



"*Bacopa monnieri*: a comprehensive clinical evaluation and neuropharmacological study unveiling enhancements in adolescent spatial working memory, cognitive function, neuroprotection, and diverse therapeutic properties —a therapeutic exposition"

Bacopa monnieri: Neurocognitive Benefits and Therapeutic Potential

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Abstract : Clinical assessment and neuropharmacology of *Bacopa monnieri*: an extensive investigation on *Bacopa monnieri* reveals that it improves cognitive function, mitigates cognitive deficits, enhances spatial working memory in adolescents, and reveals neuroprotective mechanisms. It also has nootropic and antidepressant effects. *Bacopa monnieri* (Brahmi) has shown promise in cognitive enhancement and neuroprotection, particularly in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. This study focused on GABAergic neuronal density, examining calcium-binding proteins (CBPs) such as: calbindin (CB), parvalbumin (PV), and calretinin (CR). Rats receiving PCP exhibited cognitive deficits, a reduced discrimination ratio (DR), and decreased CB, PV, and CR in various brain regions. Brahmi administration alongside PCP partially restored cognitive deficits, with increased DR and elevated CB, PV, and CR in specific brain areas, suggesting a mechanism involving the augmentation of GABAergic neurons.

Background: *Bacopa monnieri* (Brahmi) is a traditional medicinal herb widely investigated for its effects on memory, learning, cognition, and neuronal protection. Increasing experimental evidence suggests that its neuropharmacological activity may involve modulation of inhibitory neurotransmission and preservation of neuronal populations vulnerable to cognitive dysfunction. The present investigation was designed to evaluate the cognitive and neuroprotective potential of *Bacopa monnieri*, with particular emphasis on GABAergic neuronal markers in an experimental model of schizophrenia-like cognitive impairment.

Methods: A sub-chronic phencyclidine (PCP)-induced rat model was employed to examine the effects of *Bacopa monnieri* administration on behavioural and neurochemical alterations associated with cognitive deficits. Cognitive performance was assessed using behavioural measures, including discrimination-related performance and spatial working memory. The discrimination ratio (DR) was used as an indicator of recognition-related cognitive performance. Following behavioural assessment, selected brain regions were examined for changes in calcium-binding proteins (CBPs) associated with distinct populations of GABAergic interneurons. Immunohistochemical evaluation focused on calbindin (CB), parvalbumin (PV), and calretinin (CR), which serve as important markers of neuronal subtypes involved in the regulation of cortical and hippocampal network activity.

Results: Animals exposed to PCP demonstrated marked impairments in cognitive performance, reflected by a reduction in the discrimination ratio and deterioration of memory-related behaviour. These behavioural abnormalities were accompanied by reductions in CB-, PV-, and CR-positive neuronal populations in several brain regions, indicating disruption of inhibitory neuronal circuitry. Treatment with *Bacopa monnieri* in PCP-exposed animals produced a partial recovery of cognitive performance, with improvement in the discrimination ratio. In parallel, increased expression or density of CB-, PV-, and CR-positive neurons was observed in specific brain areas compared with PCP-treated animals. These findings suggest that *Bacopa monnieri* may counteract PCP-associated neuronal alterations and support the functional integrity of GABAergic interneuron networks.

Conclusion: The findings indicate that *Bacopa monnieri* possesses promising cognitive-enhancing and neuroprotective properties in a PCP-induced model of cognitive dysfunction. Its beneficial effects may be associated, at least in part, with preservation or augmentation of specific GABAergic neuronal populations identified by CB, PV, and CR. The study provides experimental support for the potential neuropharmacological role of *Bacopa monnieri* in mitigating cognitive abnormalities and warrants further investigation into its mechanisms of action and therapeutic relevance.

Index Terms - Anticonvulsants; antidepressant effects; antipsychotic drugs; anti-tumour potential; anxiolytics; *Bacopa monnieri*; bacopaside II; neuroprotective; nootropic effects.

I. INTRODUCTION

Exploring neuroprotective effects of herbal plant extracts in Alzheimer's disease: promising alternative strategies:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, memory loss, and personality changes. Conventional pharmaceutical treatments often fail to modify the course of disease progression. Recently, attention has turned to alternative approaches, including medicinal plants and herbal remedies, as potential interventions for AD. [41]

Harnessing traditional medicinal plants for cognitive enhancement and disease modulation in Alzheimer's disease:

The neuroprotective effects of herbal plant extracts, emphasising their role as alternative strategies in addressing AD advancement. These extracts harbour essential metabolites that can influence various aspects of AD progression. Traditional plant extracts discussed in this study offer diverse beneficial properties, acting as antioxidants, anti-inflammatory agents, and enhancers of cognition. Also, additionally, they demonstrate activity on AD drug targets, such as the degradation of amyloid-beta ($A\beta$). While the exploration of these neuroprotective properties in the context of AD is relatively recent, the drug discovery potential of these plant extracts holds promise for future AD treatments. [41]

Development and evaluation of the neuroprotective potential algorithm (npa): systematic screening of ayurvedic medicinal plants for alzheimer's disease research:

