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Network Pharmacology and Molecular Docking-Based Evaluation of *Bacopa monnieri* for Neuroprotection in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to memory loss, cognitive decline, and eventually functional impairment; neuropathological features include extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles of hyperphosphorylated tau in addition to synaptic dysfunction and significant neuronal cell death. Currently approved therapies include acetylcholinesterase inhibitors and the NMDA receptor antagonist memantine, which offer only modest symptomatic benefits and limited effects on pathophysiological mechanisms within AD, indicating an urgent need for multi-target disease-modifying approaches. *Bacopa monnieri* (L.) Wettst. (Brahmi), An ancient Ayurvedic nootropic, it emerged as a potent neuroprotective agent due to its broad-based profile of phytoconstituents, such as triterpenoid saponins (bacosides) and flavonoids, with antioxidant, anti-inflammatory, anti-amyloidogenic, and neurogenic activity. Biotechnological approaches such as network pharmacology and molecular docking are increasingly significant for exploring the multi-component, multi-target nature of herbal medicines like *B. monnieri* in complex disease systems like AD. This review provides a comprehensive overview on the possible neuroprotective role of *B. monnieri* in AD using network pharmacological and molecular docking-based approaches to further evaluate potential therapeutic targets. We overview AD pathophysiology and the ethnomedicinal and pharmacological background of *B. monnieri*, summarize its phytochemistry and pharmacokinetics, and critically appraise in vitro, in vivo and clinical evidence for cognitive- and neuroprotection effects. We then outline the principles and workflows of network pharmacology and docking as they apply to *B. monnieri*, review key studies that dock bacosides and related compounds against BACE1, cholinesterases, tau kinases, inflammatory mediators, and neurotransmitter receptors with experimental data when available. Combined analysis suggests that the constituents of *B. monnieri* can modulate multiple pathways associated with AD, such as PI3K/Akt, MAPK, and NF-κB signaling and neurotrophin signaling pathways, along with cholinergic synapse function and Aβ production through inhibition of BACE1 activity, while providing antioxidant effects, regulating inflammation, and supporting synaptic plasticity. Yet considerable gaps still exist, notably between brain bioavailability of active metabolites, quantitative target engagement in vivo and strong clinical evidence in AD populations. Such postulates, in conjunction with rigorous multi-omics-driven network pharmacology, better in vitro and in vivo models, rational formulation strategy, and biomarker-rich clinical trials, will be necessary for translating the traditional usage and pre-clinical therapeutic potential of *B. monnieri* into an evidence-based neuroprotective therapy against AD.

Keywords: *Bacopa monnieri*; Alzheimer's disease; Network pharmacology; Molecular docking; Neuroprotection

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1. Introduction

1.1 Alzheimer's disease: burden and unmet needs

AD is the most common cause of dementia globally and represents a significant public health milestone whose incidence is anticipated to increase dramatically through population aging. Clinically, AD presents as an insidious course and progressive decline of episodic memory, language, executive function, visuospatial ability, and behavior resulting in loss of independence and eventual mortality. At the neuropathological level, the pathology is characterized by extracellular deposition of β-amyloid peptides released as part of aberrant amyloid precursor protein (APP) processing mediated by BACE1 and γ-secretase, intraneuronal neurofibrillary tangles ravaged with hyperphosphorylated tau protein, primarily concentrated in hippocampal and cortical areas[1].

In addition to Aβ and tau pathology, AD is characterized by multi-level network dysfunction involving cholinergic degeneration of the basal forebrain, glutamatergic excitotoxicity, mitochondrial dysfunction, oxidative stress, synaptic loss and microglial and astrocyte-mediated neuroinflammation, as well as calcium dysregulation and cerebrovascular changes. These synergistic pathways interact in feed-forward loops, making it improbable that single-target drugs will produce ongoing disease modification[2].

Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine remain cornerstones of pharmacotherapy, achieving some degree of symptomatic improvement or clinical stabilization in patients, but not affecting neurodegeneration. Monoclonal antibodies that target Aβ and small-molecule BACE1 inhibitors have shown inconsistent efficacy and safety issues, with candidates in late-stage trials failing at alarming rates, underscoring a renewed call for alternative strategies that embrace the systems-level substrate of AD[3].

1.2 Rationale for exploring *Bacopa monnieri* in AD

Furthermore, traditional medical systems offer a rich repository of multi-component herbal formulations that have been empirically used for cognitive enhancement and dementia-like conditions. Of these, *B. monnieri* has been widely used in Ayurveda as a Medhya Rasayana for memory, intellect and longevity improvement [4], in addition to treating other conditions such as anxiety and epilepsy. Pharmacological and clinical research over recent decades has endorsed many of its nootropic and neuroprotective claims, making it a candidate for AD therapy [5].

