

Bacopa monnieri as a Multi-Target Therapeutic Candidate for Alzheimer's Disease: Pharmacological Evidence, Molecular Targets, and Clinical Perspectives

Hemant Dnyaneshwar Chandore¹, Jitendra Kumar², M. Ranjith³, Raghu P. S⁴, Mukesh Kumar Meena^{5*}

¹Department of Horticulture, Shikshan Maharshi Dayanandao Mohekar Mahavidyalaya Kalamb, Dist. Dharashiv, Maharashtra.

²Maa Sharda Pharmacy College, Ayodhya, Chikhari, Harringtonganj, Ayodhya 224208,

³Dr Kalam College of Pharmacy, Avanam, Thanjavur, Tamil Nadu, India. PIN: 614623

⁴Guru Kashi University, Talwandi Sabo, Bathinda, Punjab State:151302

⁵Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan-313001, India

*Corresponding Author E-mail: mukesh_meena27@mlsu.ac.in

Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by cholinergic deficit, amyloid-beta ($A\beta$) accumulation, tau hyperphosphorylation, chronic neuroinflammation, oxidative damage, and disrupted monoaminergic and neurotrophic signalling. Current pharmacotherapy, largely limited to acetylcholinesterase (AChE) inhibitors and the NMDA-receptor antagonist memantine, provides symptomatic relief without modifying disease progression, and recent amyloid-directed monoclonal antibodies and BACE1 inhibitors have shown only marginal or inconsistent cognitive benefit relative to their cost and safety burden. *Bacopa monnieri* (L.) Wettst., known in Ayurvedic medicine as Brahmi or a *medhya rasayana*, has emerged as a multi-target botanical candidate that can simultaneously address several of these pathological axes. This review synthesises pharmacological, molecular, and clinical evidence on *B. monnieri* and its principal bioactive constituents bacosides, bacopasides, and bacopasaponins across six convergent mechanisms: (i) cholinergic modulation through AChE and butyrylcholinesterase (BuChE) inhibition; (ii) attenuation of amyloidogenic processing via BACE1 inhibition and enhanced microglial clearance of $A\beta$; (iii) reduction of tau aggregation and phosphorylation; (iv) antioxidant, anti-inflammatory, and anti-apoptotic actions; (v) modulation of serotonergic, dopaminergic, and GABAergic neurotransmission; and (vi) neurotrophic support of synaptic plasticity via brain-derived neurotrophic factor (BDNF) signalling. Preclinical studies in transgenic and chemically induced rodent models demonstrate consistent improvements in spatial memory alongside reductions in amyloid plaque burden and neuroinflammatory markers. Clinical trials in healthy elderly adults and in patients with mild cognitive impairment (MCI) or AD report modest but recurrent benefits in delayed verbal recall and attention, although trial heterogeneity, small sample sizes, and variable extract standardisation limit the strength of these conclusions. Preclinical and early-phase human safety data indicate a favourable tolerability profile, with gastrointestinal complaints being the most common adverse effect. We conclude that *B. monnieri* represents a mechanistically plausible, multi-target adjunct for AD and outline priority directions for extract standardisation, pharmacokinetic characterisation, and adequately powered randomised controlled trials required before clinical translation.

Keywords: *Bacopa monnieri*; Brahmi; Alzheimer's disease; bacosides; acetylcholinesterase; amyloid-beta; tau; neuroinflammation; BDNF; cognitive function

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1. Introduction

Alzheimer's disease is the most common cause of dementia worldwide and represents one of the fastest-growing contributors to global disease burden as populations age. Analyses of the Global Burden of Disease (GBD) 2021 dataset indicate that global AD cases rose from approximately 4.08 million in 1992 to 9.84 million in 2021, and are projected to reach 19.12 million by 2036 under current demographic and age-period-cohort trends¹ (Figure 2). Women consistently show higher age-standardised incidence and prevalence than men across all world regions, and disease burden is disproportionately concentrated in high- and middle-income regions undergoing rapid population ageing¹. This escalating burden, combined with the very limited durability of currently approved pharmacotherapies, underlies the sustained interest in adjunctive and disease-modifying strategies, including well-characterised botanical agents with multiple, simultaneously accessible mechanisms of action.

