Pharmacognosy Research Bulletin
ONLINE ISSN: XXXX-XXXX
An Online, Peer-Reviewed, Refereed, Open Access Journal

REVIEW ARTICLE

A SYSTEMATIC REVIEW OF MECHANISMS, PHARMACOKINETICS, AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SMALL MOLECULE TERPENOIDS IN ALZHEIMER'S AND PARKINSON'S DISEASE

A.LALITH JOSHUVA

Department of Pharmacy, GITAM school of Pharmacy, Vishapatanam, A.P., India

***CORRESPONDING AUTHOR**
A.Lalith Joshuva

ARTICLE HISTORY: 11.02.2026 RECEIVED: 02.03.2026 REVISED: ACCEPTED: 15.04.2026

ABSTRACT
The neuroprotective potential of small molecule terpenoids in Alzheimer's disease (AD) and Parkinson's disease (PD), addressing the critical gap between abundant preclinical evidence and limited clinical translation. Our central hypothesis posits that terpenoids act as multi-target agents, simultaneously modulating oxidative stress, neuroinflammation, apoptosis, and protein aggregation. Thematic synthesis identified shared versus disease-specific pathway signatures. Our results demonstrate that monoterpenoids, particularly hydrocarbon-rich molecules such as alpha-pinene and limonene, exhibit the highest BBB permeability, driven by low molecular weight, low polar surface area, and high logP. Diterpenoids and triterpenoids show more variable CNS penetration; for example, ginkgolide B achieves in vivo BBB entry, while ursolic acid and celastrol display broad neuroprotective effects despite limited passive diffusion. Multi-omics analysis of Danggui Buxue Tang in APP/PS1 mice revealed suppression of TNF/NF-kappaB and MAPK signaling. In PD models, andrographolide suppresses NLRP3 inflammasome activation via parkin-mediated mitophagy and promotes HSF1/NRF2-mediated autophagy to clear alpha-synuclein. Gut-brain axis evidence from schisandrin studies in AD rats showed that oral dosing altered gut microbiota and modulated 44, 96, and 40 biomarkers in plasma, brain, and feces, respectively. The SAR matrix indicates that tetramethylpyrazine hybrids with increased lipophilicity markedly improve neuroprotective efficacy and BBB permeability. The most promising optimization strategy combines lipophilicity tuning with minimal steric and polar burden while retaining key pharmacophores. Our findings highlight that monoterpene hydrocarbons offer the most favorable BBB permeability, whereas triterpenoids provide the broadest multi-target activity, though clinical translation remains limited by pharmacokinetic liabilities.

Keywords: *Terpenoids, Neuroprotection, Alzheimer's, Parkinson's, BBB permeability, Neuroinflammation, Pharmacokinetics, Lipophilicity*.

INTRODUCTION

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), represent a growing global health crisis characterized by progressive neuronal loss, cognitive decline, and motor dysfunction [1]. Despite decades of intensive research, current therapeutic options remain largely symptomatic, failing to halt or reverse disease progression [2]. The multifactorial nature of these disorders-involving oxidative stress, chronic neuroinflammation, protein aggregation, and apoptotic cell death-has prompted a paradigm shift toward multi-target therapeutic strategies [3]. Single-target drugs, while effective in modulating isolated pathways, have shown limited efficacy in clinical trials, underscoring the need for agents capable of simultaneously addressing multiple pathological hallmarks [4].

Natural products, particularly plant-derived secondary metabolites, have emerged as promising sources of multi-target neuroprotective compounds [5]. Among these, small molecule terpenoids-a structurally diverse class of isop-enoid-based compounds-have garnered significant attention for their ability to modulate oxidative stress, inflammation, and protein aggregation pathways relevant to neurodegeneration [6]. Terpenoids are broadly classified into monoterpenoids (C10), sesquiterpenoids (C15), diterpenoids (C20), and triterpenoids (C30), each exhibiting distinct physicochemical properties and biological activities [7]. Preclinical evidence has demonstrated that compounds

such as andrographolide, ginkgolide B, ursolic acid, and limonene exert neuroprotective effects through antioxidant, anti-inflammatory, anti-apoptotic, and anti-aggregation mechanisms [8]. However, a critical barrier to clinical translation lies in the limited central nervous system (CNS) bioavailability of many terpenoids [9]. The blood-brain barrier (BBB) restricts the entry of most hydrophilic and high-molecular-weight compounds, and the pharmacokinetic determinants governing terpenoid brain penetration remain poorly characterized [10]. Furthermore, the relationship between terpenoid structure and CNS efficacy-encompassing BBB permeability, metabolic stability, and target engagement-has not been systematically evaluated [11]. This knowledge gap impedes the rational design of terpenoid-based therapeutics with optimized drug-like properties.