A Neuroprotective Potential Algorithm (NPA) **Table 1.** was developed to systematically guide the selection and evaluation of medicinal plants for Alzheimer's disease (AD) research. Twenty-three standardised Ayurvedic medicinal plant extracts underwent screening for various bioassays targeting oxidative stress, carbonyl stress, protein glycation, amyloid-beta ($A\beta$) fibrillation, acetylcholinesterase (AChE) inhibition, and neuroinflammation. Initial evaluations included total polyphenol content, free radical scavenging capacity, ferric reducing antioxidant power, reactive carbonyl species scavenging capacity, anti-glycative effects, and anti- $A\beta$ fibrillation effects. Twelve extracts with a cumulative NPA score ≥ 40 were selected for further evaluation, including inhibitory effects on AChE activity, *in vitro* anti-inflammatory effects on murine BV-2 microglial cells, and *in vivo* neuroprotective effects on *Caenorhabditis elegans* post $A\beta 1-42$ induction of neurotoxicity and paralysis. **Table 1.** Four extracts, namely *Phyllanthus emblica* (amla; Indian gooseberry), *Mucuna pruriens* (velvet bean), *Punica granatum* (pomegranate), and *Curcuma longa* (turmeric; curcumin), demonstrated a cumulative NPA score ≥ 60 . These extracts also exhibited protective effects on H_2O_2 -induced cytotoxicity in cholinergic human neuronal SH-SY5Y cells and murine BV-2 microglial cells and reduced tau protein levels in SH-SY5Y neuronal cells. The NPA provides a strategy to guide the selection of promising medicinal plant candidates for future AD research using animal models. The Neuroprotective Potential Algorithm (NPA) serves as a comprehensive tool for the systematic evaluation of medicinal plant extracts in Alzheimer's disease research. Through rigorous screening, four extracts—*Phyllanthus emblica*, *Mucuna pruriens*, *Punica granatum*, and *Curcuma longa*—emerged as promising candidates, exhibiting significant neuroprotective properties. These findings emphasise the potential of these extracts in mitigating AD pathology, particularly through their antioxidant, anti-inflammatory, and neuroprotective effects. The NPA framework enhances the selection process for future studies, paving the way for the development of novel plant-based therapeutic strategies against Alzheimer's disease. [42]

Investigating *Bacopa monnieri* extract as a potential treatment for Parkinson's disease: a pilot study on efficacy and symptom control:

Clinical evidence regarding the efficacy of *Bacopa monnieri* (*B. monnieri*) in controlling symptoms of Parkinson's disease is limited. A pilot study was conducted, involving 20 volunteers with Parkinson's disease, to assess the effects of a *B. monnieri* extract on Parkinson's disease-related parameters. [43] *Bacopa monnieri*, a medicinal plant belonging to the *Scrophulariaceae* family, is characterised by its creeping perennial nature, featuring small oblong leaves and white to purple flowers. Widely employed in Ayurvedic medicine, this herb goes by various names such as: brahmi, water hyssop, thyme-leaved gratiola, and the herb of grace. The Ayurvedic text "**Caraka Samhita**" has documented its utilisation for addressing diverse mental conditions. [64] [65] **Figure 1. Table 1.**

Table 1. Alzheimer's disease, neuroprotective potential algorithm (NPA), clinical evidence of *bacopa monnieri* in parkinson's disease.

References	Key research area	Significant findings
[77] [14] [55] [38] [41] [42]	Alzheimer's Disease (AD)	AD is a progressive neurodegenerative disorder marked by cognitive decline, memory loss, and personality changes. Conventional pharmaceutical treatments often fail to modify the course of disease progression. Medicinal plants and herbal remedies are explored as potential interventions for AD. Herbal plant extracts show neuroprotective effects with essential metabolites influencing various aspects of AD progression. Traditional plant extracts act as antioxidants, anti-inflammatory agents, and enhancers of cognition. Activity on AD drug targets, such as the degradation of amyloid-beta (A β), is demonstrated. Drug discovery potential of these plant extracts holds promise for future AD treatments.
[77] [14] [55] [38] [41] [42]	Neuroprotective Potential Algorithm (NPA) for AD research	NPA developed to guide the selection and evaluation of medicinal plants for AD research. Twenty-three standardised Ayurvedic medicinal plant extracts screened for various bioassays targeting oxidative stress, carbonyl stress, protein glycation, A β fibrillation, acetylcholinesterase (AChE) inhibition, and neuroinflammation. Twelve extracts with a cumulative NPA score ≥ 40 selected for further evaluation. Selected extracts (<i>Phyllanthus emblica</i> , <i>Mucuna pruriens</i> , <i>Punica granatum</i> , <i>Curcuma longa</i>) with NPA score ≥ 60 exhibited protective effects on H ₂ O ₂ -induced cytotoxicity, reduced tau protein levels, and demonstrated <i>in vivo</i> neuroprotective effects on <i>Caenorhabditis elegans</i> .
[77] [14] [55] [38] [41] [42] [43]	Clinical Evidence of <i>Bacopa monnieri</i> in Parkinson's Disease	Limited clinical evidence regarding the efficacy of <i>Bacopa monnieri</i> (<i>B. monnieri</i>) in controlling Parkinson's disease symptoms. A pilot study involving 20 volunteers [43] with Parkinson's disease assessed the effects of a <i>B. monnieri</i> extract on disease-related parameters.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [64] [65] [33] [35] [36]	<i>Bacopa monnieri</i> (<i>B. monnieri</i>)	<i>B. monnieri</i> , belonging to the <i>Scrophulariaceae</i> family, is a creeping perennial herb with small oblong leaves and white to purple flowers. Widely employed in Ayurvedic medicine, known by various names such as: brahmi, water hyssop, thyme-leaved gratiola, and herb of grace. Documented utilisation in Ayurvedic texts for addressing diverse mental conditions.

