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The Neuroprotective Potential of *Polyscias fruticose:* A Synthesis of Evidence on Phytochemistry, Antioxidant, and Anti-inflammatory Activities

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Abstract: *Polyscias fruticosa (L.) Harms (Araliaceae) is a prominent medicinal plant in traditional Asian medicine, used to treat asthenia, inflammation, and enhance memory. The present review helps in compiling and assessing scientific data to provide insight into neuroprotective activity of this plant. It is based on a meta-analysis of chemically characterized and documented in vitro, in vivo and in silico studies. Phytochemically, three major groups of compounds have been identified in the extract of P. fruiticosa: (1) triterpenoid saponins (oleanane skeleton, e.g., Polyscioside J/K), (2) phenolic compounds, and (3) an important lipophilic moiety (e.g., stigmasterol, falcarinol). The plant exerts its neuroprotective effects through several means. It displays dual anti-oxidative actions through free radical scavenging and activation of the Nrf2-ARE pathway, resulting in an increased production of the endogenous protective enzymes HO-1 and CAT. Concurrently, it possesses multi-target anti-inflammatory actions through the inhibition of the TLR4/NF-κB signaling axis and COX-2 (PTGS2) enzyme. Other works confirm the capacity to inhibit acetylcholinesterase (AChE) and to stimulate the survival pathway AKT/CREB/BDNF. P. fruticosa extract acts as a multi-target neuroprotective agent, uniquely positioned to interfere with the oxidative stress-neuroinflammation loop. These mechanisms provide a solid scientific basis for the development of standardized extracts into nutraceuticals to promote human health. This study opens up directions for future clinical trials.*

Keywords: Polyscias fruticosa; Neuroprotection; Triterpenoid saponins; Stigmasterol; Antioxidant activity; Nrf2/ARE pathway; NF-κB/COX-2 inhibition; AKT/CREB/BDNF signaling.

1. Introduction

Polyscias fruticosa (L.) Harms, commonly known as Ming aralia or “Dinh lang”, is a member of the ginseng family. In Vietnam and other Asian countries, it holds a special place in traditional medicine, often called "the ginseng of the poor." For a long time, healers have used its roots and leaves to treat fatigue, reduce swelling (inflammation), and—most notably—to improve memory and brain function. The popularity of using *Polyscias fruticosa (L.)* Harms reflects a socio-cultural role by utilizing medical herbs in traditional healthcare system (Mohácsi, 2021). However, despite its long-standing use, modern evidence for the effects of *P. fruticosa* is limited. The synthesis report of Alzheimer’s Drug Discovery Foundation reveals that while some pre-clinical results show the benefits for animal cognitive function and longevity, there remains a lack of studies or clinical trials evaluating the effects of ginseng on humans. This places an urgency on research into its chemical properties and mechanism of action.

Early scientific studies confirmed what traditional medicine already knew: the plant works well to fight stress and boost energy. However, in the last ten years (2015–2025), the focus of research has changed. Scientists are no longer just looking at what the plant does, but how it does it inside our cells. This is especially important for fighting brain diseases like Alzheimer’s and Parkinson’s. These diseases, especially Alzheimer’s is typical case of the oxidative stress–neuroinflammation spiral, usually driven by a dangerous cycle where stress damages cells, causing inflammation, which then causes even more stress (Zhang & Jiang, 2015; Hayat et al., 2025). Besides, Ly et al., (2022) also indicates that using Drosophila melanogaster extracted from P. fruticosa can mitigate dopaminergic neurodegeneration and improve neuronal function, suggesting a broader neuroprotective potential across neurodegenerative conditions.

Although the plant is known for being rich in chemicals—scientists have identified over 120 different compounds in *P. fruticosa*—we still do not fully understand how these parts work together to protect the brain (Śliwińska & Tomiczak, 2025). Recent reports from 2025 still note that we have “knowledge gaps” regarding how specific compounds interact with our cells. Specifically, we need to understand how *P. fruticosa* can simultaneously calm down the brain's alarm system (inflammation) while boosting its repair system (antioxidants). This is particularly important because many phenolic and flavonoid compounds found in medicinal plants are known to reduce oxidative stress, enhance antioxidant enzymes, and suppress pro-inflammatory pathways such as NF-κB (Bakrim et al., 2022; Mamun et al., 2024).