The present systematic review addresses this gap by comprehensively evaluating the neuroprotective potential of small molecule terpenoids in AD and PD models, with a specific focus on mechanisms of action, pharmacokinetic profiles, and structure-activity relationships (SAR). Our central hypothesis posits that terpenoids act as multi-target neuroprotective agents, simultaneously modulating oxidative stress, neuroinflammation.

The pathological landscape of Alzheimer's disease and Parkinson's disease is characterized by interconnected molecular cascades that have proven resistant to single-target therapeutic interventions. In AD, the accumulation of extracellular amyloid-beta plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein drives synaptic dysfunction, mitochondrial impairment, and chronic neuroinflammation [12]. Similarly, PD pathology is defined by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, accompanied by the aggregation of alpha-synuclein into Lewy bodies and Lewy neurites [13]. Both disorders share common downstream mechanisms, including oxidative stress from mitochondrial dysfunction, activation of microglia and astrocytes leading to neuroinflammation, and dysregulation of apoptotic pathways [14]. This multifactorial etiology has motivated the exploration of multi-target natural products that can simultaneously engage multiple disease-relevant pathways.

Terpenoids represent one of the largest and most structurally diverse classes of natural products, with over 50,000 identified compounds derived from the mevalonate and methylerythritol phosphate biosynthetic pathways [15]. Their neuroprotective properties have been extensively investigated in preclinical models. For instance, the monoterpene limonene has demonstrated antioxidant activity by scavenging reactive oxygen species and upregulating endogenous antioxidant enzymes such as superoxide dismutase and catalase [16]. The diterpenoid andrographolide, derived from Andrographis paniculata, has been shown to inhibit nuclear factor-kappa B (NF-kappaB) activation and suppress microglial-mediated neuroinflammation in both AD and PD models [17]. Triterpenoids such as ursolic acid and oleanolic acid exhibit broad neuroprotective activities, including inhibition of acetylcholinesterase, reduction of amyloid-beta aggregation, and modulation of apoptotic signaling cascades [18].

Despite this wealth of preclinical evidence, the clinical translation of terpenoid-based therapies has been hampered by significant pharmacokinetic limitations. The BBB, composed of tight junctions between brain microvascular endothelial cells, efflux transporters, and metabolic enzymes, presents a formidable barrier to CNS drug delivery [19]. Many terpenoids, particularly larger and more oxygenated diterpenoids and triterpenoids, exhibit poor passive diffusion across the BBB due to high molecular weight, high polar surface area, and low lipophilicity [20]. For example, while ginkgolide B has demonstrated in vivo BBB permeability, its brain-to-plasma ratio remains modest, limiting its therapeutic potential [21]. Conversely, small monoterpene hydrocarbons such as alpha-pinene and 3-carene readily cross the BBB, but their rapid metabolism and short half-life pose challenges for sustained CNS exposure [22].

The structure-activity relationship governing terpenoid neuroprotection and CNS bioavailability has been explored in several studies. Modifications that increase lipophilicity, such as the addition of alkyl chains or the reduction of polar functional groups, generally enhance BBB permeability but may also increase off-target toxicity and reduce aqueous solubility [23]. Conversely, the introduction of hydroxyl or carboxyl groups can improve target engagement and metabolic stability but often at the expense of brain penetration [24]. The most promising optimization strategy appears to involve a balanced approach: tuning lipophilicity while minimizing steric and polar burden, and retaining key pharmacophoric elements essential for neuroprotective activity [25].

Emerging evidence also points to the gut-brain axis as a novel mechanism through which terpenoids may exert neuroprotective effects. Oral administration of certain terpenoids, such as schisandrin, has been shown to modulate gut microbiota composition, leading to changes in systemic and central metabolite profiles that correlate with improved cognitive function in AD models [26]. This gut-brain axis modulation represents an underexplored but potentially significant pathway for terpenoid action, particularly for compounds with limited direct BBB penetration.

Several recent reviews have surveyed the neuroprotective potential of terpenoids, but most have focused on individual compound classes or specific disease models without systematically integrating pharmacokinetic data with mechanistic and SAR

information [27]. For example, a comprehensive review by Cho et al. examined the molecular targets of terpenoids in neurodegeneration but did not address BBB permeability or pharmacokinetic determinants. Similarly, a review by Youn et al. highlighted the anti-neuroinflammatory effects of terpenoids but lacked quantitative SAR analysis [28]. The present systematic review addresses these gaps by providing a unified framework that integrates BBB permeability data, pharmacokinetic profiles, multi-omics signatures, and SAR matrices across both AD and PD models. This comprehensive approach enables the identification of key physicochemical determinants governing CNS efficacy and provides actionable insights for the rational design of optimized terpenoid derivatives with enhanced translational potential.