The results of the preclinical studies mentioned above similarly indicate protective effects of *B. monnieri* extracts and bacosides against Aβ-induced neurotoxicity, including reductions in oxidative damage and lipid peroxidation, maintenance of mitochondrial function, modulation of cholinergic neurotransmission, and, finally, improved synaptic plasticity/neurotrophic signal crosstalk. In rodent models of AD and age-related cognitive impairment, *B. monnieri* treatment consistently improves performance in learning and memory tasks, correlated with beneficial alterations in biochemical and histological markers[6].

Human trials report benefits in attention, processing speed and some memory domains in healthy adults and elderly subjects, as well as those with mild cognitive impairment (MCI), while data from established AD are more mixed, often constrained by small sample sizes. Importantly, *B. monnieri* has a relatively benign safety profile, with mostly mild gastrointestinal adverse effects reported at commonly used doses; it thus appears suitable for longer-term use as either preventive or adjunctive therapy[7].In this context, the use of network pharmacology and molecular docking to systematically elucidate multi-target interactions between *B. monnieri* and AD-related pathways is both timely and conceptually in line with the poly-component nature of the herb.

2. Ethnobotany, Botany, and Phytochemistry of *Bacopa monnieri*

2.1 Ethnobotanical relevance and traditional formulations

B. monnieri is a creeping, succulent herb that grows in marshy areas and wetlands across the Indian subcontinent, Southeast Asia, Africa, and other tropical regions. In Ayurveda, it is incorporated into numerous classical formulations such as Brahmi Ghrita, Saraswata Churna, and Medhya Rasayana combinations with *Withania somnifera*, *Convolvulus pluricaulis*, and *Nardostachys jatamansi*. These formulations are prescribed for memory enhancement, neurodevelopmental disorders, epilepsy, and anxiety, reflecting a broad spectrum of neurological indications[8].

Traditional usage typically involves dried whole plants or aerial parts as powders, decoctions, or ghee-based preparations, often combined with other herbs, which may influence bioavailability and lead to synergistic interactions. Modern supplements generally employ standardized extracts with defined bacoside content, though considerable variability exists among products in extraction solvents, plant parts used, and standardization markers 9

Table 1. Major Phytochemicals of *Bacopa monnieri* and Their Reported Neuroprotective Activities

Phytochemical Class	Compounds	Major Biological Activities	Primary Molecular Targets / Effects	Relevance to Alzheimer's Disease
Triterpenoid saponins	Bacoside A, Bacopaside I,	Antioxidant, anti-inflammatory, neuroprotective	Reduction of ROS, modulation of	Protection against oxidative stress and neuroinflammation

	Bacopaside II		NF-κB signalling	
Saponin derivatives	Bacopa saponin G, Bacopa side N2	Anti-apoptotic, anti-amyloidogenic	Regulation of caspase-3 and apoptotic pathways	Reduction of neuronal apoptosis
Flavonoids	Apigenin, Luteolin, Quercetin	Antioxidant, anti-inflammatory	Scavenging free radicals and modulation of cytokines	Reduction of oxidative damage and inflammation
Phenolic compounds	Phenolic acids	Neuroprotective, anti-inflammatory	Regulation of oxidative stress pathways	Protection of neuronal integrity
Sterols and terpenoids	Betulinic acid, minor terpenoids	Neurotrophic and synaptic support	Enhancement of neurotrophic signalling	Support of neuronal survival and synaptic function

2.2 Botanical description and chemotypes

Morphologically, *B. monnieri* is characterized by small, oblong, sessile leaves arranged oppositely on creeping stems, with solitary, axillary, white or pale-blue flowers and capsule fruits containing numerous seeds. It propagates readily via stem cuttings and can be cultivated under controlled conditions to optimize phytochemical yields[10].

Chemotype variation has been reported, with environmental factors, soil conditions, and cultivation practices influencing bacoside composition and levels. Such variability can affect both pharmacological potency and reproducibility across studies, underscoring the importance of standardized cultivation and extraction[11].

2.3 Phytochemical profile

Comprehensive phytochemical analyses identify dammarane-type triterpenoid saponins as the major bioactive constituents, collectively known as bacosides. Bacoside A, traditionally considered the primary active fraction, is itself a mixture of saponins including bacoside A3, bacopasaponin C, bacopaside II, and bacopaside X, each composed of jujubogenin or pseudojujubogenin aglycones glycosylated with various sugar chains[12].

