

In Silico and Network-Based Identification of Plant-Derived Compounds Targeting Amyloid Pathways in Alzheimer's Disease

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Abstract - Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by memory loss and cognitive impairment, primarily associated with the abnormal aggregation of amyloid- β (A β) peptides in the brain. The accumulation of A β initiates a cascade of pathological events, including synaptic dysfunction, oxidative stress, neuroinflammation, and neuronal death. Although several therapeutic strategies have been developed to target amyloid pathology, most have shown limited success, largely due to the complex and multi-factorial nature of the disease. Plant-derived phytochemicals are emerging as promising candidates for AD management because of their natural origin, structural diversity, and ability to interact with multiple biological targets. This review summarizes recent computational studies that explore the anti-amyloid potential of phytochemicals using *in silico* techniques. Molecular docking analyses indicate that various flavonoids, polyphenols, and terpenoids exhibit favorable binding interactions with key AD-related targets such as amyloid- β aggregates, β -secretase (BACE1), acetylcholinesterase, and tau-related enzymes. Network pharmacology approaches further reveal that these compounds influence interconnected protein networks involved in amyloid processing, oxidative stress regulation, and neuronal survival. In addition, *in silico* pharmacokinetic and toxicity predictions suggest that several phytochemicals possess acceptable drug-likeness properties, including predicted blood-brain barrier permeability and low toxicity. Molecular dynamics simulations reported in selected studies support the stability of phytochemical-protein complexes under simulated physiological conditions. Overall, this review highlights the usefulness of computational and network-based approaches in identifying plant-derived compounds with multi-target potential, providing a foundation for future experimental and therapeutic studies in Alzheimer's disease.

Key Words: Alzheimer's disease; Amyloid- β ; Phytochemicals; *In silico* studies; Molecular docking; Network pharmacology; Neurodegeneration; Drug-likeness

1. INTRODUCTION

1.1 Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, affecting millions worldwide and contributing significantly to disability and healthcare burden. Clinically, AD is characterized by progressive decline in memory, executive function, and learning capacity caused by complex molecular and cellular disturbances. A central pathological feature is the accumulation of amyloid- β (A β) peptides produced from proteolytic cleavage of amyloid precursor protein (APP). Under pathological conditions, A β fragments misfold and assemble into soluble oligomers and insoluble extracellular plaques that disrupt neuronal communication and synaptic function (Selkoe D and Hardy J *et al.*, 2016; Roda *et al.*, 2022). Soluble A β oligomers are particularly neurotoxic, impairing hippocampal long-term potentiation, disrupting calcium homeostasis, destabilizing neuronal membranes, and triggering oxidative stress pathways (Zhang *et al.*, 2023). These early synaptic disturbances represent some of the earliest detectable events in AD progression. Amyloid pathology also interacts with other neurodegenerative processes. A β accumulation promotes hyperphosphorylation and neurofibrillary tangle formation through multiple signaling pathways, establishing a pathological feedback loop that accelerates neuronal dysfunction (Roda *et al.*, 2022; Nam *et al.*, 2025). Tau pathology correlates strongly with cognitive decline and disease severity, highlighting the synergistic relationship between A β and tau in AD progression (Nam *et al.*, 2025; Zhang *et al.*, 2023). Consequently, targeting a single pathway may be insufficient to halt disease progression.

1.2 Limitations of Current Amyloid-Targeted Therapeutic Strategies

Therapeutic strategies have therefore largely focused on reducing A β production or enhancing its clearance. Approaches such as β -secretase (BACE1) inhibition and monoclonal antibodies targeting amyloid aggregates can reduce plaque burden on imaging; however, clinical trials have shown only modest cognitive improvements (Tonegawa-Kuji *et al.*, 2025; Pernecky *et al.*, 2023). Several factors contribute to this limitation. Many antibody therapies primarily target insoluble fibrillar plaques rather than the smaller soluble oligomers responsible for major synaptic toxicity (Tolar *et al.*, 2020). In addition, A β deposition begins decades before clinical symptoms appear, meaning that by the time AD is diagnosed, downstream processes such as tau aggregation, neuroinflammation, and neuronal loss are already established (Selkoe D and Hardy J *et al.*, 2016; Zhang *et al.*, 2023). Further challenges include limited drug delivery across the blood-brain barrier for large antibody molecules and safety concerns such as amyloid-related imaging abnormalities (ARIA), which include cerebral edema and microhemorrhages (Cummings *et al.*, 2025; Tonegawa-Kuji *et al.*, 2025; Eric Larson *et al.*, 2012). Moreover, AD is now widely recognized as a multifactorial disorder involving tau pathology, chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, and vascular impairment in addition to amyloid accumulation (Nam *et al.*, 2025; Yiannopoulou & Papageorgiou *et al.*, 2020). These complexities highlight the limitations of single-target therapeutic strategies.