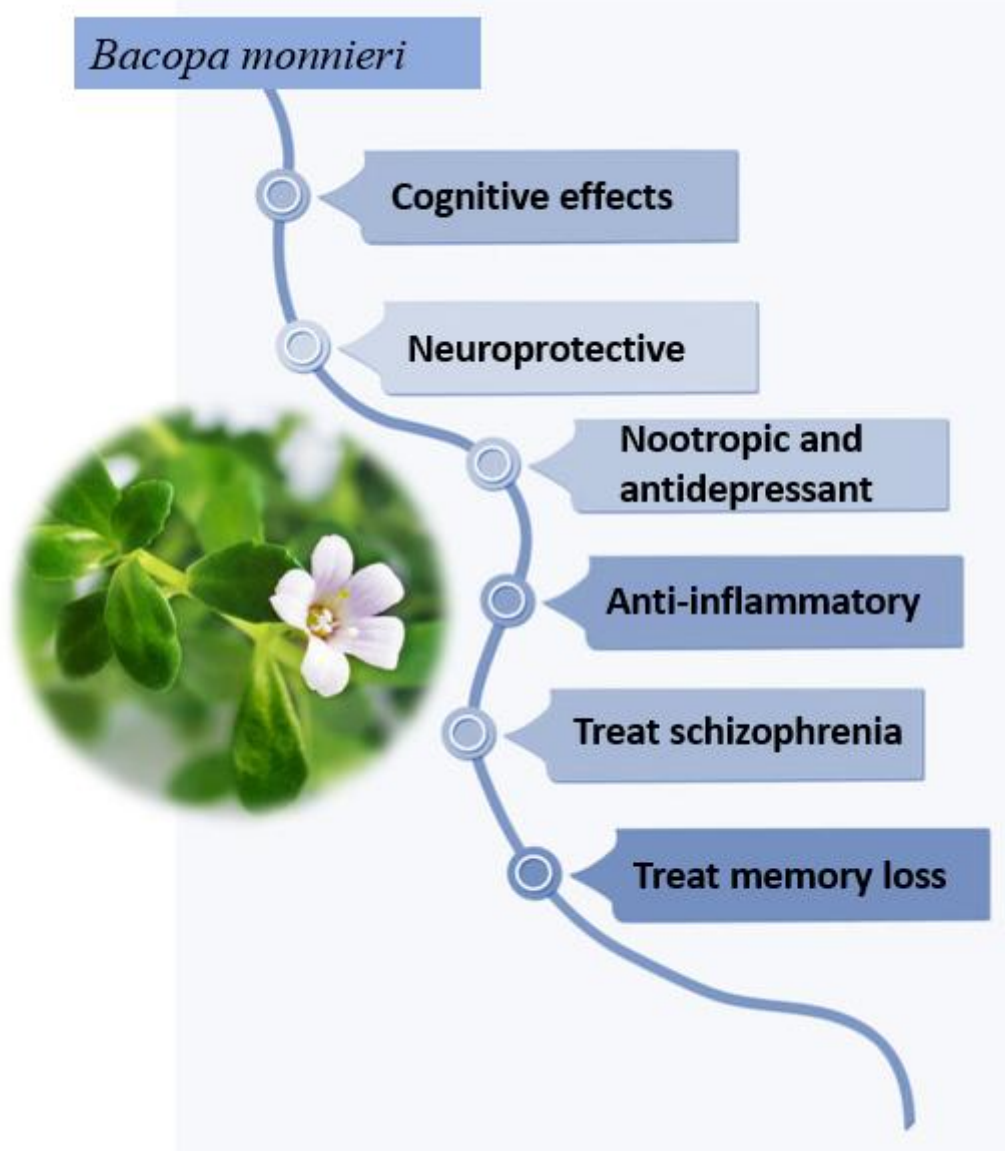


Figure 1. Essential elements of using *Bacopa monnieri* as medicine.

Behavioural and Neuromolecular Basis of *Bacopa monnieri* as a Cognitive Enhancer

Bacopa monnieri (BM), a medicinal herb widely recognised in Ayurvedic medicine, has attracted considerable scientific interest because of its potential effects on cognitive function and neuronal health. Although traditionally employed for a broad range of health conditions, BM has particularly been associated with enhancement of memory, learning, and overall mental performance [98]. Experimental investigations using animal models and *in vitro* systems have reported several biological activities that may contribute to these effects. In addition, randomised, double-blind, placebo-controlled clinical studies have provided evidence supporting the potential cognitive benefits of BM supplementation in humans [98].

The cognitive and neuroprotective actions of BM are thought to arise from multiple, interconnected molecular pathways rather than from a single pharmacological target. A prominent proposed mechanism involves protection against oxidative stress through modulation of cellular redox status and induction of endogenous antioxidant and protective enzymes. BM constituents have also been investigated for their ability to influence cholinergic neurotransmission, including inhibition of acetylcholinesterase activity and possible enhancement of choline acetyltransferase-mediated acetylcholine synthesis. Such effects could increase cholinergic signalling, which is closely associated with learning and memory processes [98].

Additional experimental evidence suggests that BM may influence pathological processes implicated in neurodegenerative disorders. These include modulation of β -amyloid accumulation, preservation of neuronal integrity, and improvement of cerebral perfusion. Further, BM has been reported to alter several neurotransmitter systems, including acetylcholine, serotonin (5-hydroxytryptamine; 5-HT), and dopamine, potentially contributing to its effects on cognition, behaviour, and neuronal function. These findings provide a mechanistic framework linking the behavioural effects observed in experimental models with the reported cognitive benefits in humans [98].

Beyond its nootropic potential, BM has been investigated in relation to neurological conditions such as dementia, Parkinsonian disorders, and epilepsy. However, much of the evidence for these applications remains preclinical or requires further clinical validation. From a safety perspective, available experimental and clinical findings generally indicate relatively low acute toxicity of BM and its preparations. Nevertheless, the available human literature is limited with respect to prolonged exposure, standardised preparations, dose-dependent adverse effects, and long-term safety. Consequently, further well-controlled clinical and toxicological

studies are necessary to establish the therapeutic potential, optimal dosing, pharmacological mechanisms, and long-term safety profile of BM [98].