Other important saponins include bacopasaponin G, bacopaside I and II, and bacopaside N2, some of which show distinct pharmacological profiles and are increasingly evaluated individually in docking and in vitro assays. Beyond saponins, *B. monnieri* contains flavonoids (apigenin, luteolin, quercetin), phenolic acids, betulinic acid, sterols, alkaloids, and minor terpenoids, many of which have independent antioxidant, anti-inflammatory, or neuromodulators activities[13].

2.4 Pharmacokinetics and blood–brain barrier considerations

The CNS activity of *B. monnieri* depends not only on the bioactivity of its constituents but also on their absorption, distribution, metabolism, and ability to cross the blood–brain barrier (BBB). Bacosides are relatively large, amphiphilic saponins with limited passive diffusion across membranes; however, in vivo they undergo metabolic transformation to aglycones and related derivatives with improved pharmacokinetic properties[14].

An in silico and in vitro study comparing parent bacosides with their aglycones (jujubogenin, pseudojujubogenin) and derivatives (ebelin lactone, bacogenin A1) showed that while intact bacosides had poor CNS drug-like properties and could not dock effectively into selected CNS targets, the aglycones and derivatives displayed favorable ADMET profiles with good predicted intestinal absorption and BBB penetration, along with higher binding affinity to muscarinic M1 and serotonergic 5-HT2A receptors. Experimental receptor binding assays confirmed that ebelin lactone has submicromolar affinity for M1 and low-micromolar affinity for 5-HT2A receptors, while some bacoside-related compounds target dopamine D1 receptors[15].

Additional in vivo work indicates that bacoside A can protect BBB integrity under conditions of oxidative stress. In a rat model, seven-day intraperitoneal treatment with bacoside A (200–400 mg/kg) significantly reduced Evans blue dye extravasation, restored antioxidant enzyme activities, and normalized expression of tight junction proteins and Nrf2 in brain microvessels, implying both direct vascular protection and modulation of oxidative stress pathways. Nanoparticle formulations of bacoside-rich extracts have been developed to enhance brain delivery; solid lipid nanoparticles loaded with bacosides show improved pharmacokinetic parameters, prolonged circulation, and superior cognitive benefits compared with unencapsulated extract in scopolamine-induced amnesia models[17].

3. Preclinical Evidence of Neuroprotection in Alzheimer's Models

3.1 In vitro models of amyloid toxicity and oxidative stress

Multiple cell culture studies have evaluated *B. monnieri* extracts and isolated constituents in AD-relevant paradigms, including Aβ-induced toxicity, glutamate excitotoxicity, and oxidative stress. Neuronal cell lines such as PC12, SH-SY5Y, and primary cortical or hippocampal neurons treated with Aβ25–35 or Aβ1–42 exhibit reduced viability, increased ROS production, mitochondrial dysfunction, and activation of caspase-3, all of which are attenuated by co-treatment with *B. monnieri* extracts or bacosides[18].

For example, bacoside A has been shown to protect cortical neurons against Aβ-induced apoptosis by preserving mitochondrial membrane potential, decreasing lipid peroxidation, and increasing antioxidant defenses (SOD, catalase, glutathione peroxidase, and GSH), thereby interrupting ROS-mediated apoptotic cascades. Bacosides also modulate intracellular calcium homeostasis and prevent glutamate-induced excitotoxicity in hippocampal neurons, effects that may be mediated partly via modulation of NMDA receptor function and downstream signaling[19].

In glial models, *B. monnieri* reduces Aβ- or LPS-induced microglial activation, suppressing NF-κB translocation and downregulating pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2, and iNOS, while upregulating anti-inflammatory cytokines and antioxidant response elements. These actions help create a more neuroprotective microenvironment and may reduce chronic neuroinflammation in AD[20].

3.2 In vivo models of cognitive impairment and AD

In vivo, *B. monnieri* has been extensively studied in rodent models of cognitive impairment induced by scopolamine, aging, stress, aluminum, and Aβ peptides. Across these models, oral administration of standardized *B. monnieri* extract (often 40–80 mg/kg, bacosides 40–55%) improves learning and memory in behavioral tests such as the Morris water maze, radial arm maze, elevated plus maze, and passive avoidance[21].

In Aβ-induced AD models, *B. monnieri* reduces hippocampal Aβ accumulation, diminishes plaque burden, and mitigates tau hyperphosphorylation while restoring synaptic markers such as synaptophysin and PSD-95. Biochemically, treated animals show decreased lipid peroxidation, increased antioxidant enzyme activities, reduced pro-inflammatory cytokines, and normalization of cholinergic markers (e.g., reduced AChE, increased choline acetyltransferase), consistent with multi-target neuroprotection[22].