1.3 Phytochemicals as Multi-Target Candidates and Scope of the Review

In this context, phytochemicals—bioactive compounds derived from plants—have gained attention as potential multi-target therapeutic candidates. Classes such as flavonoids, polyphenols, and terpenoids exhibit antioxidant, anti-inflammatory, cholinesterase-inhibitory, anti-aggregatory, and kinase-modulating activities that correspond to multiple pathological pathways of AD. Compared with many synthetic drugs, phytochemicals often demonstrate lower toxicity and favorable pharmacokinetic profiles, making them attractive scaffolds for CNS-directed drug discovery. Computational studies support their therapeutic potential, with *in silico* docking analyses showing that spice-derived phytochemicals exhibit strong binding affinity toward targets such as BACE1 and AChE, suggesting modulation of both amyloidogenic and cholinergic pathways (Alom *et al.*, 2023). Additional docking and molecular dynamics studies indicate that dietary flavonoids including quercetin, catechins, and resveratrol can inhibit A β 1-40 and A β 1-42 aggregation by stabilizing non-aggregating conformations or blocking key aggregation sites (Mariyana Atanasova *et*

al., 2024). Computational analyses have also identified phytochemicals capable of inhibiting tau-associated kinases such as MAPK14 and GSK3 β , which contribute to tau hyperphosphorylation (Zheng Zhao *et al.*, 2024). These findings highlight the broader multi-pathway potential of phytochemicals in addressing both amyloid and tau pathology. Given the growing volume of computational evidence, a systematic synthesis of phytochemical-based anti-amyloid research is needed. Therefore, this review integrates findings from molecular docking, molecular dynamics simulations, network pharmacology, and ADMET prediction studies published between 2018 and 2025. Through this integrated analysis, the review aims to map phytochemical interactions with key AD-related targets, evaluate their multi-target potential, and identify promising lead compounds for future experimental validation.

2. Computational Methods Used to Evaluate Anti-Amyloid Phytochemicals

2.1 Molecular Docking

Computational evaluation of anti-amyloid phytochemicals often begins with molecular docking, a widely used technique that predicts how strongly and in what orientation a compound binds to Alzheimer's disease-related target proteins. This approach is central to early-stage drug discovery because it enables rapid screening of interactions across multiple pathological proteins implicated in AD, including BACE1, γ -secretase, presenilin-1/2, tau, and amyloid- β (Mouchlis *et al.*, 2020). The structural diversity of these targets requires flexible computational tools capable of evaluating a broad range of ligand-protein interactions. Docking helps identify binding pockets, estimate binding affinity, and detect stabilizing interactions such as hydrogen bonds and hydrophobic contacts. These predictions indicate whether a phytochemical may inhibit enzymatic activity, disrupt substrate binding, or modulate pathogenic conformational changes. Such analysis is particularly important for phytochemicals, which often contain chemically diverse structures such as polyphenolic rings, aromatic substitutions, and glycosylation groups that influence binding behavior (Martiz *et al.*, 2022). As a first line screening tool, docking enables rapid prioritization of natural compounds capable of inhibiting amyloidogenic cleavage, blocking A β aggregation, or modulating tau-related pathways. It also supports efficient virtual screening of phytochemical libraries, which is faster and more cost-effective than conventional biochemical assays. Because AD involves multiple interacting pathways, docking also helps identify compounds with potential multi-target activity, making it an essential tool for phytochemical-based AD drug discovery (Bhogal *et al.*, 2025; Chitranshi *et al.*, 2021).

2.2 Molecular Dynamics (MD) Simulations

While docking provides a static representation of ligand binding, molecular dynamics (MD) simulations evaluate whether these interactions remain stable under physiological conditions. MD models atomic motion within ligand-protein complexes while accounting for solvent effects, temperature fluctuations, and structural flexibility. This is particularly important in Alzheimer's disease because proteins such as A β and tau exhibit significant conformational plasticity, making their interactions with small molecules highly dynamic. MD analysis is especially valuable for phytochemicals, which often contain flexible aromatic frameworks and multiple rotatable bonds that can adopt different conformations within the binding pocket (Bhogal *et al.*, 2025). By simulating molecular motion over time, MD reveals whether stabilizing interactions persist and whether structural changes in the protein influence ligand affinity. Key parameters such as RMSD, RMSF, and hydrogen-bond stability indicate whether a compound remains stably bound or becomes destabilized during simulation. These metrics also help distinguish compounds with similar docking scores by identifying those with stronger dynamic compatibility. MD simulations can further estimate binding free energy using MM-PBSA or MM-GBSA methods, refining the ranking of promising compounds. By complementing docking predictions, MD strengthens confidence in phytochemicals that demonstrate both strong binding and dynamic stability, providing a more reliable basis for selecting candidates for experimental validation in AD research (Amani A. Eshtiwi *et al.*, 2023; Martiz *et al.*, 2022; Chitranshi *et al.*, 2021).