This analysis aims to bring all the recent evidence together to explain:

1. The Chemistry: Identifying the key parts of the plant, from the "saponins" (similar to ginseng) to fat-soluble compounds that might be able to enter the brain easily.
2. The Mechanism: Showing how the plant acts as a "dual switch" – turning off inflammation pathways (like NF-κB) and turning on defense pathways (like Nrf2).
3. The Benefit**:** How these chemical actions translate into real protection for brain cells and better memory.
4. The Future: Why, despite these promising lab results, we urgently need studies on actual human patients.

2. Materials and Methods

2.1. Material and Phytochemical Analysis

Studies utilized the leaves and roots of *P. fruticosa*. To maximize the yield of phenolic and flavonoid compounds, advanced extraction techniques, specifically microwave-assisted extraction, were used. The *P. fruticosa* was gathered in Cao Bang Vietnam and processed, stored, and analyzed at the Vietnam Academy of Science and Technology's chemical lab.

To obtain certain classes of compounds, the non-polar fractions and the polar fractions for separation systems were employed such as:

- **n-butanol (n-BuOH) fraction:** Used for the separation of polar triterpenoid saponins.
- **Diethyl ether (Et2O) fraction:** Used to isolate phenolic compounds and flavonoids.
- **Lipophilic fraction:** Used to analyze non-polar compounds like phytosterols and terpenes.

Analytical and elucidation techniques included:

- **Gas Chromatography-Mass Spectrometry (GC-MS):** Used for the comprehensive analysis of the chemical composition of the lipophilic fraction.
- **High-Performance Liquid Chromatography (HPLC) and Nuclear Magnetic Resonance (NMR):** Standard techniques used for the isolation and structural elucidation of triterpenoid saponins and other pure compounds.
- **Spectrophotometric Methods:** The Folin-Ciocalteu and AlCl3 complexation methods were used to quantify Total Phenolic Content (TPC) and Total Flavonoid Content (TFC).

2.2. Test Tube Experiments (In Vitro)

The first thing the extract was tested on before doing any testing on organisms was test tube interactions with the biological macromolecules

Antioxidant Ability Testing: The Extract was test with artificial free radicals (term for a harmful particle), to experiment whether the extract had the ability to counteract the free radical.

- DPPH and ABTS assays: These tests measure how much extract is needed to neutralize 50% of the free radicals IC_{50}. A lower number means the extract is stronger.
- Specific Radical Scavenging: They also tested the extract against specific types of radicals found in the body, such as superoxide O_2^- , hydroxyl ·OH, and nitric oxide $NO^{\cdot}$.

Enzyme Blocking (AChE Inhibition): This test ascertained if the extract could inhibit the activity of the enzyme Acetylcholinesterase (AChE). This enzyme is responsible for the degradation of memory-associated neurotransmitters within the brain. By blocking its activity, the plant extract potentiates the elevation of memory-associated neurotransmitters.

2.3. Cell-Based Experiments

Investigators observed and documented what alterations the plant made cellularly using the cells in controlled microcosms.

- A Model of Protection of Neurological cells: Damage to the brain was simulated using cells from a murine brain (HT22 cells), then poisoned using glutamate (neurotoxic excitatory compound). Following the insult, the extract was added to see if the cells remained alive. Cell "Western blotting": To ascertain the learned "persistence" of the cells, the scientists lysed the cells and assessed a battery of proteins:

- Proteins of Survival: The presence of BDNF, p-AKT, and p-CREB (all signaling rescue and growth), as well as other survival proteins, was assessed.
- Proteins of Death: Their Bam (a cellular executioner protein) was monitored, and large amounts of Bcl-2 (a protective, survival factor) was quantified.
- Inflammatory Response Model: To trigger a response of irritation, macrophages in it were used, and then combined with a bacterial stimulus (LPS) to invoke inflammation. The use of the extract was to measure inflammation-activated proteins: NF-κB, COX-2, and NO (Nitric Oxide).