Nanoparticle formulations further enhance these effects. In a comparative in vivo study, bacoside-rich extract-loaded solid lipid nanoparticles produced greater improvements than plain extract in scopolamine-induced amnesia, with better pharmacokinetic parameters and prolonged drug release, supporting the feasibility of nanotechnology-based delivery systems for AD therapy[23].

3.3 Mechanistic themes emerging from preclinical studies

Preclinical data suggest several convergent mechanisms of *B. monnieri* neuroprotection relevant to AD:

- **Antioxidant and redox modulation:** Upregulation of endogenous antioxidant enzymes, increased GSH, decreased malondialdehyde and protein carbonyls, and reduced ROS.[1][9][^3]
- **Anti-inflammatory effects:** Suppression of NF-κB signaling, decreased expression of COX-2, iNOS, TNF-α, IL-1β, and IL-6, and modulation of microglial phenotype toward anti-inflammatory states[24].
- **Cholinergic enhancement:** Inhibition of AChE and BChE, increased choline acetyltransferase activity, and improved cholinergic neurotransmission, particularly in hippocampal and cortical regions[25].
- **Anti-amyloid and anti-tau actions:** Reduction in Aβ production and deposition, interference with Aβ aggregation, and mitigation of tau hyperphosphorylation through modulation of kinases and phosphatases[26].

- **Neurotrophic and synaptogenic effects:** Upregulation of BDNF, CREB, and synaptic proteins, promotion of dendritic branching and spine density, and enhancement of long-term potentiation[27].

Network pharmacology and docking approaches aim to rationalize these multimodal actions at the molecular systems level.

4. Clinical Evidence for Cognitive and Neuroprotective Effects

4.1 Trials in healthy adults and age-related cognitive decline

Randomized controlled trials in healthy adults and older individuals provide preliminary evidence that *B. monnieri* can improve specific cognitive domains. In several studies using 300–450 mg/day of standardized extract for 12 weeks, participants exhibited improvements in attention, information processing, and working memory measures compared with placebo, though effects on global cognition were modest[28].

A 2024 triple-blind, randomized, placebo-controlled trial in 62 individuals with MCI administered 160 mg/day *B. monnieri* extract or placebo for two months and assessed cognition with the Montreal Cognitive Assessment and Pittsburgh Sleep Quality Index. While there was no statistically significant difference in overall cognitive scores between groups, *B. monnieri*-treated participants showed significant improvements in attention at one and two months and in verbal fluency at two months, suggesting domain-specific benefits[29].

4.2 Trials in Alzheimer's disease and dementia

Clinical data specifically in AD are more limited and heterogeneous. A systematic review of *B. monnieri* in the treatment of dementia due to AD identified five small, randomized trials comparing *B. monnieri* with placebo or donepezil. Overall, the quality of evidence was rated very low due to small sample sizes, short durations, variable extract compositions, and inconsistent outcome measures; pooled analyses showed no clear difference between *B. monnieri* and control treatments on primary cognitive scales, although some secondary measures suggested potential benefits[30].

A 2025 narrative review focusing on *B. monnieri* in AD concluded that while preclinical data are robust, current clinical evidence is insufficient to recommend *B. monnieri* as a stand-alone therapy but supports its potential as an adjunct to standard treatment or as a preventive intervention in prodromal stages such as MCI. Ongoing and planned trials, including a 2026 protocol for a double-blind placebo-controlled study in amnestic MCI using cognitive, metabolomic, and network-based endpoints, are expected to provide more definitive data on efficacy and mechanisms in humans[31].

4.3 Safety and tolerability

Across clinical studies, *B. monnieri* is generally well tolerated, with the most commonly reported adverse events being mild gastrointestinal symptoms such as nausea, increased stool frequency, and abdominal cramps. Serious adverse events are rare, and discontinuation rates are similar to placebo in most trials. Nonetheless, potential interactions with other cholinergic

or psychoactive medications, and long-term safety in frail elderly or those with multiple comorbidities, require further systematic evaluation[32].

5. Network Pharmacology Approach to *Bacopa monnieri* in AD

5.1 Conceptual framework

Network pharmacology views drugs and diseases as interacting networks rather than one-to-one relationships between a single ligand and a single target. For herbal medicines, this paradigm is particularly relevant because they contain numerous bioactive compounds that collectively modulate multiple molecular pathways. The core idea is to integrate chemical, pharmacological, and omics data into a systems-level representation that captures how herbal constituents perturb disease-associated networks toward a healthier state[33].