Many natural compounds display excellent binding properties but fail due to inadequate pharmacokinetic or safety profiles. ADMET models are essential for predicting absorption, distribution, metabolism, excretion, and toxicity, enabling early identification of compounds with poor pharmacokinetic behavior (Mouchlis *et al.*, 2020). These predictions significantly reduce the likelihood of late-stage drug failure and help guide chemical optimization. This is particularly important in Alzheimer's disease, where therapeutic molecules must cross the blood-brain barrier while maintaining safety and metabolic stability. Only a fraction of phytochemicals naturally possesses the physicochemical properties required for efficient CNS penetration, making ADMET screening indispensable. Tools such as SwissADME, pkCSM, and ADMETlab provide predictions regarding oral bioavailability, BBB penetration, toxicity risks, P450 interactions, solubility, and other pharmacokinetic features (Martiz *et al.*, 2022). These platforms integrate machine learning models and extensive curated datasets to improve predictive power. Even compounds with strong docking scores may be unsuitable if they display poor ADMET characteristics, highlighting the importance of integrating these predictions early in computational screening pipelines. For example, compounds with poor solubility or high predicted toxicity must be modified before advancing. By combining structural evaluation with pharmacokinetic assessment, researchers can focus on phytochemicals that are not only biologically active but also possess the properties necessary for CNS delivery and therapeutic viability. (Chitranshi *et al.*, 2021)

2.4 Network Pharmacology

Because Alzheimer's disease is driven by interconnected pathological processes—including neuroinflammation, oxidative stress, metabolic dysregulation, amyloid accumulation, and tau hyperphosphorylation—network pharmacology provides an essential systems-level perspective for evaluating phytochemicals (Wen *et al.*, 2025). Natural compounds typically exert their effects on multiple biochemical pathways simultaneously, making traditional single-target drug models insufficient for evaluating their true therapeutic potential. Instead of focusing on a single protein, this approach maps how natural compounds interact with multiple targets simultaneously, revealing broader therapeutic patterns. Network models routinely identify hub genes such as IL6, STAT3, SRC, and AKT1, which play central roles in signaling pathways relevant to neuronal survival, inflammatory cascades, and amyloid metabolism (Sharifi-Rad *et al.*, 2022). Target enrichment and pathway analysis further clarify how these interactions influence disease-relevant pathways, such as PI3K-Akt signaling, MAPK cascades, synaptic plasticity regulation, and mitochondrial pathways. By integrating compound-target predictions, protein-protein interaction networks, and pathway enrichment results, network pharmacology helps clarify

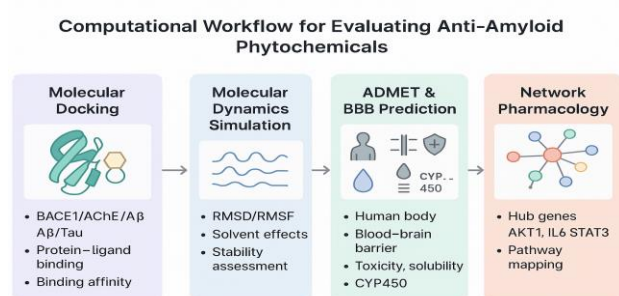


Figure 1: Computational Workflow for Evaluating Anti-Amyloid Phytochemicals

2.3 ADMET and Drug-Likeness Prediction

In addition to binding affinity and stability, drug-likeness plays a major role in determining whether a phytochemical can serve as a viable therapeutic agent.

how phytochemicals influence large-scale molecular networks rather than isolated mechanisms. Many studies further validate these predicted targets through docking and MD simulations, strengthening the mechanistic evidence for multi-target activity (Zeng *et al.*, 2019). This integrated approach makes network pharmacology especially valuable for natural products, which often exert synergistic effects across multiple disease pathways and may offer advantages over single-target synthetic drugs in complex disorders like AD (Zhao *et al.*, 2025; Aktary *et al.*, 2025).

Table 2.1: Computational Methods Used to Evaluate Anti-Amyloid Phytochemicals

Method	Purpose	Strengths	Limitations
Molecular Docking	Predicts binding of phytochemicals with AD targets (BACE1, AChE, Aβ, tau)	Fast and cost-effective; suitable for large compound screening	Uses static protein structures and simplified scoring
Molecular Dynamics (MD)	Evaluates stability of ligand-protein complexes	Captures protein flexibility and solvent effects	Computationally expensive; limited simulation time
ADMET Prediction	Assesses drug-likeness, BBB permeability, and toxicity	Filters unsuitable compounds early	Limited datasets; weaker correlation with in vivo results
Network Pharmacology	Identifies multi-target interactions and pathways	Provides systems-level insight	Dependent on database quality; may oversimplify networks

3. Phytochemical Classes with Anti-Amyloid Potential

3.1 Phytochemicals

Phytochemicals constitute one of the most diverse natural reservoirs of bioactive compounds, and growing evidence over the past decade indicates that several structural

classes—including flavonoids, alkaloids, terpenoids, polyphenols, and phenolic acids—exert significant anti-amyloid and neuroprotective activities relevant to Alzheimer’s disease. These natural molecules possess unique structural scaffolds, often with multiple hydroxyl groups, aromatic rings, or heterocyclic frameworks that allow them to interact with diverse molecular targets involved in AD pathology. Flavonoids such as hesperidin, naringenin, and hesperetin have been repeatedly highlighted for their potent inhibitory effects on BACE1, AChE, and BChE, with hesperidin demonstrating low micromolar inhibition and noncompetitive binding behavior that complements its strong antioxidant and free-radical-scavenging capacity (Lee *et al.*, 2018). Beyond direct enzymatic inhibition, these compounds influence cholinergic transmission, prevent disruption of synaptic function, and counter early oxidative insults that precipitate neuronal vulnerability. Alkaloids, including berberine, palmatine, and convolidine, contribute an additional therapeutic dimension by interacting with multiple targets such as BACE1, AChE, tau kinases, and Aβ aggregation interfaces, often with stronger binding affinities than their flavonoid counterparts (Wang *et al.*, 2022). Convolidine, for example, has shown submicromolar inhibition of BACE1, while berberine continues to be recognized for its multitarget neuroprotective properties, including modulation of inflammatory signaling, mitochondrial stabilization, and attenuation of tau phosphorylation (Gheidari *et al.*, 2024). Together, these phytochemical classes demonstrate the capacity to intervene at several pathological checkpoints within the amyloid cascade and cholinergic dysfunction that characterize AD, highlighting their potential as multifaceted therapeutic agents (Mirza *et al.*, 2022 and sukriti *et al.*, 2023).