- i. anti-convulsant
- ii. anti-depressant
- iii. analgesic
- iv. anti-inflammatory
- v. anti-microbial
- vi. anti-ulcerogenic/anti-*H. pylori*
- vii. anxiolytic
- viii. adaptogenic
- ix. anti-neoplastic
- x. hepatoprotective
- xi. Immunostimulatory

Phytochemical Constituents of *Bacopa monnieri*

The pharmacological and cognitive effects attributed to *Bacopa monnieri* (BM) are primarily associated with a group of dammarane-class triterpenoid saponins collectively referred to as bacosides. These compounds characteristically contain jujubogenin- or pseudo-jujubogenin-derived aglycone structures and are considered important contributors to the plant's reported nootropic activity. Several structurally related bacosides have been characterised, while subsequent phytochemical investigations have resulted in the identification of additional saponins designated bacosides I–XII. In addition to these saponins, BM contains a diverse range of secondary metabolites, including alkaloids such as brahmine, nicotine, and herpestine, as well as D-mannitol, apigenin, hersaponin, monnierasides, cucurbitacin derivatives, and plantainoside B [98].

Among the phytochemical constituents of BM, bacoside A has received particularly extensive investigation. Rather than representing a single chemical entity, bacoside A is considered a complex mixture comprising several related saponins, including bacoside A3, bacoside II, bacosaponin C, and a jujubogenin-related isomer of bacosaponin C. The quantitative composition of these constituents can differ substantially according to the plant material examined, the anatomical portion used for extraction, and the extraction conditions employed. Consequently, variations in phytochemical profiles should be considered when comparing biological and pharmacological findings obtained from different BM preparations [98].

For example, phytochemical analysis of one BM sample reported; identified bacoside I (5.37%), bacoside A3 (5.59%), bacoside II (6.90%), bacosaponin C isomer (7.08%), and bacosaponin C (4.18%). These findings illustrate the complex and variable saponin profile of BM. Comprehensive characterisation and standardisation of the plant's chemical constituents remain active areas of research, particularly because differences in constituent concentrations may influence the reproducibility and interpretation of pharmacological and clinical studies [98].

Plant-Based Nootropics and Cognitive Health: Pharmacological Mechanisms and Clinical Evidence

Plant-derived nootropics comprise a broad and chemically diverse class of natural substances that may support cognitive performance through multiple physiological pathways, particularly when cognitive functions are compromised. Several of these compounds appear to influence blood circulation by improving erythrocyte deformability and reducing platelet or erythrocyte aggregation, thereby enhancing blood rheology and potentially increasing cerebral perfusion. In addition, many plant-based nootropics exhibit antioxidant properties that may help protect neural tissues against oxidative and neurotoxic damage while supporting adequate oxygen availability in the brain [99].

Certain bioactive constituents have also been reported to stimulate the production of neuronal proteins, nucleic acids, and phospholipids, which are essential for the development, maintenance, and restoration of neuronal and neurohormonal membranes. Such pharmacologically active compounds occur across a wide range of plant species, including herbs, shrubs, trees, and climbing plants [99].

The plant species considered in this investigation were selected on the basis of accessible and verifiable experimental evidence, including animal investigations and clinical studies examining their potential effects on cognition. Original research, systematic reviews, meta-analyses, relevant preclinical studies, and clinical trials were considered when evaluating their nootropic properties. The principal plants discussed include: *Bacopa monnieri* (L.) Wettst., *Centella asiatica* (L.) Urban, *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim., *Ginkgo biloba* L., *Lepidium meyenii* Walp., *Panax ginseng* C.A. Meyer, *Paullinia cupana* Kunth, *Rhodiola rosea* L., *Schisandra chinensis* (Turcz.) Baill., and *Withania somnifera* (L.) Dunal [99].

For each representative species, information is presented regarding its botanical characteristics, geographical distribution, traditional and historical applications, major bioactive constituents, and proposed mechanisms underlying its cognitive effects. Available evidence concerning efficacy is also reviewed, along with reported therapeutic applications, experimental doses, administration regimens, adverse effects, and contraindications [99].

The cognitive benefits of many botanical nootropics may not become apparent immediately, as some preparations require consistent administration over an extended period before measurable effects are observed. Nevertheless, these substances are generally considered to have relatively good tolerability when used appropriately. Their pharmacological and psychoactive effects are typically attributed not to a single constituent but to interactions among multiple phytochemicals, which may act synergistically [99].

On the whole, experimental and clinical findings indicate that standardised extracts derived from selected medicinal plants may have considerable potential as complementary therapeutic agents for cognitive impairment and related disorders. However, the magnitude and consistency of these effects vary among plant species, preparations, doses, and study populations, highlighting the need for further well-controlled clinical investigations [99].

Nootropics, commonly referred to as cognitive enhancers or “smart drugs,” represent a broad and pharmacologically diverse category of substances that may influence cognitive functions such as memory, learning, attention, and reasoning. Their use is particularly relevant in conditions associated with diminished or impaired cognitive performance. This investigation presents an updated synthesis of the available evidence concerning the significance, potential effectiveness, and therapeutic applications of nootropic agents [100].

According to their pharmacological characteristics and primary effects on the central nervous system, nootropics can be broadly organised into four major categories: classical nootropic agents, compounds that enhance cerebral metabolism, cholinergic substances, and medicinal plants or plant-derived extracts with cognitive-enhancing properties. Each category encompasses several representative compounds or preparations whose therapeutic applications, clinical indications, experimental uses, dosage considerations, adverse effects, and contraindications are examined. [100]

For botanical nootropics, additional information is provided regarding the relevant medicinal plants, including their geographical distribution, historical and traditional uses, and the principal bioactive constituents present in the therapeutically important plant parts. Particular attention is given to the evidence supporting their effects on cognitive function and their potential role in the management of cognitive disorders [100].