5.2 Typical workflow for *B. monnieri*–AD network construction

Network pharmacology studies of *B. monnieri* in AD typically follow a multi-step pipeline:

1. **Compound collection and filtering:** Phytochemicals are retrieved from databases (e.g., TCMSP, IMPPAT, PubChem) and literature; duplicates and uncertain structures are removed. Drug-likeness filters (e.g., Lipinski, Veber) and oral bioavailability thresholds are sometimes applied, although this may exclude larger saponins with proven activity.
2. **Target prediction:** Putative protein targets for each compound are predicted using tools such as SwissTargetPrediction, PharmMapper, or SEA, or obtained from experimentally validated databases like ChEMBL and BindingDB.
3. **Disease gene collection:** AD-associated genes are gathered from sources such as GeneCards, OMIM, DisGeNET, and GWAS Catalog.
4. **Intersection and PPI network construction:** Overlapping genes between compound targets and AD genes are identified as potential therapeutic targets, and PPI networks are constructed using STRING or similar databases, visualized with Cytoscape.
5. **Topological analysis and hub target identification:** Network metrics such as degree, betweenness, and closeness centrality are used to identify hub nodes and key modules; compounds targeting these hubs are considered high-priority candidates.
6. **Functional enrichment:** GO and KEGG pathway analyses elucidate biological processes and pathways enriched among the intersecting targets, revealing mechanistic themes.
7. **Compound–target–pathway network construction:** Integrated networks illustrate how specific *B. monnieri* compounds are connected to AD pathways, guiding selection of targets for docking and experimental validation.

5.3 Key findings from recent network pharmacology analyses

Recent network pharmacology studies and reviews indicate that *B. monnieri* compounds potentially interact with numerous AD-relevant targets, including AChE, BChE, BACE1, APP, GSK-3β, CDK5, COX-2, iNOS, TNF, IL-1β, BDNF, TrkB, CREB, and various oxidative stress-related proteins. Enrichment analyses consistently highlight pathways such as

neuroactive ligand–receptor interaction, cholinergic synapse, glutamatergic synapse, PI3K/Akt, MAPK, NF-κB, apoptosis, and "Alzheimer's disease" KEGG pathway (hsa05010)[34].

These results provide a systems-level rationale for the observed pleiotropic effects of *B. monnieri* in preclinical models and suggest that its neuroprotective actions arise from coordinated modulation of synaptic, inflammatory, oxidative, and apoptotic networks rather than single-target inhibition.

6. Molecular Docking and In Silico Evaluation of *Bacopa* Phytochemicals

6.1 Docking against BACE1 and APP-processing machinery

BACE1 has emerged as a central target in AD drug development because it catalyzes the rate-limiting step in Aβ generation. A 2025 *Scientific Reports* study systematically compared the binding of *B. monnieri* phytochemicals to clinically investigated synthetic BACE1 inhibitors using molecular docking, molecular dynamics, and free-energy calculations. Bacopaside I demonstrated superior docking scores and a unique interaction pattern with the catalytic aspartate dyad and surrounding residues, suggesting strong and specific binding[35].

Molecular dynamics simulations confirmed the stability of the Bacopaside I–BACE1 complex, with favorable binding free energies and persistent hydrogen bonds and hydrophobic interactions across the simulation trajectory. Such results support the hypothesis that certain bacosides may act as natural BACE1 inhibitors, potentially reducing Aβ production[37].

Other docking studies testing broader sets of natural compounds against BACE1 have also reported competitive binding energies for bacosides and related saponins, although not all studies focus specifically on *B. monnieri*. Experimental validation of BACE1 inhibition by bacosides remains limited, and in vitro enzymatic assays and cell-based Aβ production assays are needed to confirm functional effects.

Table 2. Molecular Docking Targets and Key Signaling Pathways Associated with *Bacopa monnieri* in Alzheimer's Disease

Target Protein	Associated Pathway	Docked Compounds	Predicted Mechanism of Action	Therapeutic Significance
BACE1	Amyloid precursor protein processing	Bacopaside I, Bacopaside II	Inhibition of amyloid β formation	Reduction of amyloid plaque formation
AChE (Acetylcholinesterase)	Cholinergic signaling	Bacoside A, flavonoids	Enzyme inhibition	Enhancement of cholinergic neurotransmission

GSK-3β	Tau phosphorylation pathway	Bacopasaponin G	Inhibition of kinase activity	Reduction of tau hyperphosphorylation
NF-κB	Inflammatory signaling	Bacosides, flavonoids	Suppression of inflammatory mediators	Reduction of neuroinflammation
PI3K/Akt	Neurotrophic signaling	Bacosides	Activation of survival signaling pathways	Promotion of neuronal survival
MAPK	Cellular stress response	Multiple phytochemicals	Regulation of stress signaling	Neuroprotection and synaptic stability