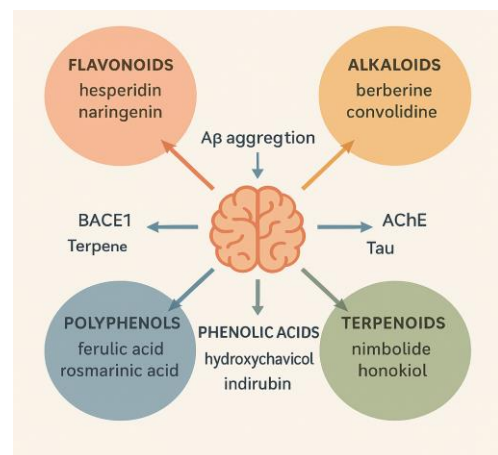


Figure 2: Phytochemical Classes and Their Molecular Targets in Alzheimer’s Disease

3.2 Terpenoids

Terpenoids represent another structurally diverse class of phytochemicals with substantial anti-Alzheimer's potential. Compounds such as nimbolide, honokiol, ursolic acid, and carnosic acid have demonstrated inhibitory actions against AChE, BACE1, GSK-3 β , and A β aggregation, reflecting their broad mechanistic range (Awasthi *et al.*, 2018). These terpenoids often feature lipophilic frameworks that facilitate interactions within hydrophobic pockets of AD-related enzymes and aggregation-prone proteins. Nimbolide and honokiol show strong docking affinities that correlate with enzymatic inhibition and neuroprotective activity in various *in vitro* and computational models (Youn & Jun *et al.*, 2024). Honokiol has been shown to inhibit BACE1, AChE, and GSK-3 β within low to moderate micromolar ranges, suggesting a strong potential to modulate both amyloidogenic and tau-related pathways. Carnosic acid further contributes by exerting synaptic protection through modulation of oxidative and inflammatory cascades, supporting neuronal resilience under various stress conditions (Upadhayay *et al.*, 2025). Phenolic acids, represented by hydroxychavicol and indirubin, provide complementary mechanisms by modulating key regulatory proteins such as COMT, HSP90AA1, GAPDH, and GSK-3 β . These compounds participate in PI3K/Akt, cAMP, HIF-1, and Rap1 signaling, influencing tau phosphorylation, mitochondrial homeostasis, and neuroinflammatory responses. Their structural simplicity belies their pharmacological versatility, and the combined structural diversity of terpenoids and phenolic acids enables them to occupy unique binding pockets and exert multipronged effects that extend beyond simple enzymatic inhibition, reinforcing their significance within natural product-based AD drug discovery (sara zarei *et al.*, 2024).

3.3 Polyphenols

Polyphenols such as ferulic acid, rosmarinic acid, and thoningianin A contribute yet another important class of neuroprotective molecules capable of modulating A β aggregation, tau fibrillization, cholinesterase activity, and mitochondrial function (Mirza *et al.*, 2022). Owing to their antioxidant and anti-inflammatory nature, polyphenols frequently counteract early neuronal toxicity and support synaptic integrity. Ferulic acid, widely studied for its antioxidant potency, has demonstrated inhibition of AChE and attenuation of A β fibril formation *in vitro*, offering biochemical evidence of its dual protective action (Mugundhan *et al.*, 2024). Rosmarinic acid and its related derivatives further suppress A β oligomerization, reduce plaque maturation, and stabilize neuronal redox balance by mitigating ROS overproduction. Thoningianin A, a more structurally complex polyphenol, has shown strong affinity for both A β and tau proteins, reflecting true multitarget potential and suggesting broader modulation

of protein misfolding pathways. These polyphenolic compounds often exhibit favorable docking scores and stable MD trajectories that support their structural compatibility with relevant AD targets (Selvan Kaviyarasu *et al.*, 2025). Additionally, they participate in regulating inflammatory mediators, restoring mitochondrial membrane potential, and controlling apoptotic pathways—processes central to preventing progressive neuronal degeneration. Their activity across diverse mechanistic domains reinforces the idea that multiphenolic scaffolds may be particularly well suited to addressing the multifactorial complexity of AD pathology (zeng *et al.*, 2022).