2.4. Animal Studies (In Vivo)

In order to determine if the effects apply to living organisms, the researchers employed animal models.

- Fruit Fly Model (Drosophila): Fruit flies were poisoned with Aluminum Chloride ($AlCl_3$) to simulate neurodegeneration.
- Intervention: The flies were given diets that had the leaf extract mixed in at concentrations of 1.0, 2.0, and 4.0 mg/mL.
- Outcomes: Researchers looked at the flies' lifespan, their motor activity and memory (how well they could climb), and the researchers looked at the flies in order to measure MDA (a marker of cellular damage) and glutathione (an endogenous antioxidant), after grinding the flies.

Rodent Models:

- Stroke Model: Mongolian gerbils had surgery where they purposely blocked the blood flow to the brain (ischemia) and the researchers looked to see how many brain cells died in the hippocampus.

Organ Toxicity Models: Mice were administered toxic medications (cyclophosphamide for the liver, cisplatin for kidneys), which were designed to induce oxidative stress on the kidneys. MDA was measured in these organs to determine if the plant extract had any damage shielding effect, and to see if the oxidative stress was mitigated.

2.5. Computer Simulations (In Silico)

To understand how compounds in a specific plant work with the body's proteins, researchers employed advanced computational systems to estimate probable interactions between proteins and various plant compounds.

Network pharmacology: This strategy creates a ‘map’ of the associations between brain disease-related plant phytochemicals and the corresponding disease-modifying genes. It highlighted PTGS2 (COX-2), NFKB1, and NFE2L2 (Nrf2) as principal targets.

Molecular docking: This involves computer modeling and simulation of a potential molecular interaction to establish 3D compatibility of a ligand and a target macromolecule.

It was hypothesized that Stigmasterol (a candidate molecule) would fit the inflammatory target proteins TLR4, NF-kB, COX-2 and blockade inflammatory pathways.

Hypotheses were built for Polysciosides to successfully lid and block the NMDA receptor which is known to be a primary activator of cell apoptosis, and the AChE (acetylcholinesterase) enzyme which is known to be a primary inhibitor of memory.

3. Results

The synthesis of data from the selected studies reveals a rich phytochemical profile that is directly linked to diverse, multi-layered pharmacological mechanisms.

3.1. Phytochemical Profile

Analysis of the literature confirms that three major groups of chemical compounds form the basis of *P. fruticosa*'s pharmacological activity.

3.1.1. Triterpenoid Saponins (Oleanane Skeleton)

This is seen as the characteristic chemical marker of the Araliaceae family polyscias genus.

- Innovative Elements: Two of the novel oleanane type triterpenoid saponins (Polyscioside J (PF4) and Polyscioside K (PF5)) have been recently described and structurally elucidated from leaves.
- Familiar Elements: VII Chikusetsusaponin (PF2) is particularly recognized as one of the saponins that has been documented.

- Aglycone Core: The common structural foundation for the saponins is oleanolic acid (PF9), a triterpenoid itself with remarkable anti-inflammatory and antioxidant properties. Substantial shifts in solubility and pharmacokinetic parameters of the saponins (PF1–PF6) glycosylated (having sugar moieties added) may help understand saponins' fate as prodrugs modified by gut microbiota.

3.1.2. Phenolic Compounds and Flavonoids

This group forms one of the principal components of the extract's direct antioxidant abilities.

The data suggest the presence of high concentrations of extractable phenolics, with considerable variability arising from the methodology performed in the TPC (Total Phenolic Content) of 60.91 mg GAE/100 mg to 156.34 mg GAE/g, TFC (Total Flavonoid Content) 62.88 to 441.79 mg QE/g extract.

In Ethyl acetate (EtOAc) extract, some phenolic and flavonoid derivatives were separated, like, Kaempferol-3-O-rhamnoside (Afzelin, PF10), Caffeic Acid (PF15), Liquiritigenin (PF12). Among the isolations, Liquiritigenin, a flavanone, is the first IPS (Isolation from a *Polyscias* species).

3.1.3. Lipophilic (Non-polar) Fraction

At first concentrating on the polar elements, the newer reviews have been assessing the role of the lipophilic fractions, especially the ones affecting the central nervous system.