Finally, the investigation summarises practical considerations concerning the use of nootropic substances in both individuals with cognitive impairments and healthy populations. These considerations emphasise the importance of appropriate selection, dosage, safety assessment, and evidence-based use of cognitive-enhancing agents [100].

Justification of the study:

The justification for the study on *Bacopa monnieri* (Brahmi) is grounded in its rich history in traditional Ayurvedic medicine, where it has been revered for its diverse therapeutic properties. The herb has demonstrated cognitive enhancement, neuroprotective effects, and anti-inflammatory benefits across various experimental models and clinical studies.

The cognitive-enhancing properties of *Bacopa monnieri* are highlighted in studies focusing on memory deficits, spatial working memory, and synaptic plasticity. Its positive impact on neuroregeneration, hippocampal neurogenesis, and protection of cholinergic neurons suggests potential applications in addressing cognitive dysfunction in conditions such as: dementia, schizophrenia, and neurotoxicity induced by substances like trimethyltin.

The herb's interaction with GABAergic neurons, calcium-binding proteins, and glutamate-related pathways provides insights into its complex mechanisms and underlying cognitive benefits, particularly in the context of a sub-chronic phencyclidine (PCP) rat model of schizophrenia. The partial restoration of cognitive deficits and neuroprotection observed in these studies reinforces the potential of Brahmi as a therapeutic agent for cognitive impairment.

Additionally, the investigation into the herb's impact on cytochrome P450 enzymes is motivated by the need to understand potential herb-drug interactions. The inhibitory effects of *Bacopa monnieri* on specific CYP isoforms, especially CYP1A2, CYP3A4, CYP2C9, and CYP2C19, raise concerns about altered drug metabolism and potential adverse reactions. This emphasises the importance of studying its impact on intestinal CYPs, given the higher concentration of orally ingested Brahmi in the gastrointestinal tract.

The diverse pharmacological effects of *Bacopa monnieri*, ranging from cognitive benefits to anti-tumour potential in colon cancer cells, make it a subject of considerable interest for researchers exploring novel therapeutics. The rationale for continued research lies in unraveling the molecular and cellular mechanisms of *Bacopa monnieri*, validating its traditional uses, and assessing its safety profile for potential integration into mainstream healthcare.

In summary, the rationale for studying *Bacopa monnieri* encompasses its traditional use, cognitive benefits, neuroprotective effects, anti-inflammatory properties, and potential herb-drug interactions. Thus, this study aims and focused to contribute to a comprehensive understanding of Brahmi's pharmacological actions and its therapeutic potential in various health conditions.

Medicinal importance of plant: Figure 2.

Bacopa monnieri, a plant belonging to the *Plantaginaceae* family, has been traditionally used for its neural tonic and memory-enhancing properties, as well as for alleviating acute pain and inflammation. [5] Medicinal formulations containing *Bacopa monnieri* extract have recently emerged, reflecting its longstanding use in Ayurvedic medicine for cognitive enhancement. Key active compounds in *Bacopa monnieri* include various saponins such as bacoside A and B, along with alkaloids and sterols. Pharmacological investigations of *Bacopa monnieri* extract align with its traditional medicinal uses, showing promising effects on memory, learning, and concentration in both adults and children, as well as potential benefits for anxiety and depression with prolonged use. While initial clinical studies suggest favourable outcomes and good tolerability, further research is warranted to validate these medical indications; that provides insights into the mechanisms of action and dietary supplements containing *Bacopa monnieri*, consolidating the current understanding of its medicinal applications. [40]