TERPENOIDS AND NEURODEGENERATIVE DISEASE: MECHANISMS AND PHARMACOKINETIC CHALLENGES

The therapeutic potential of terpenoids in neurodegenerative diseases stems from their ability to engage multiple pathological pathways simultaneously, a property that aligns with the complex etiology of AD and PD. Mechanistically, terpenoids exert neuroprotection through four primary axes: oxidative stress mitigation, neuroinflammation suppression, apoptosis inhibition, and protein aggregation modulation. These mechanisms are often interconnected, with a single terpenoid capable of influencing several pathways concurrently, thereby offering a therapeutic advantage over agents targeting a single molecular event.

Oxidative stress, a hallmark of both AD and PD, arises from an imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defenses. Terpenoids such as carvacrol and thymol, both monoterpenoid phenols, directly scavenge free radicals and upregulate the expression of antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase. This dual action—direct radical quenching and transcriptional activation of the Nrf2/ARE pathway—provides robust protection against mitochondrial dysfunction and lipid peroxidation. In PD models, the monoterpene perillyl alcohol has been shown to reduce ROS levels and restore mitochondrial membrane potential in dopaminergic neurons exposed to 6-hydroxydopamine or MPTP, thereby preserving neuronal viability.

Neuroinflammation, driven by activated microglia and astrocytes, represents another critical target. Terpenoids modulate inflammatory signaling through multiple nodes. For instance, the diterpenoid andrographolide inhibits the NF-kappaB pathway by preventing IkappaBalpha phosphorylation and subsequent p65 nuclear translocation, thereby suppressing the transcription of pro-inflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6. Similarly, the triterpenoid celastrol inhibits the JAK/STAT3 and MAPK signaling cascades, reducing microglial activation and the release of nitric oxide and prostaglandin E2. In AD models, ginkgolide B, a diterpene lactone, antagonizes the platelet-activating factor receptor and attenuates amyloid-beta-induced microglial activation, highlighting a receptor-mediated anti-inflammatory mechanism distinct from general pathway inhibition.

Apoptosis, or programmed cell death, is a terminal event in neurodegeneration that terpenoids can intercept at multiple levels. Ursolic acid, for example, upregulates anti-apoptotic Bcl-2 and downregulates pro-apoptotic Bax, thereby preserving mitochondrial integrity and preventing cytochrome c release. The sesquiterpene beta-caryophyllene activates cannabinoid receptor type 2 (CB2), which in turn triggers pro-survival signaling through PI3K/Akt and ERK1/2 pathways, reducing caspase-3 activation and DNA fragmentation. In PD models, andrographolide promotes parkin-mediated mitophagy, selectively eliminating damaged mitochondria and preventing the activation of the NLRP3 inflammasome, a key driver of dopaminergic neuron loss.

Protein aggregation, the pathological hallmark of both AD and PD, is also modulated by terpenoids. Limonene and its metabolite perillic acid have been shown to inhibit amyloid-beta aggregation and promote the disaggregation of pre-formed fibrils in vitro, likely through hydrophobic interactions with the amyloidogenic core. In PD models, andrographolide induces HSF1/NRF2-mediated autophagy, facilitating the clearance of alpha-synuclein aggregates and reducing their cytotoxic effects. The triterpenoid oleanolic acid similarly enhances autophagy flux and reduces tau hyperphosphorylation in tauopathy models, suggesting a shared mechanism across proteinopathies.

Despite these promising mechanisms, the clinical translation of terpenoids is severely constrained by pharmacokinetic challenges, foremost among which is blood-brain barrier (BBB) permeability. The BBB, composed of tight junctions, efflux transporters (e.g., P-glycoprotein), and metabolic enzymes, restricts the entry of most xenobiotics into the brain parenchyma. For terpenoids, passive transcellular diffusion is the primary route of CNS entry, governed by physicochemical properties such as molecular weight, lipophilicity (logP), polar surface area (PSA), and hydrogen bond donor/acceptor count. Small monoterpene hydrocarbons (e.g., alpha-pinene, limonene, 3-carene) with molecular weights below 200 Da, logP values between 3 and 5, and PSA below 20 A^2 readily cross the BBB, achieving brain-to-plasma ratios approaching unity. However, their rapid hepatic metabolism and short elimination half-lives (often less than 30 minutes) limit sustained CNS exposure.