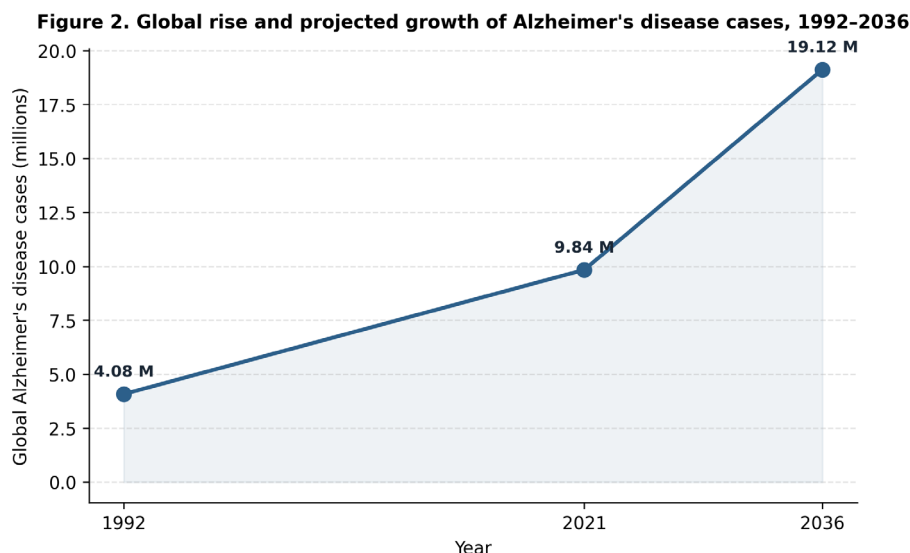


Figure 2. Global rise and projected growth of Alzheimer's disease cases, 1992-2036 (data from Xu et al., 2025).

The neuropathological hallmarks of AD extracellular A β plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau, synaptic loss, chronic microglial and astrocytic activation, oxidative damage, and cholinergic neurodegeneration originating in the basal forebrain interact across multiple, mutually reinforcing pathways to produce progressive cognitive decline³. The four AChE inhibitors currently approved for AD (donepezil,

rivastigmine, galantamine, and tacrine) and the NMDA-receptor antagonist memantine alleviate symptoms transiently but do not halt underlying neurodegeneration³. More recent disease-modifying candidates, monoclonal antibody immunotherapies directed against A β , and small-molecule BACE1 inhibitors such as atabecestat, lanabecestat, and verubecestat have demonstrated clear biomarker efficacy in lowering amyloid burden, yet several BACE1 inhibitor programmes were discontinued in Phase III owing to hepatotoxicity, worsening of cognitive measures, or an absence of meaningful clinical benefit despite effective target engagement³. These repeated late-stage clinical disappointments have reinforced the view that single-target strategies directed narrowly at amyloid are unlikely, on their own, to reverse a disease process that is fundamentally multifactorial, and have renewed interest in multi-target, network-based therapeutic strategies, including standardised botanical agents with pleiotropic mechanisms of action.

Bacopa monnieri (L.) Wettst. (family Plantaginaceae, historically classified under Scrophulariaceae) is a small creeping perennial herb of wetlands and marshy areas across South and Southeast Asia, used for over three millennia in Ayurvedic medicine as a *medhya rasayana* (cognition-enhancing rejuvenator), traditionally indicated for memory impairment, anxiety, epilepsy, and general nervous system tonification². Its principal bioactive constituents are dammarane-type triterpenoid saponins bearing jujubogenin or pseudojujubogenin aglycones, collectively termed bacosides, together with bacopasides, bacopasaponins, alkaloids (brahmine, nicotine-like alkaloids, herpestine), phytosterols (β -sitosterol, stigmasterol), and flavonoids such as luteolin and apigenin⁴. Unlike single-target synthetic drugs, these constituents act concurrently across cholinergic, amyloidogenic, tau-related, oxidative, inflammatory, monoaminergic, and neurotrophic pathways, positioning *B. monnieri* as a candidate multi-target therapeutic for AD. This review integrates *in silico*, *in vitro*, *in vivo*, and clinical evidence on *B. monnieri* in the context of AD, with particular attention to its molecular targets, and critically evaluates the current strength and limitations of the clinical evidence base, concluding with priority directions for future research.

The economic and caregiving burden associated with this rising case count is substantial: AD and related dementias require sustained, often institutional, long-term care, and affected individuals progressively lose independence in activities of daily living over a disease course that commonly spans eight to twelve years from symptom onset. Pharmacological management has historically been organised around two complementary strategies: symptomatic cholinergic and glutamatergic modulation, and, more recently, disease-modifying immunotherapy directed at removing aggregated A β from the brain. Anti-amyloid monoclonal antibodies approved in some jurisdictions over the past several years have demonstrated statistically significant slowing of cognitive decline on composite clinical scales, but the absolute magnitude of benefit has been judged clinically modest by many practising neurologists, and their use requires regular magnetic resonance imaging monitoring for amyloid-related imaging abnormalities, alongside considerable infusion-related costs and logistical burden³. This combination of marginal benefit, meaningful risk, and high cost has sustained clinical and research interest in orally administered, low-cost, well-tolerated adjuncts a profile that standardised *B. monnieri* extracts plausibly fit, provided their efficacy can be established with greater methodological rigour than has so far been achieved.

Historically, *B. monnieri* is documented in classical Ayurvedic texts including the Charaka Samhita and Sushruta Samhita, where it is described among the *medhya rasayana* class of herbs believed to nourish and rejuvenate cognitive and nervous function over sustained use, in contrast to fast-acting stimulant agents. This traditional framing a slow-acting, whole-plant tonic intended for cumulative benefit rather than an acute pharmacological effect is broadly consistent with the modern clinical trial literature reviewed in Section 4, in which cognitive benefits typically emerge only after several weeks of continuous dosing rather than acutely, and it has informed the choice of 8- to 52-week treatment durations in the majority of controlled trials conducted to date. The plant's continued and widespread use as an over-the-counter nutraceutical in many countries, without a strong signal of serious harm across decades of traditional and modern use, further supports its suitability as a candidate for rigorous clinical evaluation in AD and MCI populations, where treatment tolerability over long durations is itself a major practical consideration alongside efficacy.

