

Neuroprotective signaling pathways such as Nrf2/ARE and PPAR-γ showed good interaction with farnesol. Though farnesol can have the ability to act as a multitarget neuroprotective agent for Alzheimer's disease management, further studies need to be carried out to explore the potential of farnesol for further confirmation.

KEYWORDS: Farnesol, Alzheimer's disease, network pharmacology, ProTox-3.0, toxicity prediction, neuroprotection, GO enrichment, KEGG pathway.

INTRODUCTION

Neurodegenerative disorders are most prevalent worldwide, as they damage neurons in various areas of the brain. Depending upon the area that they affect, they are termed "different disorders." If the condition includes cognitive impairment, neuronal degeneration, memory loss, and behavioral abnormalities, then it is characterized as Alzheimer's disease1,2

The pathological hallmark of AD includes extracellular amyloid-beta plaque deposition between brain cells, which is one of the major features. Hyperphosphorylation of tau protein creates intracellular neurofibrillary tangles, oxidative stress, mitochondrial dysfunction, neuroinflammation, and synaptic loss3,4. The majority of the drug molecules available provide symptomatic relief and do not control the disease progression5

Over the last few decades, researchers have been targeting the multitarget treatment strategies for treating the complex and multifactorial pathogenesis of AD, which have gained greater attention since they modulate the pathological pathways simultaneously6. The interest in natural compound-based research has grown due to their diverse pharmacological activities, reduced toxicity, and ability to interact with several molecular targets.

Farnesol is a sesquiterpene alcohol naturally present in the essential oils of various medicinal plants. Antimicrobial, anticancer, antioxidant, anti-inflammatory, and neuroprotective activities of farnesol have been validated scientifically. Farnesol may modulate oxidative stress pathways, inflammatory signaling, apoptosis, and neuronal survival mechanisms, making it a potential therapeutic candidate for neurodegenerative diseases, as confirmed by the evidence of recent research studies7,8

Network pharmacology interlinks systems biology, bioinformatics, and pharmacology to identify the interactions between drugs, genes, proteins, and diseases. This approach is specifically for evaluating natural compounds with multitarget properties. Hence, the present study aimed to investigate the molecular mechanisms and toxicity profile of farnesol against Alzheimer's disease using network pharmacology, functional enrichment analysis, and in silico toxicity prediction9,10

MATERIALS AND METHODS

Identification of Farnesol Targets

Potential pharmacological targets of farnesol were retrieved from publicly available databases, including Swiss Target Prediction and PubChem11

Collection of Alzheimer's Disease-Associated Targets

Alzheimer's disease (AD)-associated genes were collected from the disease-related database GeneCards12

Identification of Common Targets

The common targets between farnesol-associated proteins and AD-related genes were identified using Venny 2.1.0 13. The intersecting genes obtained from the Venn analysis were considered potential therapeutic targets of farnesol against AD and were selected for downstream bioinformatics investigations.

Construction of Protein–Protein Interaction Network

The overlapping targets were uploaded to the STRING Database to construct a protein–protein interaction (PPI) network, with Homo sapiens selected as the target organism. To reduce the false positive interactions, the confidence score was fixed to get a high confidence threshold. Cytoscape software was used for visualization and analyzing the generated network.The generated interaction network was subsequently visualized andanalyzed using Cytoscape14,15

Gene Ontology and KEGG Pathway Enrichment Analysis

The biological significance of the identified targets was investigated by using functional enrichment analysis. Gene Ontology (GO) analysis was categorized into Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Major signaling pathways associated with the therapeutic mechanisms of farnesol were identified by KEGG pathway enrichment analysis16

SR Plot Construction and Functional Enrichment Analysis

Gene Ontology categories associated with the identified target genes were visualized by SR plot generation. Bioinformatics tools such as STRING, DAVID, and Cytoscape enrichment plugins are used to screen the gene set subject to enrichment analysis. The enrichment results were categorized into Biological Process, Cellular Component, and Molecular Function classes. The SR plot was constructed based on enrichment scores and statistical significance values to identify the most functionally relevant pathways and biological processes.