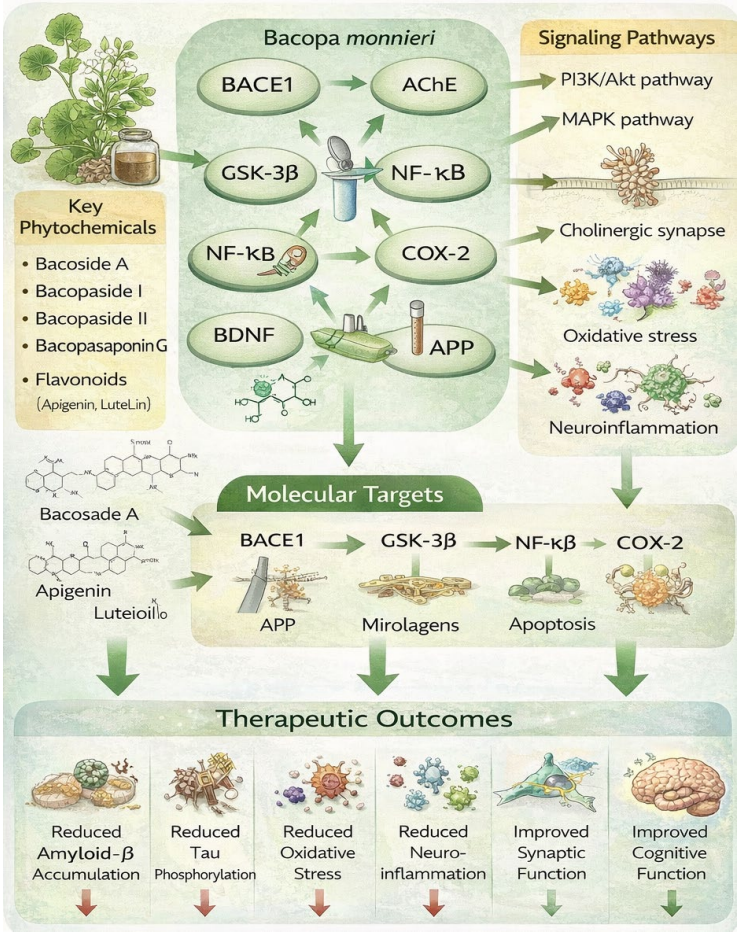

Figure 1. Multi-target neuroprotective mechanisms of *Bacopa monnieri* in Alzheimer's disease. Major phytoconstituents of *Bacopa monnieri*, including bacosides and flavonoids, interact with multiple molecular targets such as BACE1, acetylcholinesterase (AChE), GSK-3β, NF-κB, and caspase-3. These interactions modulate key signaling pathways including PI3K/Akt, MAPK, NF-κB, and neurotrophin pathways, leading to reduced amyloid β production, inhibition of tau

phosphorylation, attenuation of oxidative stress and neuroinflammation, and enhancement of synaptic plasticity and cognitive function.

6.2 Docking to cholinesterases

Docking analyses frequently include AChE and BChE, given their importance as symptomatic targets in AD. *In silico* studies show that bacosides and flavonoids from *B. monnieri* can occupy the catalytic and peripheral anionic sites of AChE, forming hydrogen bonds and π–π interactions with key residues, which may inhibit substrate access and enzymatic activity[38].

While an earlier combined *in silico*/*in vitro* study reported that none of the bacoside aglycones or derivatives significantly inhibited AChE in biochemical assays, more recent preclinical work suggests that *B. monnieri* extract can reduce AChE activity in brain tissue, implying either indirect modulation or contributions from other constituents not evaluated in the initial docking series. This discrepancy highlights the necessity of integrating docking with comprehensive phytochemical and bioassay data[39].

6.3 Docking to neurotransmitter receptors

The 2015 docking and ADMET analysis study mentioned earlier investigated interactions of bacoside-derived aglycones and derivatives with serotonergic (5-HT1A, 5-HT2A), dopaminergic (D1, D2), and muscarinic (M1) receptors. Aglycones and derivatives, particularly ebelin lactone, showed favorable docking scores and predicted CNS permeability, in contrast to parent bacosides[40].

Radioligand binding assays confirmed that ebelin lactone binds to M1 and 5-HT2A receptors, and that some bacosides interact with the D1 receptor, suggesting that metabolic conversion of bacosides may generate compounds capable of modulating neurotransmitter systems implicated in cognition and mood. Such receptor-level interactions may contribute to the clinically observed improvements in attention and mood in *B. monnieri*-treated subjects[41].