3.4 Phytochemicals against Alzheimer's using Docking studies

The therapeutic promise of these phytochemical classes is further supported by integrated computational and experimental validation strategies (Upadhayay *et al.*, 2025). Molecular docking and MD simulations consistently demonstrate that compounds from these classes bind stably to AD-related targets, often achieving binding energies that rival or exceed those of established inhibitors. Dynamic stability assessments reveal whether these interactions remain intact under physiologically relevant conditions, strengthening confidence in their true biological utility. Network pharmacology adds an essential systems-level perspective, revealing how these compounds interact with interconnected signaling axes such as PI3K/Akt, calcium regulation, neuroactive ligand-receptor pathways, and stress-response networks (Youn & Jun *et al.*, 2024). These models help identify hub genes, regulatory nodes, and potential synergistic interactions between phytoconstituents, highlighting their multi-target therapeutic promise. *In vitro* validation—including assays of AChE inhibition, BACE1 activity suppression, anti-amyloid aggregation effects, and tau phosphorylation reduction—provides experimental reinforcement for computational predictions, confirming the biological relevance of these natural scaffolds (Gheidari *et al.*, 2024). Together, flavonoids, alkaloids, terpenoids, polyphenols, and phenolic acids represent a comprehensive and mechanistically diverse group of phytochemicals with promising multi-target efficacy, offering valuable chemical templates for the development of next-generation therapeutics aimed at modifying the course of Alzheimer's disease (Lee *et al.*, 2018 and Kakarla Ramakrishna *et al.*, 2024).

Table 2: Major Phytochemical Classes with Anti-Alzheimer's Potential

Phytochemical Class	Key Compounds	Major AD Targets	Mechanistic Actions
Flavonoids	Hesperidin, Naringenin, Hesperetin	BACE1, AChE, Aβ aggregation	Antioxidant, cholinergic modulation, Aβ inhibition
Alkaloids	Berberine, Palmatine, Convolidine	BACE1, AChE, Tau kinases	Anti-inflammatory, multi-target binding
Terpenoids	Nimbolide, Honokiol, Ursolic acid, Carnosic acid	AChE, BACE1, GSK-3β	Multi-enzyme inhibition, synaptic protection
Polyphenols	Ferulic acid, Rosmarinic acid, Thonningianin A	AChE, Aβ, Tau	Antioxidant, anti-amyloid, mitochondrial protection
Phenolic Acids	Hydroxychavicol, Indirubin	COMT, GSK-3β	Tau modulation, PI3K/Akt regulation
<i>Senna auriculata</i> (plant)	Lucenin-II, Stellarin-II	PDE5	cGMP signaling, antioxidant & anti-inflammatory

to its rich content of flavonoids, polyphenols, and anthraquinones. Recent phytochemical analyses have identified flavone C-glycosides such as lucenin-II and stellarin-II as major bioactive constituents, along with a broader repertoire of phenolic compounds that contribute to its antioxidant and anti-inflammatory profile (Alshehri *et al.*, 2021 and Bellavite *et al.*, 2023). These molecules possess structural features that are frequently associated with therapeutic activity against neurodegenerative pathways, including aromatic rings capable of π-π interactions, hydrogen-bond donors essential for enzyme binding, and glycosidic linkages that enhance stability and bioavailability (Sungad *et al.*, 2024). The presence of these diverse chemical scaffolds provides *S. auriculata* with the capacity to interact across multiple neurobiological pathways relevant to Alzheimer's disease. Its phytochemical complexity mirrors that of many plants traditionally used for cognitive enhancement or neuroprotection, and recent studies increasingly support the relevance of its flavonoid-rich composition for mitigating early pathological triggers of AD such as oxidative stress, impaired neurotransmission, and pro-inflammatory signaling (Sanchez *et al.*, 2023).

4.2 PDE5 Inhibition and Its Neuroprotective Relevance in Alzheimer's Disease

A distinctive mechanistic insight into *S. auriculata* emerges from the discovery that its flavone C-glycosides strongly inhibit phosphodiesterase-5 (PDE5), a regulator of cGMP signaling implicated in synaptic plasticity and neuronal survival. Molecular docking and molecular dynamics simulations have demonstrated exceptionally strong binding of lucenin-II and stellarin-II to the active site of PDE5, with binding free energies of -38.8 kcal/mol and -34.59 kcal/mol, respectively, values that exceed those of several known PDE5 inhibitors. In vitro assays further validate these computational predictions, showing that extracts enriched in these flavonoids produce more than 50% inhibition of PDE5 activity at 100 µg/mL (Peixoto *et al.*, 2015). Because PDE5 regulates cGMP-dependent signaling pathways, its inhibition enhances neuroplastic responses, supports long-term potentiation, and improves cerebrovascular perfusion, all of which are processes that decline early in Alzheimer's disease (Newby *et al.*, 2022 and Ribauda *et al.*, 2020). Although PDE5 is not traditionally considered a core amyloid target, its modulation has been associated with improved cognitive function and attenuation of Aβ pathology in several experimental models of AD. Therefore, the strong PDE5-targeted activity of *S. auriculata* suggests a novel therapeutic angle that complements classical amyloid-centric strategies while also providing a mechanistic bridge between vascular, synaptic, and cognitive dimensions of the disease (Qu *et al.*, 2024).