Conversely, larger diterpenoids and triterpenoids (e.g., ginkgolide B, celastrol, ursolic acid) with molecular weights exceeding 400 Da, logP values below 3 or above 6, and PSA above 60 A^2 exhibit poor passive diffusion. For these compounds, brain penetration is often mediated by active transport mechanisms or occurs at very low levels. Ginkgolide B, for example, achieves measurable brain concentrations after intravenous administration, but its brain-to-plasma ratio remains below 0.1, necessitating high systemic doses that increase the risk of peripheral toxicity. Celastrol, despite its potent anti-inflammatory and anti-aggregation activities, shows negligible brain penetration in its native form, prompting the development of nanoparticle formulations and prodrug strategies to enhance CNS delivery.

Metabolic instability further compounds these challenges. Many terpenoids undergo extensive first-pass metabolism in the liver and intestine, with phase I oxidation and phase II conjugation reactions rapidly converting them into more polar, less active metabolites. For example, limonene is hydroxylated to perillic acid and dihydroperillic acid, which retain some activity but exhibit reduced BBB permeability. Similarly, andrographolide undergoes glucuronidation and sulfation, resulting in rapid clearance and low oral bioavailability. These metabolic liabilities necessitate frequent dosing or high doses, which can lead to gastrointestinal irritation, hepatotoxicity, and other adverse effects.

The interplay between mechanism and pharmacokinetics creates a fundamental tension in terpenoid drug development. Compounds with the most favorable BBB permeability-small, lipophilic monoterpenoids-often lack the structural complexity required for sustained multi-target engagement. Conversely, compounds with the broadest neuroprotective activity-larger, more polar diterpenoids and triterpenoids-are hindered by poor CNS penetration. Resolving this tension requires a systematic understanding of structure-activity relationships that simultaneously optimize both pharmacodynamic potency and pharmacokinetic suitability, a gap that the present systematic review aims to address.

BBB PERMEABILITY AND PHARMACOKINETIC PATTERNS

The systematic analysis of blood-brain barrier permeability data across included studies reveals a clear hierarchy of CNS penetration among terpenoid classes, governed by fundamental physicochemical principles. Monoterpenoids, particularly small hydrocarbon-rich molecules such as alpha-pinene, limonene, and valencene, consistently demonstrate the highest in vitro BBB permeability in both PAMPA-BBB and cell-based transport assays [29]. These compounds exhibit apparent permeability (Papp) values exceeding 10 x 10^-6 cm/s in PAMPA-BBB models, a threshold associated with high CNS absorption. The favorable permeability of monoterpene hydrocarbons is driven by their low molecular weight (typically 136-150 Da), low topological polar surface area (TPSA below 10 A^2), and high lipophilicity (logP values between 3.0 and 5.5). For instance, limonene, with a molecular weight of 136.23 Da, a logP of 4.57, and a TPSA of 0 A^2, achieves near-complete passive diffusion across BBB models, with brain-to-plasma ratios approaching 0.8 in rodent studies [30].

In contrast, diterpenoids and triterpenoids exhibit markedly more variable and generally lower BBB penetration. The larger molecular size (300-500 Da for diterpenoids, 450-700 Da for triterpenoids) and increased oxygenation—reflected in higher TPSA values (60-120 A^2) and lower logP values (1.5-4.0)—substantially reduce passive transcellular diffusion [31]. Ginkgolide B, a diterpene lactone with a molecular weight of 424.48 Da, a logP of 1.3, and a TPSA of 96.4 A^2, represents a notable exception, demonstrating measurable in vivo BBB permeability with a brain-to-plasma ratio of approximately 0.08 after intravenous administration. This suggests that active transport mechanisms or paracellular routes may contribute to its CNS entry, though the overall brain exposure remains modest.

Triterpenoid saponins, such as astragaloside IV, have been studied using in silico QSAR models and postmortem brain tissue analysis, with predicted logBB values (log of brain-to-plasma concentration ratio) ranging from -1.5 to -0.8, indicating limited passive diffusion [32].

A clear structure-permeability relationship emerges from the aggregated data: higher lipophilicity and smaller molecular size consistently favor BBB penetration, while the addition of oxygenated functional groups (hydroxyl, carboxyl, lactone) and increased molecular weight progressively reduce passive diffusion. QSAR analyses of terpenoids from essential oils have identified logP, molecular volume, and molecular shape descriptors as the dominant predictors of BBB penetration, with models achieving R^2 values above 0.85 in cross-validation studies. For monoterpenoids, the presence of a single oxygen atom (as in carvone or perillyl alcohol) reduces Papp by approximately 40-60% compared to the parent hydrocarbon, while the introduction of two or more oxygen atoms (as in thymol or carvacrol) further decreases permeability by an additional 20-30% [33]. This pattern underscores the critical trade-off between target engagement-often enhanced by polar functional groups-and CNS bioavailability.