Structuring: 71 lipophilic compounds have been classified chromatographically with the use of GC-MS.

Some of the more articulate and important structural classes are as follows:

Phytosterols: Stigmasterol, PF8, is one of the notable ones.

Sesquiterpenes: Some of the notable ones being Ylangene, Germacrene D, Copaene, and a few others.

Polyacetylenes: It is Falcarinol that is the most notable being very bioactive. Since the compounds e.g., sterols, terpenes are lipophilic, they are expected to cross the blood-brain barrier (BBB) more easily than the polar saponin glycosides.

Table 1. *Key Bioactive Phytochemical Compounds Identified in Polyscias fruticosa*

Compound Name	Chemical Class	Source (Part/Extract)	Main Related Biological Activity
Polyscioside J (PF4)	Triterpenoid Saponin	Leaf / n-BuOH Extract	Novel compound, activity undefined
Polyscioside K (PF5)	Triterpenoid Saponin	Leaf / n-BuOH Extract	Novel compound, activity undefined
Chikusetsusaponin IVa (PF2)	Triterpenoid Saponin	Leaf / n-BuOH Extract	Anti-inflammatory, antioxidant (1st time in *Polyscias*)
Oleanolic Acid (PF9)	Triterpenoid (Aglycone)	Leaf / EtOAc Extract	Anti-inflammatory, hepatoprotective, antioxidant
Stigmasterol (PF8)	Phytosterol	Leaf / EtOAc, Lipophilic	Anti-inflammatory, antioxidant, Nrf2/NF-κB modulator

Falcarinol	Polyacetylene	Leaf / Lipophilic fraction	Anti-inflammatory, neuroprotective, anti-cancer
Kaempferol-3-O-rhamnoside (Afzelin, PF10)	Flavonoid	Leaf / EtOAc Extract	Antioxidant, anti-inflammatory
Caffeic Acid (PF15)	Phenolic Acid	Leaf / EtOAc Extract	Strong antioxidant, anti-inflammatory
Liquiritigenin (PF12)	Flavanone	Leaf / EtOAc Extract	Antioxidant (1st time in *Polyscias*)

3.2. Antioxidant Activity: A Dual-Action Mechanism

The evidence suggests *P. fruticosa* employs a sophisticated, two-tiered antioxidant strategy: direct scavenging and endogenous defense fortification.

3.2.1. Tier 1: Direct Free Radical Scavenging (In Vitro)

The leaf extracts, rich in phenolics and flavonoids, demonstrate potent free radical neutralizing capacity. Quantitative studies using optimized extraction (e.g., microwave-assisted) have reported very low 50% inhibitory concentration (IC_{50}) values, indicating high potency:

- **DPPH assay:** IC_{50} = 20.38 μg/mL
- **ABTS assay:** IC_{50} = 12.60 μg/mL
- Other studies confirmed broad-spectrum activity of fractions (especially lipophilic) against various other radicals, including hydroxyl, superoxide, and nitric oxide.

3.2.2. Tier 2: Activation of Endogenous Defense (Cellular and In Vivo)

This is an even greater and durable form of protection.

In Vivo Damage Reduction: Animal studies showed that *P. fruticos*a extracts protect cell membranes from oxidative damage. In toxicity studies of the liver (induced by cyclophosphamide) and kidney (induced by cisplatin), treatment with the leaf and root extracts significantly lowered Malondialdehyde (MDA) (a byproduct of lipid peroxidation) levels. This effect of lowering MDA was also seen in neurotoxicity models like the $AlCl_3$ Drosophila model. Nrf2-ARE Pathway Activation: The Nrf2 (Nuclear factor erythroid 2-related factor 2) pathway is considered the master regulator of the cell's antioxidant response.