Protox 3.0 Toxicity Prediction Analysis

The computational toxicity prediction tool ProTox 3.0 was used to predict the toxicity profile of farnesol. The canonical SMILES structure of farnesol was obtained from PubChem and uploaded to the ProTox-3.0 web server for in silico toxicity assessment. ProTox-3.0 predicted different toxicological endpoints by machine learning techniques and molecular similarity-based methodologies17.The oral toxicity (LD50), toxicity class, hepatotoxicity, carcinogenicity, mutagenicity, immunotoxicity, cytotoxicity and other organ toxicity parameters of the selected chemical were analyzed by ProTox-3.0 platform. The toxicity categorization was interpreted on the basis of the globally harmonized system (GHS) toxicity categories provided by the server.

Determination of the safety profile of farnesol was done by analyzing toxicity data and evaluating its suitability as a potential therapeutic candidate against Alzheimer's disease. The predicted toxicity parameters were further correlated with pharmacological findings to assess the balance between efficacy and safety in the context of network pharmacology-based drug discovery.

RESULTS

Target Classification Analysis

The target classification analysis was carried out for farnesol, and it was categorized into different protein classes, including enzymes, kinases, nuclear receptors, cytochrome P450 enzymes, and G-protein-coupled receptors (Figure 1). The highest proportion of identified targets was enzymes, followed by nuclear receptors and kinases, suggesting that farnesol possesses broad-spectrum biological activity.

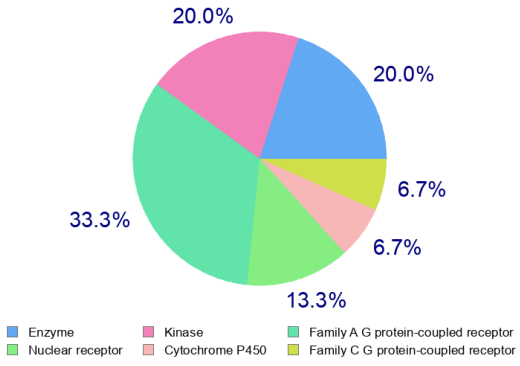

Figure 1.Pie chart showing classification of farnesol-associated targets into enzymes, kinases, nuclear receptors, cytochrome P450 enzymes, and G-protein-coupled receptors.

Identification of Common Targets Between Farnesol and Alzheimer's Disease

Venn diagram analysis identified 80 overlapping targets between farnesol-associated proteins and AD-related genes (Figure 2). These common targets were considered potential therapeutic targets involved in the anti-Alzheimer's effects of farnesol.

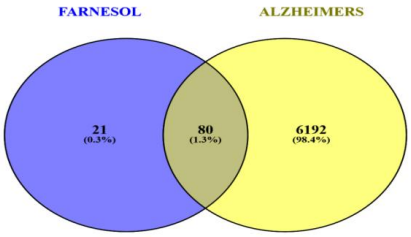

Figure 2.Venn diagram representing overlapping targets between farnesol-associated genes and Alzheimer's disease-related genes.

Protein–Protein Interaction Network Analysis

The PPI network generated through STRING analysis revealed extensive interactions among the common targets (Figure 3). Highly interconnected nodes in the network suggest that it has high regulation of multiple biological pathways involved in AD pathogenesis. High connectivity degrees were shown by multiple targets, indicating their importance in disease progression and therapeutic intervention.

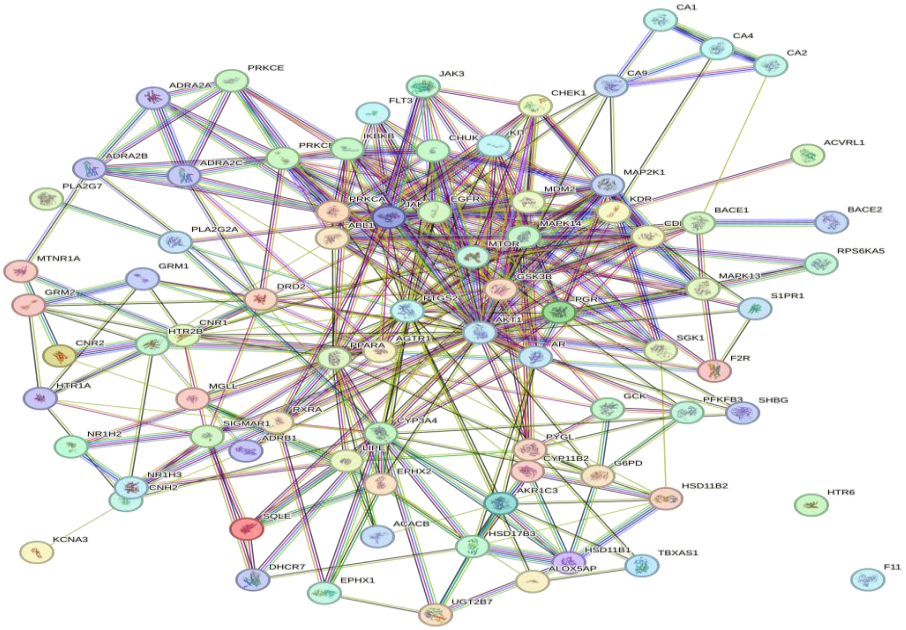

Figure 3. STRING-generated protein–protein interaction network demonstrating interactions among overlapping targets.