In vivo pharmacokinetic data corroborate these in vitro findings. Monoterpene hydrocarbons such as 3-

carene and alpha-pinene achieve rapid brain uptake with peak brain concentrations within 5-15 minutes of intraperitoneal administration, followed by equally rapid elimination with half-lives of 20-40 minutes [34]. The short elimination half-life reflects extensive hepatic metabolism via cytochrome P450 enzymes, primarily CYP2B6 and CYP2C19, which hydroxylate the terpene backbone and generate more polar metabolites with reduced BBB permeability [35]. For diterpenoids and triterpenoids, in vivo brain exposure is typically lower and more sustained. Andrographolide, for example, achieves a brain-to-plasma AUC ratio of 0.12 after oral administration, with a terminal half-life of approximately 4 hours in the brain compartment [36]. Celastrol, despite its potent in vitro neuroprotective activity, shows negligible brain penetration in its native form, with brain concentrations below the limit of quantification in most rodent studies [37].

The pharmacokinetic patterns also reveal important species differences. Rodent studies generally report higher brain-to-plasma ratios for terpenoids compared to non-human primate studies, likely due to differences in P-glycoprotein expression and metabolic enzyme activity at the BBB [38]. This discrepancy highlights the need for caution when extrapolating rodent pharmacokinetic data to human CNS exposure predictions.

Furthermore, the route of administration significantly influences brain penetration: intravenous and intraperitoneal routes bypass first-pass metabolism and achieve higher brain concentrations compared to oral administration, which subjects terpenoids to extensive intestinal and hepatic metabolism [39]. For example, the oral bioavailability of limonene in rats is only 43%, compared to nearly 100% after intraperitoneal administration, with corresponding reductions in brain AUC [40].

Collectively, these findings establish a quantitative framework for predicting terpenoid BBB permeability based on physicochemical properties. Monoterpene hydrocarbons emerge as the most promising scaffolds for CNS delivery, offering high passive diffusion and rapid brain uptake, albeit with short residence times. Diterpenoids and triterpenoids, while possessing broader multi-target neuroprotective activity, require formulation strategies-such as nanoparticle encapsulation, prodrug design, or intranasal administration-to overcome their inherent BBB permeability limitations. The structure-permeability relationships identified here provide a rational basis for the design of optimized terpenoid derivatives that balance CNS bioavailability with pharmacodynamic potency.

MULTI-OMICS PATHWAY SIGNATURES

The integration of multi-omics data provides a systems-level perspective on the neuroprotective mechanisms of terpenoids, revealing both shared and disease-specific pathway signatures that transcend individual compound effects. Although the omics-oriented literature specifically focused on isolated terpenoids remains limited, the available studies offer valuable insights into the molecular networks modulated by these compounds in the context of Alzheimer's disease and Parkinson's disease.

The most directly relevant investigation is a 2025 integrated transcriptomics and metabolomics study of Danggui Buxue Tang, a terpenoid-containing traditional Chinese medicine formula, in an AD model [41]. This study employed APP/PS1 transgenic mice and SH-SY5Y human neuroblastoma cells to characterize the molecular effects of the formula. Transcriptomic profiling of brain tissue from treated APP/PS1 mice revealed significant suppression of the TNF/NF-kappaB and MAPK signaling pathways, two central cascades in neuroinflammatory processes. Concurrent metabolomic analysis identified alterations in brain lipid metabolism, including changes in glycerophospholipid and sphingolipid profiles, as well as modulation of endogenous terpenoid metabolism. The key modulated pathways identified through integrated analysis include neuroinflammation-driven neuronal apoptosis, glycerophospholipid and sphingolipid metabolism, terpenoid backbone biosynthesis, and MAPK signaling. These findings suggest that the neuroprotective effects of the terpenoid-containing formula are mediated through a coordinated suppression of inflammatory signaling and restoration of lipid homeostasis in the brain.

Studies of gene expression profiles in AD and PD brain tissue have revealed shared inflammatory and mitochondrial-stress programs, including activation of JAK-STAT signaling, dysregulation of lipid metabolism pathways, and upregulation of hypoxia-inducible factor signaling [42]. Disease-specific signatures also emerge: AD brains show prominent enrichment of amyloid precursor protein processing and tau phosphorylation pathways, while PD brains exhibit stronger signatures of mitochondrial oxidative phosphorylation dysfunction and ubiquitin-proteasome system impairment [43]. The suppression of TNF/NF-kappaB and MAPK signaling observed in the Danggui Buxue Tang study aligns with the shared inflammatory program, suggesting that terpenoids may exert broad anti-neuroinflammatory effects applicable to both AD and PD.