In Silico Predicting: The Network Pharmacology analysis spotted NFE2L2 (the gene coding Nrf2) and its negative regulator KEAP1 as key molecular targets of the lipophilic compounds. This was reinforced by molecular docking analysis that showed Stigmasterol having the most clavable binding to KEAP1 (binding energy -9.9~kcal/mol). Theoretically, this could upset the KEAP1-Nrf2 complex and Nrf2 could be free to move to the nucleus. In Vitro Validation: All these hypotheses were validated with cellular models. It was shown that the lipophilic fractions increased the expression of Nrf2 target gene Catalase (CAT) and Heme oxygenase-1 (HO-1) in LPS stimulated Macrophages. Stigmasterol was also shown in separate studies to enhance antioxidant enzymes like CAT and Superoxide Dismutase (SOD).

***Table 2**. Summary of In Vitro and In Vivo Antioxidant Activities of Polyscias fruticosa Extract*

Assay Type	Extract / Compound	Key Result
DPPH Radical Scavenging	Leaf / Ethanol (Microwave)	IC_{50} = 20.38 µg/mL

ABTS Radical Scavenging	Leaf / Ethanol (Microwave)	IC_{50} = 12.60 µg/mL
In vivo MDA Reduction (Liver)	Leaf & Root / Total & n-BuOH	Significant reduction of MDA (cyclophosphamide)
In vivo MDA Reduction (Kidney)	Leaf & Root / Total & n-BuOH	Significant reduction of MDA (cisplatin)
In vivo MDA Reduction (Fly Brain)	Leaf / Ethanol	Reduced MDA levels ($AlCl_3$-induced)
Nrf2 Activation (Docking)	Stigmasterol	Strong binding affinity to KEAP1 (9.9~kcal/mol)
Nrf2 Activation (*In vitro*)	Leaf / Lipophilic fraction	Increased expression of CAT and HO-1 enzymes

3.3. Anti-inflammatory Activity: Multi-Point Inhibition of the Inflammatory Cascade

In parallel with oxidative stress, *P. fruticosa* targets central neuro-inflammatory pathways, which are a core feature of neurodegenerative diseases.

- ***In Vivo* Systemic Effects:** Classical pharmacological studies have established potent anti-inflammatory (up to 54.14% inhibition in rat paw edema model) and analgesic (up to 71.0% protection in acetic acid-induced writhing model) effects, comparable to aspirin.
- **Molecular Mechanism:** Targeting the TLR4/NF-κB/COX-2 Axis: Chronic neuroinflammation is driven by microglial activation, primarily via the NF-κB (Nuclear Factor kappa B) pathway.
- ***In Silico* Prediction**: Network pharmacology analysis of lipophilic compounds identified NFKB1 (the gene for the p50 subunit of NF-κB) and its upstream activating receptor TLR4 (Toll-like Receptor 4) as key molecular targets.
- **Molecular Docking:** Docking analysis confirmed a strong binding affinity of Stigmasterol to both NFKB1 (binding energy -7.0~kcal/mol) and TLR4 (binding energy -7.0~kcal/mol).
- **COX-2 Enzyme Inhibition:** The Cyclooxygenase-2 (COX-2) enzyme, encoded by PTGS2, is a critical inflammatory effector in the brain. PTGS2 was identified as one of the top central genes modulated by *P. fruticosa* compounds. Docking revealed very strong binding affinities of Stigmasterol (-8.9~kcal/mol) and the sesquiterpene Copaene (-8.0~kcal/mol) to the COX-2 enzyme.
- ***In Vitro* Validation:** These *in silico* predictions were validated in cellular models. Lipophilic fractions were shown to reduce the levels of pro-inflammatory factors in LPS-stimulated macrophages (a classic model for TLR4/NF-κB activation). Independent studies also confirm that Stigmasterol inhibits COX-2 and reduces the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6.

These results indicate a multi-point intervention in the inflammatory cascade: at the receptor (TLR4), transcription factor (NFKB1), and effector enzyme (COX-2) levels.

3.4. Specific Neuroprotective and Cognitive Mechanisms

Outside the ‘baseline’ oxidative stress/anti-inflammation effects, many studies have pinpointed mechanisms working against certain cognitive disorders.

3.4.1. Cholinergic and Glutamatergic Modulation

Such mechanisms form the basis of the drugs that have been approved by the FDA to treat Alzheimer's disease.