6.4 Docking to tau kinases, apoptotic proteins, and inflammatory mediators

In silico approaches against GSK-3β, TPK I, caspase-3 and COX-2 and iNOS have been detailed recently in several studies that dock bacosides and related synthetic compounds. In several instances, bacopasaponin G (10), bacopaside N2 (11) and related saponins are predicted to interact with comparable or better docking scores than reference ligands, indicating their putative ability to modulate events including tau phosphorylation, execution of apoptosis and action of pro-inflammatory enzymes[42].

Details of direct enzymatic inhibition are still limited, but the preclinical reports mentioned earlier of decreased tau phosphorylation and reduced activation of caspase-3 as well as lower expression levels of COX-2 and iNOS observed in models treated with *B. monnieri* compounds strongly support these docking based findings although causality cannot be assumed without further mechanistic studies[43].

6.5 ADMET and drug-likeness profiling

Docking studies often incorporate ADMET prediction to evaluate oral bioavailability, CNS penetration, toxicity and other off-target liabilities. Parent bacosides usually do not meet traditional drug-likeness guidelines due to high molecular weight and multiple sugar moieties, while aglycones and derivatives display more auspicious physicochemical properties (logP, polar surface area) as well as predicted BBB penetration[44].These findings support a "prodrug-like" perspective in which ingested bacosides are converted to smaller, more lipophilic metabolites that exert effects at CNS targets. However, experimental pharmacokinetic studies that quantify the levels of individual metabolites within the brain is required to validate this model[45].

7. Integration of Network, Docking, and Experimental Data

7.1 Mapping computational predictions to biological outcomes

In summary, network pharmacology and docking studies provide an in-depth view of potential interactions between *B. monnieri* constituents and targets related to AD. Several predicted targets and pathways are validated by data from preclinical, and less commonly clinical, investigations—cholinergic synapse>neurotrophin signaling>NF-κB-mediated inflammatory response>oxidative stress response (OSR)>APP processing[46].

This includes predicted modulation of BACE1 with the APP protein that explains observed decreases in Aβ burden seen in rodent models, both models induced through an injection of Aβ; predicted interactions with cholinesterases and muscarinic receptors correspond to improvements in cholinergic markers and cognitive performance; and predicted effects on NF-κB, as well as other inflammatory enzymes, are mirrored with experimentally reported reductions in pro-inflammatory cytokines and COX-2/iNOS expression[47].Discrepancies such as the absence of AChE inhibition from certain docked compounds in biochemical assays exemplify the drawbacks of relying on docking scores alone and stress the necessity for iterative rounds of computational prediction and experimental validation[48].

7.2 multi-target synergy and systems-level effects

Our network perspective reveals that the activity of *B. monnieri* in disease-like states is better explained by multidimensional, multifunctional modulation than through high-affinity binding to a single target, resulting in compounding effects on resilience and cognitive impairment. This "network pharmacology" mode of action may prove advantageous in heterogenic diseases such as AD, where redundancy and compensatory pathways mitigate the effectiveness of single target drugs[49].Similarly, synergistic effects from various bacosides, flavonoids, and other components would enhance neuroprotective effects through concurrent suppression of oxidative stress and neuroinflammation as well as stabilization of synapses and neurotransmission. Understanding these synergies will require the quantitative modelling and experimental designs that can be used to help understand combination effects[49].

8. Methodological Strengths and Limitations

8.1 Strengths of network pharmacology and docking

Network pharmacology and docking offer several advantages in the context of herbal neuroprotectants:

- They provide a structured, systematic framework to integrate diverse datasets and generate mechanistic hypotheses for multi-component mixtures.
- They enable prioritization of key compounds and targets for experimental testing, reducing the search space and cost of preclinical studies.
- Docking and molecular dynamics simulations furnish atomistic insights into ligand–protein interactions, informing rational design of derivatives and analogues.
- ADMET predictions highlight pharmacokinetic and toxicity issues early in the discovery pipeline, guiding formulation and optimization strategies.

8.2 Limitations and sources of uncertainty

Despite these strengths, several limitations merit consideration:

- **Data quality and completeness:** Inaccurate phytochemical cataloguing, misannotated structures, and incomplete metabolite coverage can skew network topology and docking results.
- **Target prediction biases:** Ligand-based target prediction tools are biased toward well-characterized targets and may overlook novel or plant-specific interactions.
- **Docking approximations:** Docking scores do not always correlate with experimental binding affinities or functional effects; protein flexibility, solvation, and allosteric modulation are imperfectly captured.
- **Neglect of pharmacokinetics:** Many studies dock parent bacosides without considering metabolic transformation and realistic brain exposure, potentially overestimating their direct CNS actions.
- **Lack of integrated validation:** Few studies close the loop by validating network-predicted targets and docking interactions with targeted biochemical or omics experiments.