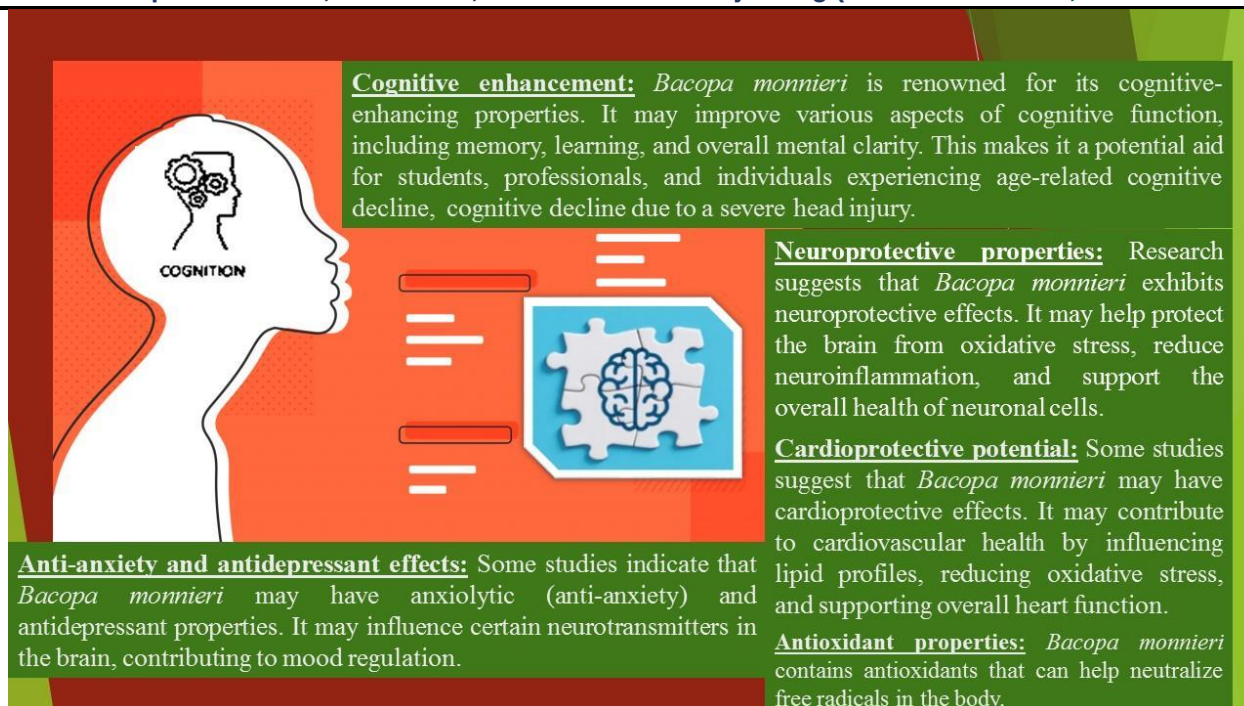


Figure 2. Medicinal properties that *Bacopa Monnieri* exhibits.

Evaluating *Bacopa monnieri*: cognitive enhancements, stress response, and potential therapeutic benefits for neurodegenerative disorders

In Ayurvedic medicine, *Bacopa* is categorised as a "medhya rasayana," denoting a group of herbs thought to enhance mental well-being, memory, and intellect while fostering rejuvenation and longevity. *Bacopa monnieri*'s role as a cognitive enhancer was showcased in a limited-scale randomised control trial from 2014 involving 17 participants. The study revealed statistically significant enhancements in cognitive performance, including mental arithmetic, Stroop test, letter search, and visual tracking. Additionally, mood improvement and a reduced cortisol response to stress were observed after a single dose of *Bacopa*, with the 640 mg dose showing a more pronounced effect. [66] *Bacopa monnieri* is extensively available and utilised in the global market, enjoying widespread marketing and use. Its popularity stems from its role as a neuropharmacological agent. [70] Products containing *B. monnieri* are categorised as herbal or natural products, and in many countries, the regulatory standards for marketing natural products are less rigorous compared to conventional drugs due to the perception of natural products as low-risk items. [72] An analysis that pooled data from nine randomised controlled trials involving 437 participants revealed enhancements in attention and cognitive speed, accompanied by a reduction in response time. [67] In a randomised, double-blind study involving 81 adults aged 55 years and older, *Bacopa* demonstrated significant improvement in memory acquisition and retention over a 12-week period. Additionally, in animal tissue models, *Bacopa* was found to enhance adaptive responses to stressors, normalising levels of monoamines and corticosterone in experimental stress models. [69] In a randomised, double-blind, placebo-controlled trial, 54 adult participants were administered either a 300 mg standardised extract of *Bacopa* or a placebo. Assessments were conducted by evaluating attention, memory, and psychological state tasks at the beginning and after a 12-week trial. The group receiving the *Bacopa* extract exhibited improved scores in delayed word recall memory and increased capability to disregard irrelevant information in comparison to the placebo group. [68] The participants were divided into groups receiving either a commercial *B. monnieri* extract (225 or 450 mg/day) or a placebo. The Parkinson's Disease Quality-of-Life (PDQL) questionnaire and motor activity assessments were conducted at various intervals. While no significant differences were observed in parkinsonian and systemic symptoms, emotional function, or social function between the groups, there were time-dependent improvements in emotional function with *B. monnieri* treatment at a daily dose of 450 mg. The study suggests that *B. monnieri* extract may improve emotional function in Parkinson's disease patients, but further clinical trials are needed to confirm these findings. [43] Alzheimer's disease is a neurodegenerative disorder characterised by neuronal degeneration and apoptosis in the brain. Bacoside A and B, derived from *Bacopa monnieri*, play a crucial role in cognitive improvement. These compounds contribute to the repair of damaged neurons by enhancing kinase activity, restoring synaptic function, and improving nerve transmission. A study investigated the impact of bacoside-A3 on β -amyloid-induced reduction in U87MG cell viability, oxidative radical generation, and nuclear factor- κ B (NF- κ B) activation. U87MG cells were exposed to β -amyloid with or without prior bacoside-A3 pretreatment, simulating Alzheimer's disease characteristics *in vitro*. [77]

***Bacopa monnieri* in neuroprotection: mechanisms, efficacy, and therapeutic potential in neurodegenerative disorders**

The Sulforhodamine B (SRB) assay assessed cell viability, while an ELISA kit analysed prostaglandin E2 (PGE2) secretion. Bacoside-A3 pretreatment effectively prevented the β -amyloid-induced decline in U87MG cell proliferation. Moreover, it suppressed reactive oxygen species (ROS) generation in a concentration-dependent manner and inhibited the dose-dependent induction of inducible nitric oxide synthase (iNOS) in response to β -amyloid stimulation. Bacoside-A3 pretreatment also mitigated β -amyloid-induced PGE2 secretion and cyclooxygenase-2 (COX-2) overexpression in U87MG cells in a dose-dependent manner. Additionally, bacoside-A3 prevented the dose-dependent nuclear translocation of NF- κ B in U87MG cells. In conclusion, bacoside-A3 exhibited protective effects against β -amyloid-induced cytotoxicity, oxidative stress, and inflammatory responses in U87MG cells. This suggests that bacoside-A3 holds therapeutic potential for Alzheimer's disease, warranting further *in vivo* investigations. [77] The customary dosage range for *Bacopa monnieri* in traditional medicine and contemporary clinical trials includes the use of the crude herb (5 to 10 grams per day, administered in 2 or 3 divided doses), 1:5 tincture (10 to 20 mL per day, taken in 2 or 3 divided doses), and extract (300 to 450 mg per day of extracts typically standardised to 24% to 55% bacosides for adults). In children aged 6 to 12 years, *Bacopa* can be used for up to 6 months at a daily dose of 225 mg. It's noteworthy that a study observed a potential decrease in fertility in animals with *Bacopa* extract, where sperm count, motility, and viability were reduced when a dose of 250