2. Phytochemistry and Pharmacokinetic Considerations

Bacopa monnieri whole-plant extracts are typically standardised to bacoside content, commonly 20–55% bacosides A and B by dry weight in commercial nutraceutical extracts. The major triterpenoid saponins bacoside A3, bacopaside I, bacopaside II, bacopaside X, and bacopasaponins C, G, and N2 together with minor alkaloidal, sterol, and flavonoid constituents, are considered jointly responsible for the plant's neuroactive effects (Table 1 lists the principal constituent classes)⁴. Extraction solvent (aqueous versus ethanolic or methanolic), harvest season, and plant part used all measurably affect the relative proportions of these constituents, which is one source of the pharmacological and clinical heterogeneity discussed later in this review.

Bioavailability of the intact triterpenoid saponins is limited by poor aqueous solubility and extensive first-pass hepatic and gut-microbial metabolism, and no fully validated human pharmacokinetic profile currently exists for bacoside A3 or the individual bacopasides, which constrains rational dose–response modelling and cross-study comparison of clinical trial results⁴. Newer delivery approaches including phospholipid complexation, nanoparticle encapsulation, and self-nanoemulsifying drug delivery systems are being explored to improve systemic absorption and central nervous system exposure, but none has yet reached late-stage clinical evaluation⁴. Establishing a validated pharmacokinetic profile for the major bacosides, ideally correlated with cerebrospinal fluid or plasma biomarker changes, remains one of the most significant unmet methodological needs in this field.

Quality control of commercial *B. monnieri* extracts is further complicated by the existence of several distinct proprietary standardised formulations used across the pharmacological and clinical literature including CDRI-08 (also marketed as BacoMind®), Bacognize®, and Bacopa-loaded Bacumen® preparations each characterised to a different bacoside or bacopaside profile and each tested in a largely non-overlapping set of preclinical and clinical studies. This lack of a single reference standard means that pharmacological findings obtained with one proprietary extract cannot automatically be assumed to generalise to another, even when both are labelled as containing a nominally similar percentage of “total bacosides.” Analytical standardisation using high-performance liquid chromatography (HPLC)

fingerprinting of the major saponins, alongside mass-spectrometric confirmation of bacoside A3, bacoside I, and bacoside II content, has been proposed as a minimum quality benchmark for extracts entering future clinical trials, so that pharmacological and clinical results can be meaningfully compared and pooled across studies.

Table 1. Principal phytochemical constituent classes of *Bacopa monnieri* and their proposed neuropharmacological relevance

Constituent class	Representative compounds	Proposed relevance to AD pathology
Triterpenoid saponins (bacosides)	Bacoside A3, bacoside A	Cholinergic modulation; antioxidant activity; membrane fluidity effects on synaptic membranes
Bacopasides	Bacopaside I, II, X, XII	BACE1 interaction; amyloid clearance; tau-aggregation interference
Bacopasaponins	Bacopasaponin C, G, N2	Anti-apoptotic activity (caspase-3, tau-protein-kinase I binding)
Alkaloids	Brahmine, herpestine, nicotine-like alkaloids	Monoaminergic and cholinergic neurotransmission
Flavonoids	Luteolin, apigenin, quercetin	AChE/BuChE inhibition; free-radical scavenging
Phytosterols	β -sitosterol, stigmasterol, daucosterol	Cholinesterase active-site binding; membrane stabilisation

3. Pharmacological Evidence and Molecular Targets

Bacopa monnieri's proposed multi-target profile in AD is summarised schematically in Figure 1 and is discussed mechanism-by-mechanism in the subsections below, drawing on in silico docking, in vitro, and in vivo evidence.