4. Network Pharmacology Insights for Anti-Amyloid Phytochemicals

4.1 Phytochemical Composition and Structural Features of *S. auriculata*

Senna auriculata, also known as *Cassia auriculata*, has recently gained attention as a medicinal plant with promising neuroprotective properties, largely attributed

4.3 Broader Anti-Alzheimer's Mechanisms of Flavonoids and Polyphenols

Beyond its PDE5-targeted effects, the broader classes of phytochemicals found abundantly in *S. auriculata*—particularly flavonoids and polyphenols—align closely with well-established mechanisms of anti-Alzheimer's activity documented across numerous medicinal plants (Kruszka *et al.*, 2025 and Rębas *et al.*, 2025). Extensive research supports that these compounds exert potent antioxidant effects by scavenging reactive oxygen species, upregulating endogenous antioxidant enzymes, and mitigating mitochondrial dysfunction (Calderaro *et al.*, 2022). They also demonstrate anti-inflammatory properties by modulating NF- κ B, Nrf2, and cytokine signaling pathways, thereby reducing microglial activation and neuronal stress (Uddin *et al.*, 2020). Given that oxidative imbalance and chronic neuroinflammation are central amplifiers of amyloid and tau pathology, the ability of these phytochemicals to intervene early in these cascades provides significant therapeutic value (Li *et al.*, 2022). Moreover, reviews consistently show that flavonoids and polyphenols can inhibit AChE, reduce A β oligomerization, interfere with fibril maturation, and modulate tau phosphorylation (Vicente-Zurdo *et al.*, 2024). Even though these specific mechanisms have yet to be directly validated within *S. auriculata*, the strong mechanistic parallels between its phytochemical profile and that of other neuroprotective plants suggest that similar anti-amyloid properties are likely. As such, the plant's flavonoid- and polyphenol-rich extracts can be reasonably positioned within the broader framework of multi-target agents capable of addressing the complex interplay of oxidative stress, amyloid burden, and synaptic dysfunction characteristic of AD progression (Jalouli *et al.*, 2025 and Minocha *et al.*, 2022).

4.4 Integrative Computational and Experimental Evidence Supporting Multi-Target Activity

The convergence of computational prediction and experimental validation further strengthens the case for *S. auriculata* as a viable source of neuroprotective phytochemicals (Ghosh *et al.*, 2023). Docking and MD simulations confirm that its constituent molecules bind stably to PDE5, while analogous phytochemicals from related species are repeatedly shown to exhibit strong affinity for key Alzheimer's targets such as AChE, BACE1, A β monomers and fibrils, and tau kinases. Network pharmacology studies—from broader phytochemical research—highlight the ability of structurally similar molecules to modulate PI3K/Akt signaling, enhance mitochondrial stability, and suppress neuroinflammatory mediators (Pradeep *et al.*, 2025). In vitro assays complement these computational insights by demonstrating direct effects such as suppression of AChE and BACE1 activity, attenuation of oxidative stress, and

reduction of pro-inflammatory markers. Although direct anti-amyloid evidence for *S. auriculata* remains limited, the mechanistic overlap between its phytochemical constituents and well-characterized anti-Alzheimer's compounds strongly supports its potential as a multi-target therapeutic contributor. Collectively, these findings indicate that *S. auriculata* may serve not only as an antioxidant and anti-inflammatory neuroprotective agent but also as a promising candidate for future experimental exploration against amyloidogenic pathways, thereby positioning this plant as a valuable addition to the natural-product-based drug discovery landscape for Alzheimer's disease (Alom *et al.*, 2023).

5. Limitations of Computational Approaches

5.1 Limitations of Molecular Docking

Molecular docking is one of the most widely used computational techniques for predicting ligand-protein interactions, but it has several inherent limitations that restrict its predictive accuracy in Alzheimer's disease (AD) research (Khanna *et al.*, 2023). Docking relies on static, pre-defined protein structures, meaning the conformational flexibility of enzymes like BACE1, AChE, and tau kinases is not fully captured. This becomes a critical weakness because AD-related proteins exhibit dynamic binding pockets and undergo conformational shifts that strongly influence ligand affinity. Additionally, simplified scoring functions cannot reliably distinguish between true binders and false positives, particularly for phytochemicals that possess large, flexible, and highly polar structures. As a result, docking often overestimates binding affinity for certain compounds while overlooking others that may possess more realistic biological activity (Pradeep *et al.*, 2025). These limitations have meaningful implications for phytochemical-based AD research, where natural compounds display diverse chemical scaffolds that are not always compatible with standard docking algorithms. Furthermore, docking frequently fails to model solvation effects, metal ion coordination, or induced-fit changes—factors that significantly affect amyloid- and tau-related target interactions. In the context of drug discovery, this can lead to the prioritization of candidates that perform well computationally but lack biological relevance in vitro or in vivo systems. Therefore, while docking remains a valuable initial screening tool, its results must be interpreted cautiously and validated with complementary computational and experimental approaches to reduce the risk of misleading conclusions about phytochemical efficacy in AD pathways (Guerguer *et al.*, 2025).