Identification of Hub Genes

Several major key target proteins, such as AKT1, MTOR, PTGS2, JUN, CASP3, EGFR, KDR, and MAPK family proteins, were identified by the MCC algorithm to distinguish the hub gene (Figure 4). Among these, AKT1 and MTOR exhibited strong centrality, highlighting the importance of PI3K-Akt signaling in the neuroprotective effects of farnesol. PTGS2 and JUN are related to brain inflammation and stress response in neuronal cells, whereas CASP3 was linked to apoptosis-mediated neuronal death.

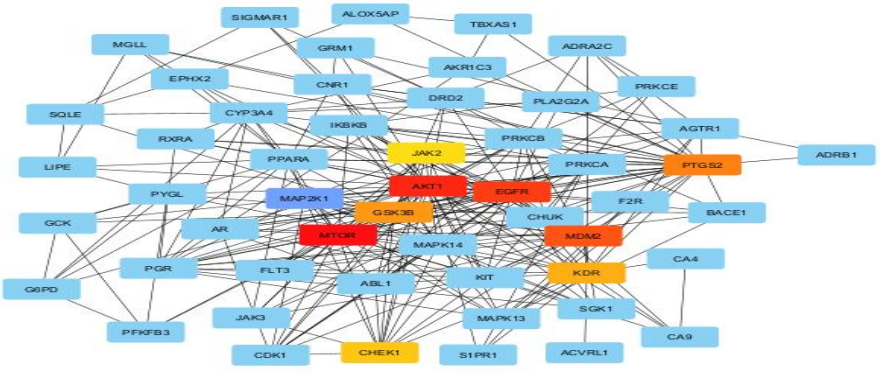

Figure 4. Hub gene network illustrating the top-ranked genes identified using maximal clique centrality analysis.

KEGG Pathway Enrichment Analysis

KEGG pathway enrichment analysis showed that the identified targets were significantly enriched in pathways associated with neurodegeneration, inflammation, oxidative stress, apoptosis, and neuronal survival (Figure 5).

The major enriched pathways included:

Apoptosis pathway, Oxidative stress-related pathways, Neuroactive ligand–receptor interaction, Alzheimer's disease pathway, TNF signaling pathway, EGFR tyrosine kinase signaling, PI3K-Akt signaling pathway, and MAPK signaling pathway

The enrichment results suggest that farnesol may exert neuroprotective effects through coordinated modulation of multiple signaling cascades.