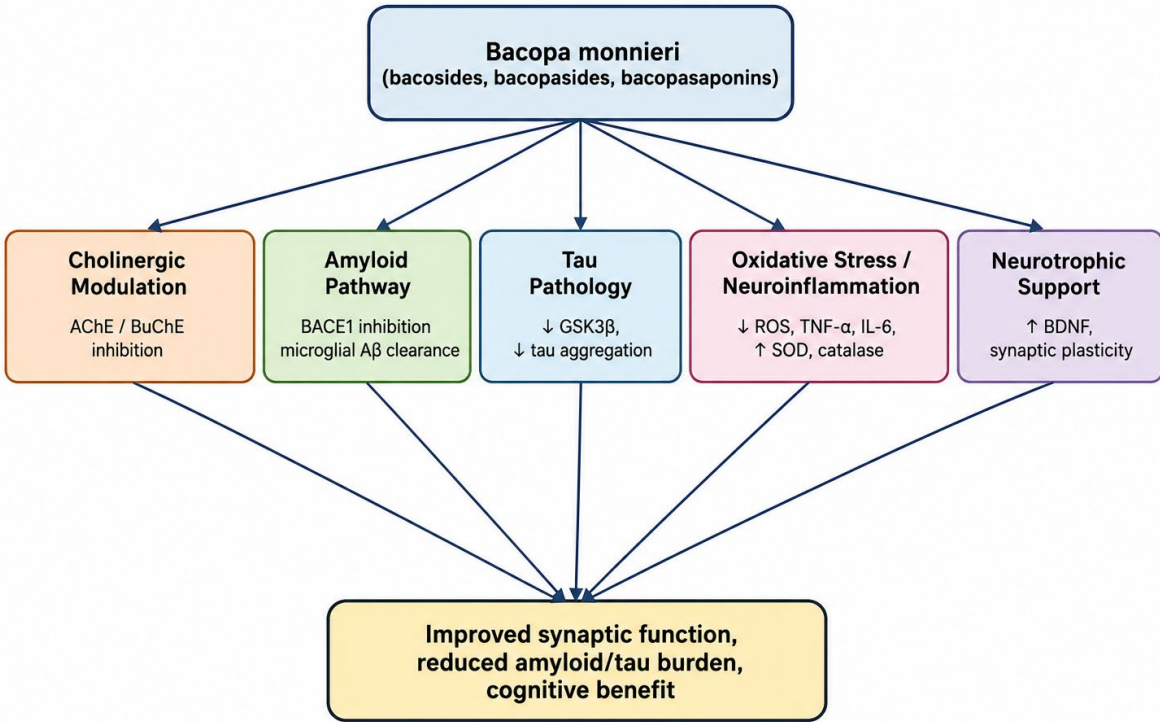


Figure 1. Proposed multi-target mechanisms of *Bacopa monnieri* in Alzheimer's disease, spanning cholinergic, amyloid, tau, oxidative/inflammatory, and neurotrophic pathways.

3.1 Cholinergic Modulation: AChE and BuChE Inhibition

The cholinergic hypothesis remains central to symptomatic AD pharmacotherapy, reflecting the marked loss of cholinergic neurons in the nucleus basalis of Meynert and the resulting deficit in cortical acetylcholine. In silico molecular docking and biochemical inhibition assays show that bacopaside X, apigenin, quercetin, and wogonin bind the catalytic and peripheral anionic sites of AChE with micromolar IC₅₀ values (approximately 12.7–15.5 μ M), several orders of magnitude weaker than donepezil (IC₅₀ $\approx$ 0.02 μ M) but consistent with a genuine, reproducible inhibitory interaction rather than non-specific activity³. Complementary docking studies against both AChE and BuChE identify bacoside X, bacoside A, 3- β -D-glucosylstigmasterol, and daucosterol as favourable ligands at the enzymes' active-site gorges, suggesting that *B. monnieri* constituents may act on both cholinesterase isoforms relevant to AD, since BuChE activity increases relative to AChE as the disease progresses and cortical AChE declines². Functionally, this cholinergic action is proposed to underlie part of the memory-enhancing effects observed in animal and human studies, although the inhibitory potency of individual bacoside constituents is substantially lower than that of clinically approved cholinesterase inhibitors, implying a supportive, adjunctive rather than a stand-alone mechanism of symptomatic benefit.

It is worth emphasising that the cholinergic contribution of *B. monnieri* should be interpreted as one component of a broader multi-target profile rather than as a rationale for its use as a monotherapy replacement for approved cholinesterase inhibitors. Combination regimens whether formal co-administration in a clinical trial, as tested in the phase 2b donepezil-comparator study discussed in Section 4.2, or informal concurrent use as commonly occurs in practice raise open pharmacodynamic questions about whether *B. monnieri*'s weak cholinesterase inhibition is additive to that of a full-dose synthetic inhibitor, and pharmacokinetic questions about whether shared hepatic metabolic pathways could alter systemic exposure to either agent. Neither question has yet been formally addressed in a dedicated drug-interaction study, representing a further, practically important gap in the current evidence base.

3.2 Amyloid Pathway: BACE1 Inhibition and A β Clearance

BACE1 (β -site amyloid precursor protein-cleaving enzyme 1) catalyses the rate-limiting step of amyloidogenic APP processing and has been a prominent drug target; however, as noted above, the BACE1 inhibitors atabecestat, lanabecestat, and verubecestat were discontinued in Phase III trials owing to hepatotoxicity or lack of cognitive benefit despite effective A β lowering, indicating that A β reduction alone may be insufficient to alter disease course³. Molecular docking analyses indicate that several *B. monnieri* phytoconstituents occupy the BACE1 active site, which is bordered by the catalytic aspartate dyad (Asp32/Asp228) and a flexible flap region (residues 67–77) that closes over bound ligands³, suggesting a plausible route by which *B. monnieri* may reduce A β generation upstream of plaque formation, in a manner that is complementary to, rather than duplicative of, discontinued synthetic BACE1 inhibitors.