Limitations of Computational and Network Pharmacology Methods in Alzheimer's Phytochemical Research





<p>Docking and MD Limitations</p> <ul style="list-style-type: none"> • Static protein models • Short simulations • False poses 	<p>ADMET and BBB Prediction Issues</p> <ul style="list-style-type: none"> • Poor in vivo correlation • Toxicity errors 
<p>Network Pharmacology Bias</p> <ul style="list-style-type: none"> • Incomplete databases • Missing interactions 	<p>Lack of Experimental Validation</p> <ul style="list-style-type: none"> • Few in vitro or in vivo confirmations 

Figure 3: Key Limitations of Computational and Network Pharmacology Approaches in AD Phytochemical Research

5.2 Limitations of Molecular Dynamics (MD) Simulations

Molecular dynamics simulations provide far deeper insight into protein–ligand interactions than docking, but they also carry notable challenges that affect their reliability in AD-related phytochemical research. MD requires extensive computational power, and most studies operate within short simulation windows—typically 10–100 nanoseconds. Such timescales are insufficient to model major conformational rearrangements in proteins like amyloid- β , tau, or gamma-secretase, all of which undergo slow, complex structural transitions. Additionally, inaccuracies in force fields can lead to incorrect sampling of ligand orientations, especially for phytochemicals with unusual glycosidic, aromatic, or polyphenolic groups that are not optimally parameterized in standard MD libraries (Wen *et al.*, 2025). These constraints create substantial uncertainty when evaluating the stability of ligand binding in AD targets. Since phytochemicals often interact with intrinsically disordered proteins such as A β and tau, short MD simulations may fail to capture critical intermediate states, aggregation-prone conformations, or long-range structural shifts (Pradeep *et al.*, 2025). Furthermore, the high flexibility of natural compounds increases the likelihood of simulation artifacts that may appear as false stabilization or misleading interaction patterns. In drug development contexts, this may contribute to false confidence in weak candidates or the dismissal of compounds that could behave differently under physiological conditions. Thus, while MD is a crucial extension of docking, it must be interpreted alongside

experimental assays and advanced enhanced-sampling techniques to provide accurate mechanistic insights (Guerguer *et al.*, 2025).

5.3 Challenges in ADMET and Drug-Likeness Prediction

ADMET prediction tools—such as pkCSM, SwissADME, and ADMETlab—play a vital role in assessing the drug-likeness of phytochemicals, yet they remain limited by significant uncertainties that affect translational potential. These models rely heavily on pre-existing datasets, which are often biased toward synthetic, small-molecule pharmaceuticals rather than complex natural products. Phytochemicals typically contain multiple rings, glycosidic bonds, and large polar regions that violate Lipinski rules, making them poorly represented in ADMET training datasets. As a result, predictions for blood–brain barrier penetration, cytochrome P450 metabolism, and toxicity risks may be inaccurate or inconsistent when applied to plant-derived compounds (Wen-Ye *et al.*, 2022). Furthermore, ADMET models struggle to account for metabolic biotransformation, especially for phytochemicals that undergo rapid conjugation, hydrolysis, or microbial degradation in vivo. These transformations can significantly alter biological activity, sometimes producing metabolites that are either more potent or more toxic than the parent compound—outcomes that current in silico tools rarely predict effectively. In the context of AD, where central nervous system penetration is a strict requirement, inaccurate ADMET predictions may lead to the dismissal of compounds that are CNS-active or the advancement of molecules unlikely to succeed in vivo models. Therefore, while computational ADMET screening is indispensable for early-stage filtering, it must be integrated with empirical pharmacokinetic and toxicity studies to avoid misinterpretation of phytochemical potential (Patil *et al.*, 2024).

5.4 Constraints of Network Pharmacology and Multi-Target Modeling

Network pharmacology has become a powerful approach for understanding multi-target actions of phytochemicals, but its effectiveness is constrained by several methodological challenges. Most network models rely on heterogeneous datasets consolidated from databases that may contain incomplete, outdated, or low-confidence annotations. This is particularly problematic for phytochemicals, for which experimentally validated target information is sparse, leading to reliance on predicted interactions that may not reflect true biological activity. In addition, network models often assume linear and additive interactions between pathways, overlooking the nonlinear, dynamic feedback loops characteristic of AD pathology (Li *et al.*, 2025). These limitations complicate the interpretation of network-derived insights, especially

when predicting multi-target synergy or identifying hub genes for therapeutic modulation. In AD research, network models may incorrectly inflate the relevance of pathways simply because they are better studied or more represented in databases, contributing to biased mechanistic conclusions. Moreover, experimental validation of multi-target predictions is extremely challenging because phytochemicals act across diverse molecular systems, and isolating their individual contributions requires extensive *in vitro* and *in vivo* work. Without such validation, network predictions remain hypothetical and may misguide therapeutic prioritization. Thus, while network pharmacology is invaluable for generating hypotheses and mapping complex interactions, it must be treated as an exploratory tool that requires careful confirmation through laboratory-based approaches (Aktary *et al.*, 2025 and Pradeep *et al.*, 2025).