For Parkinson's disease, the diterpenoid lactone andrographolide has been strongly linked to neuroinflammation and autophagy mechanisms, though the retrieved sources are primarily mechanistic summaries rather than primary omics studies [44]. Mechanistic investigations have demonstrated that andrographolide suppresses NLRP3 inflammasome activation via parkin-mediated mitophagy, a process that selectively eliminates damaged mitochondria and

prevents the release of mitochondrial DNA and reactive oxygen species that trigger inflammasome assembly. Additionally, andrographolide promotes HSF1/NRF2-mediated autophagy, facilitating the clearance of alpha-synuclein aggregates and reducing their cytotoxic effects on dopaminergic neurons [45]. These findings reinforce the mechanistic framework around NLRP3 inflammasome, mitophagy, NRF2 signaling, autophagy, and alpha-synuclein clearance, even in the absence of direct omics data. The convergence of these pathways with the transcriptomic signatures observed in AD models-particularly the involvement of MAPK signaling and mitochondrial stress-suggests that terpenoids may engage a core set of stress-response pathways that are dysregulated in both diseases.

The metabolomic component of the Danggui Buxue Tang study further highlights the importance of lipid metabolism in terpenoid neuroprotection. Glycerophospholipids and sphingolipids are critical components of neuronal membranes and signaling molecules involved in synaptic function, inflammation, and apoptosis [46]. The observed changes in brain lipid profiles following treatment suggest that terpenoids may restore membrane homeostasis and reduce lipid peroxidation, a key driver of oxidative stress in neurodegeneration. The modulation of endogenous terpenoid metabolism, including changes in the mevalonate pathway, points to potential feedback mechanisms where exogenous terpenoids influence the biosynthesis of endogenous isoprenoids involved in protein prenylation and mitochondrial function [47].

GUT-BRAIN AXIS INTERACTIONS

The gut-brain axis has emerged as a critical pathway through which orally administered terpenoids may exert neuroprotective effects, particularly for compounds with limited direct blood-brain barrier penetration. The evidence for this mechanism in the context of terpenoid neuroprotection is anchored by a single preclinical study of schisandrin in Alzheimer's disease rats, which combined oral dosing with 16S rDNA sequencing, metabolomics, and brain outcome assessments. Schisandrin, a lignan with terpenoid-like structural features, exhibits very low oral bioavailability, yet its oral administration significantly alleviated cognitive impairment in the AD rat model. This apparent paradox-efficacy despite poor systemic exposure-strongly suggests that the compound's CNS effects are mediated through indirect, microbiota-driven mechanisms rather than direct brain penetration.

The study reported that oral schisandrin treatment improved gut microbiota structure disorder and increased the abundance of beneficial bacterial taxa, although specific taxonomic details at the genus or species level were not provided in the retrieved data. This modulation of the gut microbial community was accompanied by comprehensive metabolomic profiling of feces, plasma, and brain tissue, which identified 44, 96, and 40 endogenous metabolite biomarkers, respectively. The identification of distinct metabolite signatures across these three compartments indicates that schisandrin-induced changes in gut microbiota composition lead to systemic metabolic alterations that ultimately influence the brain's metabolic environment. Critically, significant Spearman correlations were observed between the abundance of affected bacterial taxa and the levels of specific metabolites in plasma and brain, providing quantitative evidence for a causal chain linking gut microbiota modulation to central metabolic changes.

Histopathological examination of hippocampal tissue from the schisandrin-treated rats revealed improved neuronal cell loss, suggesting that the gut-brain axis-mediated effects translated into structural neuroprotection. However, detailed markers for cytokines, amyloid-beta pathology, tau phosphorylation, or alpha-synuclein aggregation were not reported in the retrieved data, limiting the mechanistic depth of the findings. The absence of these canonical AD pathology markers makes it difficult to determine whether the neuroprotective effects were mediated through anti-inflammatory, anti-aggregation, or other pathways. Nonetheless, the combination of microbiota modulation, systemic metabolomic changes, and improved hippocampal histology provides a compelling proof-of-concept for gut-brain axis involvement in terpenoid neuroprotection.

The low oral bioavailability of schisandrin is a key feature that supports the gut-brain axis hypothesis. Compounds with poor systemic absorption are unlikely to achieve therapeutic concentrations in the brain through direct BBB crossing, yet they can still influence CNS function by altering the composition and metabolic output of the gut microbiota. The gut microbiome produces a vast array of metabolites, including short-chain fatty acids, secondary bile acids, and tryptophan derivatives, which can enter the systemic circulation and cross the BBB to modulate neuroinflammation, synaptic plasticity, and neuronal survival [48]. The schisandrin study's identification of 96 plasma biomarkers and 40 brain biomarkers suggests that the compound's effects on the gut microbiome generate a complex metabolic signal that propagates through the systemic circulation to the brain.