In vivo, bacopaside I administered to APP/PS1 transgenic mice significantly ameliorated spatial learning deficits and reduced cerebral plaque load; network pharmacology analysis

mapping bacopaside I's targets onto protein–protein interaction networks implicated enhanced microglial phagocytic clearance of A β , rather than cholinesterase inhibition alone, as a key contributing mechanism⁹. In a chemically induced rat model of AD combining intracerebroventricular streptozotocin or comparable amyloidogenic insults, *B. monnieri* extract improved learning and memory performance on maze-based tasks and reduced markers of neuronal injury in the hippocampus, supporting cognitive benefit in a model that more closely mimics sporadic, late-onset AD than purely transgenic overexpression models¹¹. In primary cortical neuronal cultures, *B. monnieri* extract protected against A β (25–35)-induced but not glutamate-induced cytotoxicity, with protection attributed in part to suppression of neuronal AChE activity and reduction of oxidative stress rather than direct interference with glutamatergic excitotoxicity¹⁰, indicating that the extract's neuroprotection in this model is amyloid-pathway-specific rather than a generic anti-excitotoxic effect.

3.3 Tau Pathology

Hyperphosphorylation and aggregation of tau protein, driven substantially by glycogen synthase kinase-3 β (GSK-3 β) activity, is a second core pathological process in AD that runs partly independently of amyloid deposition. In vitro studies show that *B. monnieri* extract attenuates tau aggregation directly and reduces formaldehyde-induced tau phosphorylation in neuronal (Neuro2a) cells via decreased GSK-3 β phosphorylation, while also restoring normal nucleoporin (NUP358) distribution disrupted by formaldehyde stress, indicating a protective effect on nucleocytoplasmic transport machinery relevant to tauopathy³. In silico docking work further suggests that bacopaside II, bacopaside XII, and nicotine-like constituents interact with the hyperphosphorylation-prone R-domain of tau, potentially interfering with fibril formation, although this evidence remains preclinical and requires confirmation in tau-transgenic animal models such as P301S or rTg4510 mice before firm conclusions on in vivo tau-modifying efficacy can be drawn³.

3.4 Oxidative Stress, Neuroinflammation, and Apoptosis

Reactive oxygen species (ROS) generation, chronic microglial and astrocytic activation, and downstream apoptotic signalling amplify both A β and tau pathology in AD and are now regarded as a self-reinforcing pathological axis rather than a purely downstream consequence of amyloid deposition. In the colchicine-induced rodent model of dementia, *B. monnieri* extract reduced lipid peroxidation and protein carbonylation, and attenuated colchicine-induced elevations in interleukin-6, tumour necrosis factor- α , ROS, and A β -42, consistent with combined antioxidant and anti-inflammatory activity³. A systematic review of twenty-two clinical trials and associated preclinical studies concluded that *B. monnieri* reduces nuclear factor- κ B phosphorylation and lowers levels of pro-inflammatory biomarkers and oxidative-stress markers across multiple experimental and clinical settings, while improving emotional function, attention, and memory retention¹². Complementing this, in silico protein–protein interaction analyses have linked selected bacopasaponins to more favourable predicted binding energies at caspase-3 and tau-protein-kinase I than the reference drug donepezil, implicating anti-apoptotic activity as an additional contributing mechanism to the extract's overall neuroprotective profile³. Preclinical dose-ranging work summarised in recent pharmacological reviews further reports that *B. monnieri* extracts administered at 30–1500 mg/kg in rodents produce dose-dependent reductions in malondialdehyde and nitric oxide, alongside increases

in superoxide dismutase and catalase activity, providing a biochemically coherent basis for the antioxidant component of its mechanism.

Mechanistically, this antioxidant and anti-inflammatory activity is thought to arise from at least three overlapping actions: direct free-radical scavenging by flavonoid and phenolic constituents; upregulation of endogenous antioxidant enzyme expression, including superoxide dismutase, catalase, and glutathione peroxidase; and suppression of microglial NF- κ B and NLRP3-inflammasome signalling, which in turn reduces downstream production of interleukin-1 β , interleukin-6, and tumour necrosis factor- α . Because chronic low-grade neuroinflammation is now understood to precede overt cognitive symptoms by years in the natural history of AD, an agent capable of dampening this inflammatory tone at an early, pre-symptomatic or MCI stage could in principle have disease-course-modifying potential distinct from, and potentially additive to, purely amyloid- or tau-targeted interventions though this remains a hypothesis to be tested rather than an established clinical finding.

3.5 Modulation of Serotonergic, Dopaminergic, and GABAergic Neurotransmission

Beyond cholinergic and amyloid/tau-directed effects, a substantial and long-standing body of pharmacological work has characterised *B. monnieri*'s influence on monoaminergic and inhibitory neurotransmitter systems. Preclinical studies indicate that *B. monnieri* extract can displace radiolabelled antagonists from 5-HT_{2A} and 5-HT_{1A} serotonin receptor subtypes in rat brain tissue, consistent with partial agonist or modulatory activity at these receptors, and has been shown to upregulate tryptophan hydroxylase-2 (TPH2) expression, the rate-limiting enzyme in serotonin synthesis⁵. Because serotonergic signalling fine-tunes synaptic plasticity that underlies memory formation, this monoaminergic action is considered a plausible complementary mechanism, distinct from but potentially synergistic with the cholinergic and neurotrophic pathways discussed elsewhere in this review⁵. In models of induced parkinsonism and dopaminergic stress, *B. monnieri* treatment has been shown to reverse reductions in dopamine, serotonin, and their metabolites and to normalise monoamine oxidase activity across multiple brain regions, suggesting a broader monoamine-stabilising action that may be relevant to the mood and behavioural symptoms that frequently accompany AD⁵. *B. monnieri* has additionally been reported to enhance GABAergic transmission, an action proposed to underlie its traditional anxiolytic use and which may contribute to reduced excitotoxic vulnerability of hippocampal neurons in the AD brain.