- *Acetylcholinesterase (AChE) Inhibition*: More the AChE is inhibited, more there is the spillage of acetylcholine into the synapses, thereby aiding in cognitive with functions. One study reported that leaf extract of *P. fruticosa* had AChE inhibitory ability at IC50 = 266.10mu g/mL.

- *NMDA Receptor Antagonism*: Glutamate-induced excitotoxicity, primarily through the NMDA receptor, is one of the most important mechanisms of neuronal death.
- *Mediating Compounds:* Saponins Polyscioside A to E were pinpointed by a computer program that simulates molecular binding (docking) in PFLE as being the most likely compounds to account for both AChE inhibition and NMDA receptor antagonism.

3.4.2. Activation of Neuro-Survival Pathway (AKT/CREB/BDNF)

Research has been conducted on whether *P. fruticosa* has protective abilities with respect to neurotoxins.

- One of the most important studies showed that HT22 hippocampal neurons neurotoxicity caused by glutamate was prevented by an ethanol extract of *P. fruticosa* (EEPF).
- The mechanism of protection was discovered to be via the intractivation of the AKT / CREB / BDNF survival signaling pathway. It was shown that EEPF enhanced the phosphorylation of AKT (p-AKT) and CREB (p-CREB) that resulted in overexpression of BDNF. Protein is important because it is one of the essential neuronal survival, growth and plasticity.

3.4.3. In Vivo Behavioral Improvement

These molecular and cellular mechanisms ultimately translate to measurable functional outcomes. In a *Drosophila* model of $AlCl_3$-induced neurotoxicity, treatment with *P. fruticosa* leaf extract (PFLE) (at 1.0, 2.0, and 4.0 mg/mL) showed significant improvements in lifespan, memory, and motor behavior.

Table 3. *Summary of the Multi-Target Neuroprotective Mechanisms of Polyscias fruticosa*

Pathological Process	Modulated Target / Pathway	Key Mediating Compounds / Extract
Neuroinflammation	Inhibition of TLR4/NF-κB/COX-2 axis	Stigmasterol, Copaene (Lipophilic fraction)
Oxidative Stress	Activation of Nrf2/ARE pathway (↑ HO-1, CAT)	Stigmasterol (Lipophilic fraction)
Cholinergic Decline	Inhibition of Acetylcholinesterase (AChE)	Polyscioside A-E
Excitotoxicity (Glutamate)	1. NMDA Receptor Antagonism 2. Activation of AKT/CREB/BDNF pathway	1. Polyscioside A-E 2. Components of Ethanol Extract (EEPF)

4. Discussion

This section looks at what our findings really mean and compares them with other international studies to understand the true potential of *Polyscias fruticosa* for brain health.

4.1. Stopping the Cycle: A Two-Pronged Attack on Brain Stress

One of the most important findings from this analysis is how *P. fruticosa* attacks the main problem in neurodegenerative diseases: the dangerous loop between oxidative stress and inflammation. Think of it as a cycle where cell damage causes inflammation, and inflammation causes more cell damage.

Our results show that *P. fruticosa* can intervene and break this cycle in two ways:

- Fires of inflammation were put out.

Particular attention is paid to a specific pathway TLR4/NF-κB/COX-2 (Kim et al., 2023). We found that on top of Stigmasterol, other fat-soluble compounds in the plant can block this pathway as well. This is important because NF-κB is one of the leading mechanisms that allow the brain's immune cells, the microglia, to overreact and damage the surrounding environment.

- A defense system is built.

In addition to reducing inflammation, P. fruticosa is able to strongly activate the Nrf2–ARE pathway, the cell's internal defense system. Molecular simulations and cellular experiments show that stigmasterol can bind to KEAP1, allowing Nrf2 to be released and then increasing the production of key protective enzymes such as Catalase and HO-1 (Choi et al., 2021)—a finding that also supports the restoration of redox balance through the SIRT1–FoxO3a axis. Moreover, another review confirms that polyphenols in medicinal plants can activate Nrf2 and inhibit NF-κB, thereby reducing oxidative stress in the brain (Mamun et al., 2024).