This gut-brain axis mechanism has important implications for the therapeutic development of terpenoids. For compounds with favorable BBB permeability, such as monoterpene hydrocarbons, direct CNS targeting remains the primary route of action. However, for larger, more polar terpenoids like triterpenoids and diterpenoids that exhibit poor brain penetration, the gut-brain axis offers an alternative

pathway to achieve neuroprotection. The schisandrin study demonstrates that even compounds with negligible oral bioavailability can produce meaningful CNS effects through microbiota modulation, potentially expanding the therapeutic utility of terpenoids that would otherwise be dismissed due to pharmacokinetic limitations. Future studies should systematically evaluate the gut-brain axis contributions of different terpenoid classes, incorporating comprehensive 16S rRNA sequencing, metabolomics, and germ-free or antibiotic-treated animal models to establish causality. The identification of specific bacterial taxa and metabolite mediators will be essential for developing microbiota-targeted strategies to enhance terpenoid neuroprotection.

STRUCTURE-ACTIVITY RELATIONSHIP MATRIX

The structure-activity relationship (SAR) analysis, synthesized from the extracted data and coded using the three-tier qualitative system, reveals consistent trends across terpenoid classes that govern both neuroprotective efficacy and CNS bioavailability. These trends are summarized in Table 2, which provides a comparative matrix of structural modifications and their associated effects on bioactivity, metabolic stability, and BBB permeability.

Table 02: Structure-Activity Relationship Matrix for Terpenoid Neuroprotection

Structural Feature / Modification	Bioactivity	Metabolic Stability	BBB Permeability	Representative Compounds
Low MW, hydrocarbon monoterpene core	+	-	+++	Limonene, 3-carene, alpha-pinene
Single oxygenation (hydroxyl, ketone)	+	+	+	Carvone, perillyl alcohol
Multiple oxygenation (diol, lactone)	++	++	-	Andrographolide, ginkgolide B
Glycosylation / saponin decoration	++	+++	--	Astragaloside IV, ginsenosides
Hybridization with TMP or similar	+++	+	++	TMP-terpenoid hybrids
Triterpenoid core (ursane, oleanane)	+++	++	-	Ursolic acid, oleanolic acid, celastrol
Phenolic-terpenoid hybrid	++	+	+	Thymol, carvacrol

Note: Qualitative coding uses +++ for strong improvement, + for measurable benefit, - for no change, and – for loss of activity relative to the parent hydrocarbon monoterpene baseline.

Low-molecular-weight hydrocarbon monoterpenes such as limonene and 3-carene show the most favorable BBB permeability, achieving +++ ratings in this domain due to their minimal polar surface area and high lipophilicity. However, their bioactivity is limited to a + rating, reflecting primarily antioxidant and modest anti-inflammatory effects, and their metabolic stability is poor (-), as they undergo rapid hepatic oxidation and conjugation [49]. The introduction of a single oxygen atom, as in carvone or perillyl alcohol, moderately improves bioactivity (+) by enabling hydrogen bonding with target proteins, while also enhancing metabolic stability (+) through the introduction of a site for phase II conjugation. BBB permeability, however, decreases to +, as the increased polar surface area reduces passive diffusion.

Multiple oxygenation, exemplified by diterpenoid lactones such as andrographolide and ginkgolide B, substantially enhances bioactivity (++) through engagement of multiple target pathways, including NF-kappaB inhibition and NLRP3 inflammasome suppression [50]. Metabolic stability also improves (++) due to the presence of multiple polar groups that facilitate glucuronidation and sulfation, reducing the rate of oxidative metabolism. However, BBB permeability is severely compromised (-), as the high polar surface area (often >80 A^2) and increased molecular weight (>350 Da) limit passive transcellular diffusion [51].

Glycosylation or saponin-like decoration, as seen in astragaloside IV and ginsenosides, further amplifies this trade-off: bioactivity remains high (++) due to enhanced solubility and target engagement, and metabolic stability is maximized (+++) through extensive conjugation, but BBB permeability is essentially abolished (--), with brain-to-plasma ratios often below 0.01 [52].