6. Limitations and Future Directions in Computational Evaluation of Anti-Amyloid Phytochemicals

6.1 Structural and Predictive Limitations in Docking, MD, and ADMET Modeling

Despite major advancements in computational drug discovery, several limitations continue to challenge the accurate evaluation of phytochemicals for Alzheimer's disease. Molecular docking remains widely used, yet its reliance on static protein structures and simplified scoring functions causes significant discrepancies between predicted and actual binding behavior (Hamdan *et al.*, 2022). These inaccuracies are amplified in AD research due to the dynamic and intrinsically disordered regions of targets such as A β and tau, which cannot be captured through rigid docking models. Molecular dynamics simulations provide a more realistic depiction of protein-ligand interactions, but they are often constrained by short timescales and high computational cost, limiting their ability to represent large-scale conformational changes that govern binding stability (Piccialli *et al.*, 2022). Similarly, ADMET and blood-brain barrier (BBB) predictions suffer from dataset limitations, especially structurally diverse phytochemicals that fall outside typical drug-like chemical space. As a result, computational models frequently misclassify BBB permeability or metabolic stability, leading to false positives or premature elimination of promising compounds. These limitations highlight the continued need for refined scoring algorithms, ensemble docking, enhanced force fields, and improved machine-learning-based ADMET models that can better account for natural-product complexity. (Zhao *et al.*, 2024 and Mishra & Krishnamurthy, 2024)

6.2 Dataset Bias, Multi-Target Modeling Challenges, and Network Pharmacology Constraints

Network pharmacology has transformed natural-product research by enabling multi-target predictions, yet it suffers from major structural weaknesses. The accuracy of network models depends on the completeness and quality of underlying databases, many of which are biased toward well-studied compounds and canonical signaling pathways. Phytochemical-target interactions are especially underrepresented, resulting in network topologies that overlook several relevant proteins or incorrectly exaggerate the role of others (Friel *et al.*, 2019). Furthermore, Alzheimer's disease involves complex crosstalk between amyloid, tau, inflammatory, and metabolic pathways, but many computational networks oversimplify this interconnected biology into linear or partially connected models. Synergistic or antagonistic actions of phytochemicals—central to botanical therapeutics—are rarely captured, limiting the predictive strength of multi-target modeling (Kurt *et al.*, 2025). Even when network predictions identify hub genes or key pathways, the absence of integrated multi-omics data reduces mechanistic clarity. These issues underscore the need for expanded phytochemical databases, standardized interaction scoring, and hybrid computational pipelines that merge network pharmacology with transcriptomics, proteomics, and metabolomics to reflect disease complexity more accurately. (Ye *et al.*, 2022 and Rahman *et al.*, 2020)

6.3 Lack of Experimental Validation and the Path Forward for Translational Reliability

A consistent weakness across nearly all computational studies on AD phytochemicals is the limited translation of *In silico* predictions into biological validation. Many studies conclude at docking, MD, or network analysis without confirming the predicted activity through *in vitro* enzyme assays, anti-aggregation experiments, or cell-based neuroprotection models (Waiwut *et al.*, 2025). This gap is particularly problematic in Alzheimer's research, where complex molecular events—such as oligomer formation, tau phosphorylation, mitochondrial collapse, and microglial activation—cannot be reliably inferred from computational statistics alone (Aktary *et al.*, 2025). Even when experimental work is performed, it often focuses on isolated targets such as AChE or BACE1, leaving multi-target predictions untested. Moreover, phytochemicals frequently suffer from low bioavailability, poor stability, or rapid metabolism, meaning that strong computational predictions may still fail in biological systems. Future progress requires standardized pipelines where computational outputs are systematically linked to biochemical assays, cell-line validation, and eventually *in vivo* testing. Integration of machine learning, improved training sets, and deeper structural characterization of AD

targets may further enhance predictive accuracy. Ultimately, computational tools must evolve from hypothesis-generating methods into components of a unified discovery pipeline that consistently converges with experimental evidence. (Lin & Sun *et al.*, 2025)

Conclusion

Phytochemicals continue to emerge as promising multi-target candidates for addressing the complex and multifactorial nature of Alzheimer's disease, offering therapeutic potential that extends beyond the capabilities of single-target synthetic drugs. Over the past decade, advances in computational methodologies—spanning molecular docking, molecular dynamics simulations, ADMET prediction, pharmacophore modeling, and network pharmacology—have significantly accelerated the early discovery and mechanistic characterization of these natural compounds. Collectively, these tools have enabled deeper insights into phytochemical interactions with key Alzheimer's-related targets, including A β , BACE1, AChE, tau kinases, oxidative stress regulators, and inflammatory mediators. However, despite these capabilities, persistent limitations in computational precision, dataset completeness, multi-target modeling accuracy, and biological validation continue to restrict their translational impact. Many phytochemicals demonstrate strong binding energies, stable MD trajectories, or promising network connectivity, yet remain untested in biological systems, highlighting the critical gap between *In silico* predictions and real-world therapeutic relevance. Future research must focus on integrating multi-omics data, improved blood-brain barrier modeling, machine learning-based predictive algorithms, and robust experimental pipelines to enhance the reliability of computational findings. Standardizing network pharmacology workflows and expanding phytochemical-target databases will further strengthen systems-level insights and reduce false-positive predictions. Ultimately, the successful development of phytochemical-based therapeutics will depend on close collaboration between computational and experimental approaches, enabling the identification and validation of biologically relevant candidates for Alzheimer's disease drug development.

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