mg/kg/day was administered for 28 and 56 days. *Bacopa* is mildly sedative, contributing to its anxiolytic effects. [63] Nootropics, substances known for their cognitive enhancement properties, have been derived largely from plants. A systematic study aimed to present up-to-date information on the established and unproven effects of plant-derived nootropics (PDNs) on human cognition in both healthy and diseased conditions; Ginkgo biloba's impact on perceptual and motor functions, *Bacopa monnieri*'s positive effects on language, learning, and memory, *Withania somnifera* (Ashwagandha) influencing anxiety and social-related cognitions, and caffeine enhancing attention and executive functions. While these studies highlight the cognitive benefits of PDNs, inconsistencies exist, emphasising the need for further research in this area. [44] The prevalence of cognitive enhancer (CE) **Table 2.** use among Medical University students in Poland and identify the substances most commonly used. A total of 479 students from Medical (88%) and Dentistry (12%) Faculties participated in the anonymous online questionnaire, with a majority being women (63%). Results indicated that 53% of respondents used CEs, with caffeine, ginseng, nicotine, theanine, ginkgo, and lecithin being the most frequently used. Some students also used prescription-only CEs. The primary reasons for CE use were to enhance arousal and improve concentration, cited by 81% and 73% of participants, respectively. However, more than 65% of students reported experiencing undesired effects, with tachycardia and sleep disturbances being the most common. The findings raise concerns about young individuals' knowledge regarding CEs, emphasising the need for educational initiatives in universities. [45] A study aims to offer clinical guidance on enhancing cognitive performance in individuals without objective cognitive impairment, particularly those with subjective cognitive decline (SCD). The focus is on cognitive, mental, or physical training (CMPT), non-invasive brain stimulations (NIBS), drugs, or nutrients. The systematic view of CMPT studies, using the GRADE method, reveals that CMPT has clinically relevant effects on cognitive and non-cognitive outcomes. The evidence quality varies across different outcomes, with high quality for metamemory, moderate for executive functions, attention, global cognition, and daily life generalisation, and low for objective memory, subjective memory, motivation, mood, and quality of life. Specific interventions, such as repeated practice-based CMPT (e.g., video games or mindfulness), show significant improvements in attention and executive functions, while strategic learning-based CMPT enhances objective memory. Encouraging evidence is found for the potential impact of NIBS on memory performance and reducing self-perceived memory decline in SCD. However, the heterogeneity of stimulation protocols hinders clear recommendations. There is no conclusive argument to recommend cognitive enhancement drugs or herbal extracts in those without cognitive impairment. Overall, the study supports CMPT for cognitive improvement, suggests promising results for NIBS, but does not endorse the use of drugs or nutrients for cognitive enhancement. [46]

Table 2. *Bacopa monnieri* therapeutics and medicinal utilisation with side effects observed.

References	Key research area	Major significant findings
[5] [77] [63] [40] [66] [70] [44] [69] [68]	<i>Bacopa monnieri</i> as a cognitive enhancer	Categorised as a "medhya rasayana" in Ayurvedic medicine, indicating enhancement of mental well-being, memory, and intellect. Limited-scale randomised control trial (2014) with 17 participants showed statistically significant enhancements in cognitive performance, mood improvement, and reduced cortisol response to stress after a single dose. Extensive global availability and utilisation of <i>Bacopa monnieri</i> in herbal or natural products with perceived lower regulatory standards. Pooled data from nine randomised controlled trials (437 participants) demonstrated enhancements in attention and cognitive speed with <i>Bacopa monnieri</i> . Randomised, double-blind study with 81 adults aged 55 and older showed significant improvement in memory acquisition and retention over a 12-week period. Animal tissue models demonstrated <i>Bacopa</i> 's ability to enhance adaptive responses to stressors.
[77] [14] [55] [38] [41] [42] [43]	<i>Bacopa monnieri</i> in Parkinson's disease	Pilot study involving 20 volunteers with Parkinson's disease suggested potential effects of a <i>Bacopa monnieri</i> extract on disease-related parameters. Study with 54 adult participants receiving a <i>Bacopa monnieri</i> extract (225 or 450 mg/day) showed time-dependent improvements in emotional function in Parkinson's disease. Emphasises the need for further clinical trials to confirm the effects of <i>Bacopa monnieri</i> extract on Parkinson's disease.
[77] [14] [55] [38] [41] [42] [9]	Bacoside-A3 and Alzheimer's disease	Bacoside A and B derived from <i>Bacopa monnieri</i> play a crucial role in cognitive improvement. Study investigated the impact of bacoside-A3 on β -amyloid-induced reduction in U87MG cell viability, oxidative radical generation, and NF- κ B activation. Bacoside-A3 exhibited protective effects against β -amyloid-induced cytotoxicity, oxidative stress, and inflammatory responses in U87MG cells, suggesting therapeutic potential for Alzheimer's disease.
[5] [77] [63] [40] [66] [70] [44]	Dosage and side effects of <i>Bacopa monnieri</i>	Customary dosage range in traditional medicine and clinical trials for <i>Bacopa monnieri</i> includes crude herb (5 to 10 grams per day), 1:5 tincture (10 to 20 mL per day), and extract (300 to 450 mg per day standardised to 24% to 55% bacosides for adults). Limited study observed a potential decrease in fertility in animals with <i>Bacopa</i> extract. <i>Bacopa</i> is mildly sedative, contributing to its anxiolytic effects.
[5] [77] [63] [40] [66] [70] [44]	Plant-derived nootropics and cognitive enhancement	Systematic study of plant-derived nootropics (PDNs) on human cognition in healthy and diseased conditions. Noteworthy findings include <i>Ginkgo biloba</i> 's impact on perceptual and motor functions, <i>Bacopa monnieri</i> 's positive effects on language, learning, and memory, <i>Withania somnifera</i> 's influence on anxiety and social-related cognitions, and caffeine's enhancement of attention and executive functions. Inconsistencies exist in the studies, emphasising the need for further research on PDNs.