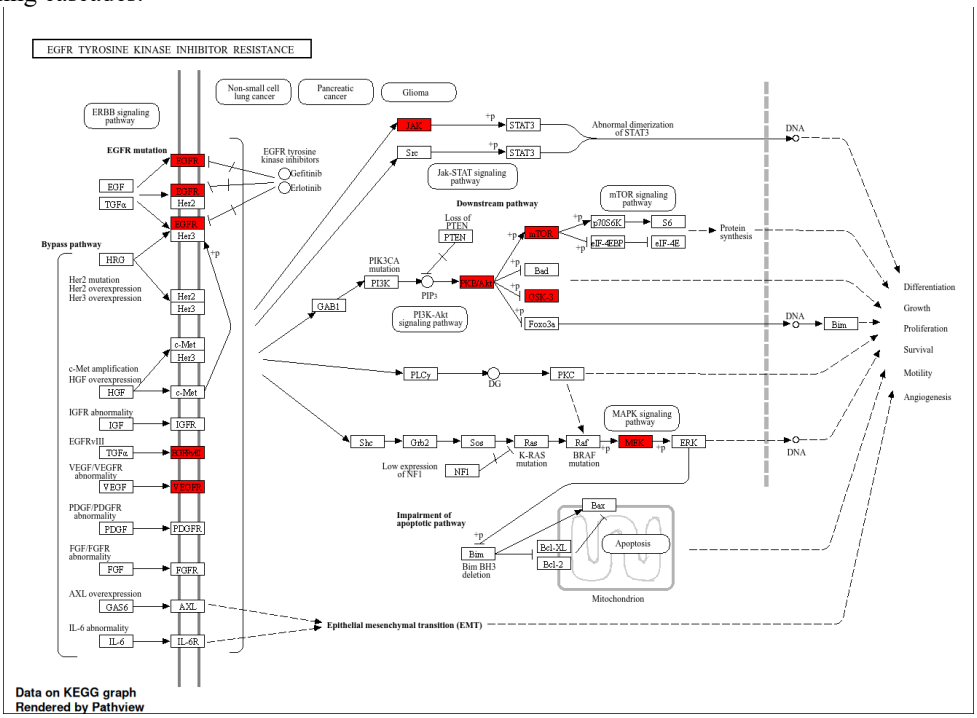

Figure 5.KEGG pathway enrichment analysis indicating the major signaling pathways involved in the anti-Alzheimer's effects of farnesol.

Gene Ontology and Enrichment Analysis

The SR plot and GO enrichment analysis demonstrated significant enrichment of biological processes associated with regulation of signal transduction by p53 class mediator, negative regulation of apoptotic signaling, response to oxidative stress, inflammatory response, and neuronal signaling.

The molecular function analysis revealed enrichment in receptor binding, transcription factor activity, kinase activity, and antioxidant-related functions. Cellular component analysis indicated the involvement of membrane-associated proteins, cytoplasmic vesicles, and receptor complexes.

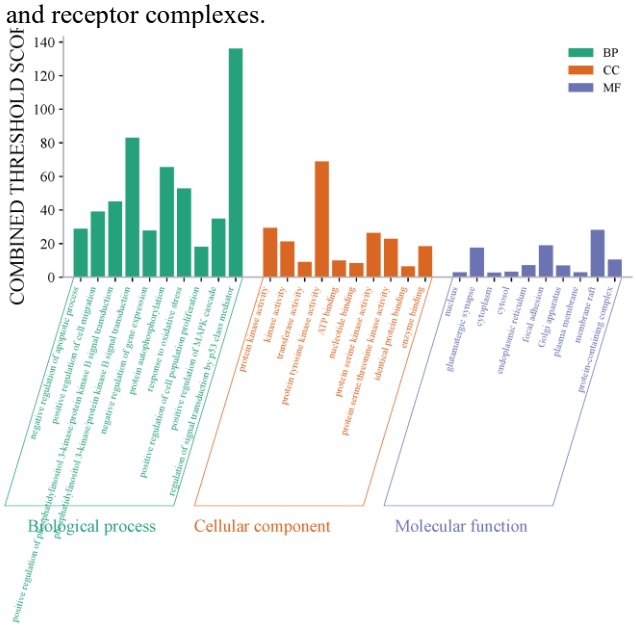

Figure 6. SR Plot of Gene Ontology Enrichment Analysis for Alzheimer's Disease-Associated Targets

Toxicity Prediction Analysis

The toxicity prediction analysis demonstrated that farnesol possesses a predominantly favorable safety profile. The results suggested that carcinogenicity, mutagenicity, cardiotoxicity, nephrotoxicity, hepatotoxicity, respiratory toxicity, and immunotoxicity, exhibited low activity probabilities.

The radar chart analysis confirmed that farnesol has strong blood-brain barrier permeability.Acetylcholinesterase (AChE), neurotransmitter receptors, and stress-response pathways, including Nrf2/ARE and PPAR-γ, were shown to have moderate interaction probabilities.

Hepatic drug-metabolizing enzymes CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 exhibited moderate chances of interaction, indicating a possible but limited effects on drug metabolism.

The network cluster analysis demonstrated that the majority of toxicological endpoints were grouped within the inactive cluster, supporting the low systemic toxicity profile of farnesol. Blood–brain barrier permeability and limited CYP2C9 interaction were among the few endpoints associated with the active cluster.