Addressing these limitations will be crucial to unlocking the full potential of *B. monnieri* and similar herbal leads.

9. Future Directions and Biotechnological Opportunities

9.1 multi-omics and systems biology integration

Emerging multi-omics technologies provide opportunities to refine *B. monnieri* network models using empirical data. Transcriptomic, proteomic, and metabolomic profiling of AD models treated with standardized *B. monnieri* extracts can validate predicted targets and reveal previously unrecognized pathways[50].

Single-cell RNA sequencing and spatial transcriptomics could delineate cell type-specific effects on neurons, astrocytes, microglia, and endothelial cells, while phosphoproteomics might clarify impacts on kinase signaling cascades involved in tau phosphorylation and synaptic plasticity. Integration of such datasets with network pharmacology platforms will enable more accurate, dynamic models of herbal–disease interactions[51].

9.2 Advanced in vitro and in vivo models

Human iPSC-derived neurons and brain organoids carrying familial AD mutations, along with microfluidic brain-on-chip systems, can provide more physiologically relevant platforms to test network-derived hypotheses on *B. monnieri* mechanisms and to study BBB transport of bacosides and metabolites[52].

In vivo, transgenic mouse models recapitulating Aβ and tau pathology, coupled with longitudinal imaging (MRI, PET) and behavioral batteries, offer opportunities to assess disease-modifying effects of standardized *B. monnieri* formulations under chronic dosing regimens[53].

9.3 Formulation science and targeted delivery

Continued development of nanocarrier systems (solid lipid nanoparticles, polymeric nanoparticles, nanoemulsions) and prodrug strategies tailored to bacoside chemistry could significantly improve brain exposure and therapeutic indices. Smart delivery systems responsive to pathological cues such as oxidative stress or pH may enable targeted release at sites of neuroinflammation or amyloid deposition[54].

9.4 Rational clinical trial design and regulatory considerations

Rigorous characterization and standardization (including pharmacokinetics) of *B. monnieri* formulations, adequate dosing (at least based on pharmacokinetic modeling) and sufficiently powered sample sizes to detect clinically meaningful effects should be considered in future clinical trials. Adaptive trial designs that rely on biomarker end points (CSF, Aβ/tau, neurofilament light chain, inflammatory markers) and digital measures of cognition and function may serve as sensitive indices of disease modification[55].

In the case of botanical drugs, regulatory pathways increasingly acknowledge multi-component mixtures, although they demand strong quality, safety and efficacy evidence. Findings from network pharmacology and docking-derived mechanistic insights can facilitate regulatory dossiers by illuminating mode of action, target engagement and rationale for dose selection.

10. Conclusion

Bacopa monnieri is a classic Ayurvedic nootropic whose extensive phytochemical characterization and pleiotropic pharmacology provides an intuitive match to the complex pathobiology of Alzheimer's disease. In silico studies using network pharmacology and molecular docking have suggested that the possible AD targets of bacosides, their analogs, and other phytochemicals overlap with several classes of known druggable proteins involved in

AD pathobiology including BACE1, cholinesterases, tau phosphorylating kinases, inflammatory mediators/regions/molecules, synaptic neurotransmitter receptors and oxidative stress modulators converging on pathways such as PI3K/Akt signaling pathway, MAPK signaling pathway, NF -κB signaling pathway neurotrophins signal transduction and Cholinergic synapse.

These computational predictions harmonize with a wealth of preclinical data showing that *B. monnieri* mitigates Aβ and tau pathology, lessens oxidative stress and neuroinflammation, promotes cholinergic and serotonergic neurotransmission, and improves cognitive performance across the animal kingdom; early clinical trials in healthy adults and MCI show modest domain-specific cognitive benefits along with an encouraging safety profile. However, clinical trials in AD populations remain limited and inconclusive, with many uncertainties regarding the pharmacokinetics and CNS penetration of active metabolites, the degree of target engagement in humans (yet to be established quantitatively), and optimal dosing/administration strategies.

In conclusion, ethnomedicinal usage coupled with mechanistic preclinical data and network pharmacology/docking analyses has identified *B. monnieri* as a potential multi-target neuroprotective candidate for AD. Realisation of this potential will require interdisciplinary approaches spanning phytochemistry, systems biology, and advanced biotechnological models, as well as carefully designed clinical trials, to translate computational insights and preclinical promise into clinically meaningful, evidence-based interventions for individuals at risk of or living with Alzheimer's disease.

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