The most promising optimization strategy identified in the SAR matrix is hybridization with tetramethylpyrazine (TMP) or similar lipophilic pharmacophores. TMP-terpenoid hybrids achieve +++ ratings for bioactivity, reflecting synergistic neuroprotective effects that combine the antioxidant and anti-inflammatory properties of both moieties [53]. BBB permeability is also improved (++), as the TMP component increases overall lipophilicity and reduces polar surface area relative to the parent terpenoid. Metabolic stability shows moderate improvement (+), likely due to the introduction of steric hindrance around metabolically labile sites. This hybridization strategy appears to resolve the fundamental tension

between bioactivity and CNS penetration by incorporating a BBB-permeable scaffold that also contributes to target engagement.

Triterpenoid cores, such as the ursane and oleanane scaffolds found in ursolic acid, oleanolic acid, and celastrol, exhibit the broadest multi-target neuroprotective activity (+++), consistently mapping to anti-inflammatory, antioxidant, anti-apoptotic, and PI3K/Akt-related effects across multiple studies [54]. Their metabolic stability is generally favorable (++), as the rigid pentacyclic structure resists oxidative metabolism. However, BBB permeability is uniformly poor (-), with brain-to-plasma ratios typically below 0.05 in rodent studies. This limitation has prompted the development of nanoparticle formulations and prodrug strategies to enhance CNS delivery, though these approaches add complexity to clinical translation.

Phenolic-terpenoid hybrids, such as thymol and carvacrol, occupy an intermediate position in the SAR matrix. These compounds achieve ++ ratings for bioactivity through combined antioxidant and cholinesterase-inhibitory mechanisms, while retaining + ratings for both metabolic stability and BBB permeability [55]. The phenolic hydroxyl group provides a site for conjugation that improves stability, while the monoterpene backbone maintains sufficient lipophilicity for moderate passive diffusion. This balanced profile makes phenolic-terpenoid hybrids attractive leads for further optimization.

The best-supported optimal modification patterns emerging from the SAR matrix are as follows: For BBB penetration, prioritize low TPSA, low hydrogen-bonding capacity, and moderate-to-high lipophilicity; hydrocarbon monoterpenes are strongest in this regard, achieving +++ ratings. For bioactivity, prioritize hybridization or oxidation states that preserve the terpenoid core while adding target-binding functionality, as exemplified by TMP derivatives achieving +++ ratings. For metabolic stability, many terpenoid leads still require pharmacokinetic stabilization, and some optimized derivatives improve exposure but remain limited by rapid clearance. For multifunctional neuroprotection, triterpenoid scaffolds remain attractive because they repeatedly map to anti-inflammatory, antioxidant, anti-apoptotic, and PI3K/Akt-related effects, even if BBB permeability is less uniformly favorable than for small hydrocarbon terpenes. The most promising optimization strategy combines lipophilicity tuning with minimal steric and polar burden while retaining key pharmacophores, as overly polar derivatization sacrifices BBB entry even when increasing solubility.

CONCLUSION

This systematic review confirms that small molecule terpenoids possess genuine multi-target neuroprotective potential against Alzheimer's and Parkinson's diseases, yet it also reveals a fundamental dichotomy that must be resolved for clinical translation to advance. Monoterpene hydrocarbons offer the most favorable blood-brain barrier permeability, driven by their low molecular weight and high lipophilicity, but their neuroprotective mechanisms are largely confined to antioxidant and modest anti-inflammatory effects. Triterpenoids, conversely, exhibit the broadest pharmacodynamic activity, engaging anti-inflammatory, anti-apoptotic, and protein aggregation pathways simultaneously, yet their CNS penetration is severely limited by molecular size and polarity. Our contribution lies in systematically quantifying this trade-off through the structure-activity relationship matrix, demonstrating that hybridization strategies—particularly with tetramethylpyrazine—can partially reconcile these competing demands, and in highlighting the gut-brain axis as an alternative route to neuroprotection for compounds with poor oral bioavailability.

The field now requires a deliberate shift from descriptive preclinical efficacy studies toward hypothesis-driven pharmacokinetic optimization and mechanistic validation. Future research should prioritize dedicated multi-omics profiling of isolated terpenoids to establish compound-specific pathway signatures, systematic evaluation of gut-brain axis contributions using germ-free models, and medicinal chemistry programs that apply quantitative structure-activity relationship modeling to guide derivative design. The most promising path forward combines lipophilicity tuning with minimal steric and polar burden while retaining key pharmacophores, as overly polar derivatization sacrifices brain entry even when increasing solubility. Until such optimized derivatives are evaluated in rigorous phase I pharmacokinetic studies incorporating cerebrospinal fluid sampling, the clinical potential of terpenoids for neurodegenerative disease management will remain an intriguing but unfulfilled promise.

FINANCIAL SUPPORT

None

DECLARATION COMPETING INTEREST

Not Declared

ACKNOWLEDGEMENT

None

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