3.6 Neurotrophic Support and Synaptic Plasticity

Beyond its antioxidant, anti-amyloid, and monoaminergic actions, *B. monnieri* has been reported to modulate signalling pathways implicated in synaptogenesis and long-term potentiation, providing a rationale for combining *B. monnieri* supplementation with structured cognitive training interventions. A randomised controlled trial in healthy older adults measured serum brain-derived neurotrophic factor (BDNF) alongside cognitive and mood outcomes after combined *B. monnieri* supplementation and cognitive training, and preclinical dose-ranging studies report increases in BDNF expression of approximately 40–70% alongside reduced caspase-3 activity, reflecting growing interest in neurotrophic mechanisms as a further, complementary axis of action alongside the cholinergic, amyloid, tau, and monoaminergic effects discussed above⁵.

3.7 A Network Pharmacology Perspective on Multi-Target Action

A recurring theme across the mechanistic literature reviewed above is that no single *B. monnieri* constituent, and no single molecular target, is likely to account for the extract's overall neuroprotective and cognitive-enhancing profile. Network pharmacology analyses that map the predicted protein targets of bacosides, bacopasides, and bacopasaponins onto human protein–protein interaction databases consistently identify convergence on nodes central to synaptic signalling, apoptosis regulation, and neuroinflammatory cascades, rather than isolated action on a single canonical AD target such as AChE or BACE1 alone⁹³. This pattern is consistent with the traditional Ayurvedic characterisation of *B. monnieri* as a whole-plant *rasayana* rather than a single-molecule drug, and it offers a plausible pharmacological explanation for why extract-level clinical effects (Section 4) have sometimes proven more consistent than would be predicted from the comparatively modest potency of any individual constituent at any single enzyme or receptor target. At the same time, this same multi-target complexity is a methodological complication for drug development, since it is difficult to attribute an observed clinical effect to any one mechanism, and it argues for continued combined use of reductionist (single-target enzyme or receptor assay) and systems-level (network pharmacology, transcriptomic, proteomic) approaches in future mechanistic work.

Table 2. Representative preclinical studies of *Bacopa monnieri* in models relevant to Alzheimer's disease

Model	Intervention	Key findings	Ref.
APP/PS1 transgenic mice	Bacopaside I	Ameliorated spatial learning deficits; reduced cerebral A β plaque load via enhanced microglial clearance	9
Primary cortical neuronal culture	<i>B. monnieri</i> extract	Protected against A β (25–35)-induced cytotoxicity; reduced AChE activity and oxidative stress	10
Chemically induced AD-like rat model	Standardised <i>B. monnieri</i> extract	Improved maze-learning performance; reduced hippocampal neuronal injury markers	11
Colchicine-induced dementia model (rat)	<i>B. monnieri</i> extract	Reduced lipid peroxidation, IL-6, TNF- α , ROS, and A β -42; suppressed BACE1 activity	3
Neuro2a cells (formaldehyde-stress model)	<i>B. monnieri</i> extract	Reduced GSK-3 β -mediated tau phosphorylation; restored NUP358 distribution	3
In silico docking (AChE/BuChE/BACE1/tau/caspase-3)	Bacoside X, bacopasides, bacopasaponins	Favourable binding at cholinesterase, BACE1, tau R-domain, and caspase-3 sites	2,3

4. Clinical Perspectives

4.1 Cognitive Effects in Healthy and Ageing Populations

In a randomised, double-blind, placebo-controlled trial, 54 community-dwelling adults aged 65 years and older received a standardised *B. monnieri* extract (300 mg/day) or placebo for 12 weeks following a 6-week placebo run-in. Relative to placebo, the *B. monnieri* group showed significantly enhanced delayed word recall on the Rey Auditory Verbal Learning Test and improved performance on the Stroop task, together with reductions in depression and anxiety scores; the supplement was well tolerated, with gastrointestinal upset as the principal adverse event⁸. These findings are broadly consistent with earlier trials in younger and middle-aged healthy adults showing improvements in verbal learning after 5 and 12 weeks of comparable dosing, and with subsequent trials in older participants demonstrating improved memory performance with an adequate sample size and follow-up duration^{8,12}, supporting reproducible, dose-consistent nootropic effects of standardised *B. monnieri* extracts across age groups, albeit predominantly in cognitively healthy rather than demented populations.

Methodologically, these healthy-population trials share several recurring features that are relevant to interpreting their results: treatment periods of 8–12 weeks, doses in the range of 300–450 mg/day of standardised extract, and a consistent pattern in which delayed free recall and working-memory measures improve before simple attention or reaction-time measures, suggesting that *B. monnieri*'s cognitive effects may act preferentially on consolidation-dependent memory processes rather than on general psychomotor speed. Several of these trials also incorporated placebo run-in periods specifically to reduce practice-effect confounding on repeated neuropsychological testing, strengthening confidence that the observed differences reflect a genuine pharmacological effect rather than differential learning of the test battery between groups.