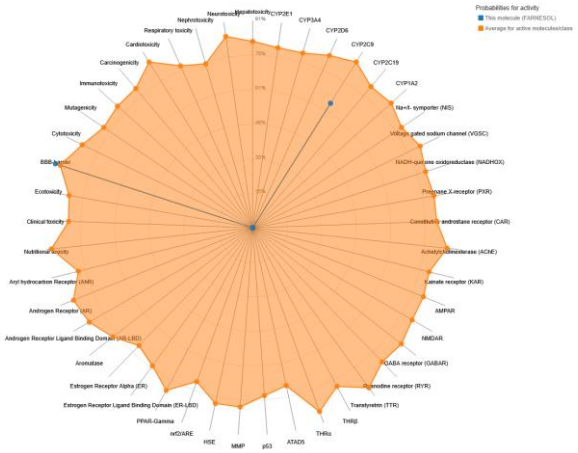

Figure 7. The toxicity radar chart illustrating the confidence of positive toxicity results

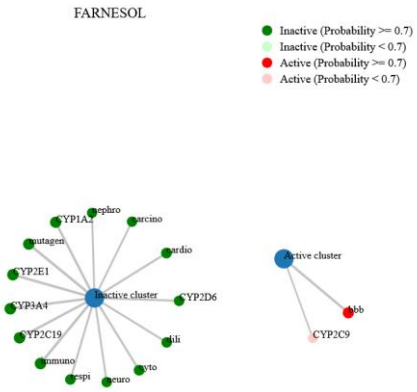

Figure 8. The network chart illustrating the connection between selected compound and predicted activities

DISCUSSION

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by multiple pathogenic pathways involving amyloid-beta (Aβ) accumulation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic degradation, and neuronal death. Because AD is multifactorial, treatment medicines that can modulate many molecular targets at the same time are regarded as more successful than single-target medications. In the present study, network pharmacology and in silico toxicity assessments suggested that farnesol may have neuroprotective effects by regulating multiple interrelated signaling pathways related to AD pathogenesis.

The buildup of amyloid-beta (Aβ) peptides is one of the earliest and most important processes in AD development, inducing oxidative stress and neurotoxicity18, 19.Reactive oxygen species were generated due to the excessive deposition of amyloid- beta in neuronal cells, which leads to lipid peroxidation, protein oxidation, mitochondrial damage, and DNA harm. Neuronal degeneration occurred further due to oxidative stress, which increases tau hyperphosphorylation, therefore eventually influencing synaptic transmission and cognitive function.

The neuroprotective effects of farnesol have already been reported in experimental and computational studies in models of Alzheimer's disease. Molecular docking studies showed good binding affinity of farnesol towards major AD associated targets viz acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and angiotensin-converting enzyme (ACE)20 which points towards its role in cholinergic regulation, amyloid-beta modulation and neuronal protection. Inhibition of AChE and BuChE can increase synaptic acetylcholine availability and cognitive function, while modulation of ACE may decrease amyloidogenic and neuroinflammatory processes. Impaired cholinergic function is thought to be a defining clinical feature of Alzheimer's disease and closely correlates with memory impairment and cognitive decline. In the present toxicity prediction investigation, farnesol exhibited a moderate interaction with

acetylcholinesterase (AChE). Excess AChE activity causes fast breakdown of acetylcholine in synaptic clefts and so impairs cholinergic neurotransmission. The current FDA-approved treatments for AD primarily work by inhibiting AchE, hence increasing the availability of acetylcholine. The interaction of farnesol with AchE indicates that this molecule could ameliorate synaptic signaling and cognitive performance by cholinergic regulation.

Notably, farnesol exhibited favourable pharmacokinetic properties and complied with Lipinski's Rule of Five, suggesting good drug-likeness and oral bioavailability. The low molecular weight, suitable lipophilicity and favorable ADMET properties of farnesol are promising for efficient membrane permeability and blood–brain barrier penetration, which are important features of neurotherapeutic agents20

Farnesol has shown considerable involvement of oxidative stress-related biological processes and apoptotic signaling pathways, which were confirmed by GO enrichment analysis. It's evidently shown that farnesol interefere with ROS-mediated neurodegenerative mechanisms

The study results proved that farnesol activates the Nrf2/ARE signaling pathway, which supports the antioxidant defense system. During oxidative stress, Nrf2 translocates to the nucleus and it activates the antioxidant response element (ARE)-dependent genes encoding endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Farnesol decreases the ROS generation and maintains mitochondrial integrity and protect neuronal cells from oxidative stress by promoting Nrf2-mediated antioxidant defense mechanisms21, 22.This mechanism is very important since oxidative stress is regarded as one of the key causes of neuronal death in Alzheimer's disease23