Conclusion*, P. fruticosa* is more than just a vitamin or a simple analgesic. It is a regulator because it can re-establish a cellular equilibrium by counterbalancing symptoms of stress to halt on the overreactive signals and, simultaneously, strengthen the cellular defenses.

4.2. Better Than Standard Drugs? A Multi-Tasking Approach

Current Alzheimer's drugs typically target only one mechanism, resulting in limited clinical efficacy. In contrast, the combined results suggest that Polyscias fruticosa may act simultaneously on three important brain systems, creating a more prominent "multi-tasking" approach.

- **Like Donepezil (Boosting Memory Chemicals):**

We confirmed that the leaf extract can prevent the enzyme from breaking down acetylcholine (AChE), a chemical vital for memory ($IC_{50} = 266.10\ \mu g/mL$). While the extract is weaker than a pure drug, it contains specific compounds called Polysciosides that likely do the heavy lifting. This is consistent with the results of Phan et al. (2025), in which the Polysciosides group was predicted to be the main contributor to this activity.

- **Like Memantine (Protecting Cells):**

In Alzheimer's, brain cells often die because they get over-excited by a chemical called glutamate. Our analysis identified the same Polyscioside compounds as potential blockers for the NMDA receptor, which could stop this "excitotoxicity".

- **The Bonus Effect (Repair and Survival):**

This is the most exciting part. Standard drugs treat symptoms or slow down damage, but they don't usually help cells repair themselves. Evidence shows that *P. fruticosa* extract activates the AKT/CREB/BDNF pathway. This increases BDNF, a protein that acts like fertilizer for brain cells, helping them survive and grow. This suggests the plant could offer a restorative benefit that current drugs lack.

4.3. Getting Into the Brain: The Blood-Brain Barrier

A major question for any brain treatment is: "Can it actually get into the brain?"

Some compounds in *P. fruticosa*, like saponins, are large and water-soluble, meaning they struggle to cross the Blood-Brain Barrier (BBB). However, we identified a significant group of fat-soluble (lipophilic) compounds, such as Stigmasterol and Falcarinol. Because they are fat-soluble, these are much more likely to cross into the brain directly.

This leads us to a "Dual-Impact" theory:

1. **Body-wide effects:** The large saponins might act in the gut or blood to lower overall inflammation in the body. Since body inflammation can stress the brain, this helps indirectly.
2. **Direct Brain effects:** The fat-soluble compounds likely cross into the brain to directly calm down brain cells and switch on protection pathways.

This mix of compounds might explain why the whole plant extract often works better than single isolated chemicals.

4.4. The "Vietnamese Ginseng" and the Missing Human Proof

For a long time, people called *P. fruticosa* "the ginseng of the poor". Science now backs this up. We found Chikusetsusaponin IVa in the plant-a compound typically found in Panax Ginseng. This provides a direct chemical link between the two species.

However, there is a big problem. Despite all these promising lab results, a report from the Alzheimer's Drug Discovery Foundation points out that there are "no human studies" and "no clinical trials" testing *P. fruticosa* for cognitive health.

This creates a strange situation: we have a plant with mechanisms that look superior to some drugs (protecting, repairing, and boosting memory chemicals), but we have zero proof that it works in actual patients. This gap represents the biggest opportunity for future research.

5. Conclusion

This study provides insights into the significant neuroprotective potential of *P. fruticosa* through multi-mechanism, including antioxidant, anti-inflammatory and cell signaling regulator activities. Synthesized evidence from in vitro, in vivo and in silico analyses reveal that major groups of compounds such as triterpenoid saponins, polyphenols and especially lipophilic compounds such as stigmasterol, falcarinol, sesquiterpenes, play a central role. They simultaneously activate the Nrf2–ARE axis, potently inhibit the TLR4/NF-κB/COX-2 axis, reduce oxidative damage, improve AKT/CREB/BDNF survival signaling, and modulate the cholinergic–glutamatergic system. Behavioral results in animal models also demonstrate improvements in memory, motor coordination, and lifespan. In conclusion, the research supports the potential of *P. fruticosa* as a promising neuroprotective candidate.

However, the large gap in clinical research suggests that human trials are needed to confirm efficacy and safety before practical application.

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