4.2 Trials in Mild Cognitive Impairment and Alzheimer's Disease

Evidence specific to clinical AD populations is more limited. A 52-week, randomised, double-blind, parallel-group phase 2b trial directly compared 300 mg/day standardised *B. monnieri* (Brahmi) with 10 mg/day donepezil in 48 patients with AD or MCI; after one year, no statistically significant between-group difference was observed on the Alzheimer's Disease Assessment Scale-Cognitive subscale or the Postgraduate Institute Memory Scale, an outcome interpreted as encouraging non-inferiority evidence for *B. monnieri* rather than a demonstration of superiority⁷. A Cochrane-methodology systematic review of randomised controlled trials in dementia due to AD and MCI-AD identified a high risk of bias across the available trials, small sample sizes (typically 30–40 participants), wide confidence intervals, and considerable heterogeneity in dosing (125–500 mg twice daily), treatment duration, and outcome measures, concluding that current evidence is insufficient to establish definitive clinical efficacy and calling for larger, more rigorously designed trials⁶. An ongoing exploratory, double-blind, randomised, placebo-controlled protocol is specifically designed to assess *B. monnieri*'s effect on cognitive function and plasma metabolite alterations in patients with amnesic MCI and early AD, reflecting continued efforts to generate higher-quality clinical evidence in this population¹⁴.

Table 3. Summary of key clinical trials and systematic reviews of *Bacopa monnieri* relevant to cognitive function and Alzheimer's disease

Study design	Population (n)	Dose / duration	Key outcome	Ref.
RCT, double-blind, placebo-controlled	Healthy adults ≥ 65 y (n=54)	300 mg/day, 12 wk	↑ delayed verbal recall (RAVLT); ↑ Stroop performance; ↓ anxiety/depression	8
RCT, double-blind, parallel, phase 2b (vs. donepezil)	AD / MCI patients (n=48)	300 mg/day vs. donepezil 10 mg/day, 52 wk	No significant difference vs. donepezil on ADAS-Cog or PGI Memory Scale (non-inferiority signal)	7
Cochrane-methodology systematic review of RCTs	Dementia due to AD / MCI-AD (multiple trials)	125–500 mg twice daily (heterogeneous)	High risk of bias; insufficient evidence for definitive efficacy; larger trials needed	6
Systematic review (22 clinical trials)	Mixed healthy and clinical populations	Heterogeneous dosing	↓ NF-κB phosphorylation; ↓ inflammatory/oxidative markers; improved memory, attention, mood	12
Ongoing RCT protocol (registered)	Amnesic MCI and early AD	Exploratory dosing, planned duration	Protocol stage; designed to assess cognition and plasma metabolite changes	14

Taken together, the phase 2b donepezil-comparator trial and the Cochrane-methodology systematic review illustrate both the promise and the present limitation of the clinical evidence base in diagnosed AD and MCI populations. The absence of a statistically significant difference from donepezil is encouraging in the sense that it is at least compatible with comparable symptomatic efficacy, but the trial was not statistically powered as a formal non-inferiority study, and the systematic review's identification of high risk of bias across the available literature means that a true placebo-controlled efficacy signal in diagnosed AD has still not been established with confidence. Head-to-head and placebo-controlled trials with larger sample sizes, pre-registered outcome measures, and standardised extract dosing will be necessary before *B. monnieri* can be positioned as more than a promising but unproven adjunct in this population.

4.3 Safety, Tolerability, and Toxicology

Across preclinical and clinical studies, *B. monnieri* demonstrates a favourable safety profile and a high therapeutic index. Subchronic (90-day) oral toxicity and genotoxicity studies of a standardised extract conducted under Good Laboratory Practice and OECD guidelines found no toxicologically significant treatment-related changes in haematology, serum biochemistry, urinalysis, ophthalmic examination, body weight, or organ weight, and no evidence of genotoxic potential¹³. Human trials consistently report gastrointestinal complaints (increased stool frequency, nausea, abdominal cramping) as the most common adverse events, with no serious adverse drug reactions attributable to *B. monnieri* identified to date⁸. Caution is nonetheless warranted regarding possible interactions with thyroid medications and other cholinergically or hepatically active drugs, and safety in pregnancy and lactation has not been established⁴.

5. Challenges and Future Directions

Four limitations currently constrain the translation of *B. monnieri* from a promising multi-target botanical into an evidence-based adjunct AD therapy. First, extract standardisation is inconsistent across studies: differences in plant source, extraction solvent (aqueous versus ethanolic/methanolic), and bacoside quantification method reduce comparability and reproducibility of pharmacological and clinical findings⁴. Second, human pharmacokinetic data for individual bacosides and bacopasides remain largely absent, limiting rational dose selection and correlation of plasma or brain exposure with clinical response⁴. Third, existing randomised trials in AD and MCI populations are underpowered and methodologically heterogeneous, as formally identified in systematic review, precluding meta-analytic pooling of effect sizes with confidence⁶. Fourth, mechanistic studies to date rely heavily on in silico docking and rodent models; direct confirmation of BACE1 inhibition, tau-aggregation interference, and monoaminergic receptor modulation in human tissue or clinical biomarker studies remains limited.