Neuroinflammation is also a key player in AD etiology. Activated brain immune cells called microglia and astrocytes release pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which in turn create chronic neuronal inflammation and synaptic dysfunction. When an inflammation persists for a longer period forms the amyloid-beta, and neuronal death occurs. Enrichment of MAPK signaling and TNF signaling was confirmed by a KEGG enrichment study. It implies that farnesol may modulate neuroinflammatory responses.Regulation of MAPK signaling by farnesol may control excessive inflammatory cytokine release and minimize neuronal stress-induced damage24,25

The PPAR-γ signaling pathway is responsible for reducing inflammation, glucose metabolism, mitochondrial homeostasis, and neuronal survival.Activation of PPAR-γ by farnesol decrasesmicroglial activation and inflammatory mediators, thus inhibiting neuroinflammation and oxidative stress. Therefore, farnesol helps in the reduction of inflammatory burden and the enhancement of neuronal protection.

The enrichment analysis discovered the PI3K-Akt signaling pathway, which is another important pathway involved in neuronal survival and synaptic plasticity.The activation of PI3K-Akt signaling inhibits pro-apoptotic proteins and increases cell survival by modulating downstream targets such as mTOR and GSK-3β. The dysregulation of GSK-3β has an important role in tau hyperphosphorylation and neurofibrillary tangle development in AD. Farnesol may modulate PI3K-Akt signaling to inhibit apoptotic pathways and tau-associated neurotoxicity, therefore maintaining neuronal integrity and cognitive function.

The results also found the interactions with neurotransmitter receptors such as GABA receptors, NMDA receptors, AMPA receptors, and kainate receptors.

The role of farnesol in modulating the NMDA and AMPA receptor activation may aid in preserving synaptic balance and minimizing excitotoxicity. Excitotoxic neuronal death in AD occurred due to excessive calcium influx and mitochondrial dysfunction. Modulation of GABAergic transmission may maintain neuronal excitability and promote neural communication. These receptor interactions suggest that farnesol may exert broader neuromodulatory effects beyond antioxidant and anti-inflammatory processes.

In the present investigation, the high blood–brain barrier (BBB) permeability of farnesol was confirmed by a pharmacokinetic study.BBB penetration is one of the challenging factors in the development of neurotherapeutic medicines26, 27.The projected BBB permeability indicates that farnesol is able to efficiently access neural regions and interact directly with molecular targets involved in AD pathogenesis. This characteristic feature of farnesol acts as a potential therapeutic candidate for the treatment of neurodegenerative illnesses.

The lower toxicity profiling of carcinogenicity, mutagenicity, cardiotoxicity, nephrotoxicity, hepatotoxicity, and respiratory toxicity was confirmed in silico toxicity studies28. Most of the toxicity-related endpoints were concentrated in the inactive group, showing a relatively safe toxicological profile.

In addition, cytochrome P450-related endpoints (CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were mostly inactive, indicating reduced chances of metabolic toxicity and drug–drug interactions. Such safety features are very important for chronic neurodegenerative disease therapy, as AD treatment generally involves long-term dosing.

Collectively, the combination of previous molecular docking evidence and the current network pharmacology, enrichment analysis, pharmacokinetic evaluation, and toxicity prediction strongly supports the idea that farnesol might serve as a promising multitarget neuroprotective agent against Alzheimer's disease. Further validation is required through molecular dynamics studies, in vitro neuronal assays, in vivo animal experiments and clinical investigations to confirm these computational findings and to prove its therapeutic applicability.

In summary, the present results suggest that farnesol may exert neuroprotection via a synergistic multitarget mechanism, including activation of antioxidant defense, inhibition of neuroinflammation, regulation of cholinergic neurotransmission, inhibition of apoptosis, modulation of synaptic signaling, and maintenance of mitochondrial function. The combined network pharmacology and toxicology evaluations provide compelling evidence for the therapeutic potential of farnesol as a multifunctional option for Alzheimer's disease treatment. However, further validation using molecular docking, in vitro neuronal models, animal studies, pharmacokinetic studies, and clinical trials is required to verify these computational predictions and to determine their practical application.

CONCLUSION

The research report of the present study revealed that farnesol is a promising multi target therapeutic agent for Alzheimer's disease. It can modulate oxidative stress, inflammation, apoptosis, and neuronal signaling pathways. In silico toxicity analysis showed lower systemic toxicity and effective blood-brain barrier permeability, and a network pharmacology study confirms the favourable neuroprotective potential. However, farnesol favours the curation of AD via a different pathway, as indicated by network pharmacology; further clinical investigation and experimental validation are needed to confirm its therapeutic potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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