Addressing these gaps will require internationally harmonised extract standardisation criteria, dedicated human pharmacokinetic and bioavailability studies (potentially using nanoparticle or phospholipid-complex delivery platforms), and adequately powered, biomarker-stratified randomised controlled trials such as the amnesic MCI/early-AD protocol currently underway using standardised cognitive endpoints and, where feasible, cerebrospinal fluid or imaging biomarkers of amyloid and tau burden¹⁴. Combination studies pairing *B. monnieri* with approved cholinesterase inhibitors, and studies stratifying participants by baseline amyloid/tau biomarker status, would help clarify whether its benefit is additive to, or independent of, existing standard-of-care pharmacotherapy. Given the reproducibility of its cognitive effects in healthy older adults, near-term clinical priority should arguably focus on well-defined MCI populations, where a multi-target, favourable-safety-profile agent may have the greatest opportunity to delay progression to overt dementia.

A practical translational roadmap emerging from the evidence reviewed here would prioritise, in sequence: (i) adoption of a single, HPLC/mass-spectrometry-verified reference extract for use across future pharmacological and clinical studies; (ii) a dedicated human pharmacokinetic study of the major bacosides and bacopasides, ideally using labelled tracer or sensitive mass-spectrometric methods capable of detecting low plasma concentrations; (iii) a large, multi-centre, placebo-controlled randomised trial in amnesic MCI, powered on a validated cognitive composite endpoint and incorporating amyloid or tau positron emission tomography or cerebrospinal fluid biomarkers as secondary outcomes; and (iv) mechanistic sub-studies nested within such a trial to directly test, in human participants rather than solely in vitro or in rodents, whether cholinergic, amyloid-clearance, tau-modifying, anti-inflammatory, or neurotrophic mechanisms best account for any observed clinical benefit. This sequence mirrors the standard translational pathway for other plant-derived neuroactive compounds that have progressed from traditional use to evidence-based clinical adjuncts, and would place *B. monnieri* on a comparable evidentiary footing to that already achieved by other widely studied nutraceutical cognitive agents.

5.1 Strengths and Limitations of the Present Evidence Base

The principal strength of the evidence reviewed here is its consistency across levels of analysis: in silico docking predictions, in vitro cell-culture findings, in vivo rodent behavioural and biochemical outcomes, and human cognitive trial results all point in the same qualitative direction, namely modest but reproducible benefit accompanied by a favourable safety margin. This vertical consistency across the translational pipeline is relatively unusual among botanical nootropic candidates and is one reason *B. monnieri* continues to attract sustained research interest more than two decades after the first modern randomised trials were published.

The principal limitation is horizontal: within each level of analysis, and particularly within the clinical trial literature, studies differ substantially in extract source, standardisation method, dose, treatment duration, comparator (placebo versus active comparator), and outcome measure, such that formal meta-analysis remains difficult and the true effect size in any specific population healthy ageing adults, amnesic MCI, or diagnosed AD cannot yet be stated with precision. Publication bias is also a plausible concern in a literature dominated by small, single-centre trials, several of which appear to have been conducted or funded by extract manufacturers; independent, investigator-initiated replication in diagnosed AD and MCI populations, of the kind now underway in the ongoing amnesic MCI/early-AD protocol, will be particularly valuable in establishing the credibility of this evidence base going forward¹⁴.

6. Conclusion

Bacopa monnieri and its principal bacoside, bacopaside, and bacopasaponin constituents act concurrently on cholinergic, amyloidogenic, tau-related, oxidative/inflammatory, monoaminergic, and neurotrophic pathways relevant to Alzheimer's disease pathogenesis, providing a mechanistically coherent rationale for its investigation as a multi-target therapeutic candidate. Preclinical evidence is consistent and supportive across multiple independent models, and early clinical trials in healthy older adults demonstrate reproducible, modest cognitive benefits with a favourable safety profile. However, clinical evidence in diagnosed MCI and AD populations remains preliminary, heterogeneous, and underpowered. Rigorous extract standardisation, human pharmacokinetic characterisation, and large, well-designed randomised controlled trials are required before *B. monnieri* can be recommended as an evidence-based adjunct in the clinical management of Alzheimer's disease.

Given the scale of the projected global rise in AD cases summarised in Figure 2, and the persistent gap between amyloid-lowering efficacy and meaningful cognitive benefit demonstrated by recently approved immunotherapies, low-cost, well-tolerated, multi-target adjuncts such as *B. monnieri* warrant continued, methodologically rigorous investigation. The next decade of research on this botanical should prioritise standardisation and pharmacokinetics over further exploratory pharmacology, so that the considerable existing mechanistic and early clinical promise summarised in this review can be either confirmed or refuted with the level of evidentiary certainty that patients, clinicians, and regulators require before any therapeutic recommendation can be made with confidence.

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