[63] [39]	Cognitive enhancer use among medical university students	Study investigated the prevalence of cognitive enhancer (CE) use among medical university students in Poland. 53% of respondents used CEs, with caffeine, ginseng, nicotine, theanine, ginkgo, and lecithin being the most frequently used. Primary reasons for CE use were to enhance arousal and improve concentration. More than 65% of students reported experiencing undesired effects, raising concerns about knowledge regarding CEs.
[63] [39] [46]	Cognitive enhancement strategies for individuals with subjective cognitive decline	Systematic study on enhancing cognitive performance in individuals without objective cognitive impairment, particularly those with subjective cognitive decline (SCD). Cognitive, mental, or physical training (CMPT) showed clinically relevant effects on cognitive and non-cognitive outcomes. Encouraging evidence for the potential impact of non-invasive brain stimulations (NIBS) on memory performance in SCD. No conclusive argument to recommend cognitive enhancement drugs or herbal extracts in those without cognitive impairment.
[77] [14] [55] [38] [41] [42]	Platelet-derived A β 1-42-containing extracellular vesicles (PEV-A β 1-42) in Parkinson's Disease Dementia	Plasma PEV-A β 1-42/PEV ratio identified as a potential diagnostic and prognostic biomarker for Parkinson's Disease Dementia (PDD) patients. PDD patients exhibited higher PEV-A β 1-42 concentrations than healthy controls. The PEV-A β 1-42/PEV ratio correlated with cognitive decline over 14 months, suggesting its utility in assessing disease progression.

Activated platelet-derived extracellular vesicles as biomarkers for cognitive decline in parkinson's disease dementia

Cortical amyloid deposition is commonly observed in Parkinson's disease dementia (PDD) patients, and A β 1-42, linked to rapid dementia progression, is primarily sourced from platelets. As peripheral extracellular vesicles (EVs) can partially reach the central nervous system, this study investigates the role of activated platelet-derived A β 1-42-containing EVs (PEV-A β 1-42) in the cognitive decline of Parkinson's disease (PD) patients.

189 participants (66 non-dementia PD, 73 PDD, and 50 healthy controls), utilised a nano-scale flow cytometry assay to detect PEVs and PEV-A β 1-42. PDD patients exhibited higher PEV-A β 1-42 concentrations than healthy controls. The PEV-A β 1-42/PEV ratio was significantly elevated in PDD patients compared to non-dementia PD and healthy controls, influencing the odds of dementia development. Moreover, the change in the PEV-A β 1-42/PEV ratio correlated with cognitive decline over 14 months.

The plasma PEV-A β 1-42/PEV ratio emerges as a potential diagnostic and prognostic biomarker for PDD patients. [47] **Table 2.**

Exploring the cognitive and cardiovascular benefits of *Bacopa monnieri*: insights into memory enhancement, synaptic plasticity, and vascular effects

Within the nonappearance of a remedy or compelling treatment for dementia, consideration has moved towards recognising hazard components for avoidance. Subjective Cognitive Decay (SCD) **Table 3.** depicts self-perceived compounding of cognition in spite of whole execution on neuropsychological tests. SCD has been related with an expanded dementia chance and more extreme memory decrease. Repetitive negative thinking (RNT) may be a transdiagnostic prepare that shows over a few mental wellbeing clutters related with expanded defenselessness to dementia. RNT has hence been proposed as a candidate marker of chance for dementia and, relatedly, may contribute to the appearance of SCD. To examine the relationship between SCD and RNT nearby other proposed mental risk or protective variables for dementia and cognitive decay. [48] In a cross-sectional online survey, 491 older adults (mean = 64.9 years, SD = 4.2; 63.1% female) completed measures of RNT, personality traits, purpose in life, worry, rumination, and meditation practice. SCD was evaluated ceaselessly by means of self-perceived cognitive work (Neuro-QoL) and categorically through support (yes/no) of memory complaints. Regression models, using a stepwise backwards elimination, assess associations between SCD, demographics, and all risk/protective factors. A total of 24.2% of participants reported memory complaints. Within the last expectation models, RNT was the as it were mental variable related with lower self-perceived cognitive function and with a better probability of memory complaints. Think about observationally authenticates the hypothetical relationship between SCD and RNT. Longitudinal studies are needed to establish whether RNT is a prodromal symptom or an independent risk factor, and whether RNT can be a promising construct for future research on SCD and dementia risk. [48] As the elderly population continues to grow, addressing age-associated cognitive decline becomes increasingly important. Cognitive training has demonstrated efficacy in enhancing cognitive functions in older adults, impacting memory, processing speed, executive function, and attention. Similarly, *Bacopa monnieri* has shown positive effects on specific cognitive domains sensitive to age-related decline, such as: processing speed and memory. *Bacopa monnieri* is believed to influence neuro-molecular mechanisms, particularly in promoting synaptogenesis, which is crucial for strengthening neural connections. [49]

A proposed hypothesis that combining cognitive training with *Bacopa monnieri* supplementation could synergistically enhance cognitive outcomes. While cognitive training improves brain connectivity, *Bacopa monnieri*'s neuro-molecular effects on synaptogenesis may further strengthen and optimise the synaptic changes facilitated by cognitive training. The synergistic effect of these interventions is proposed as a potential treatment to alleviate age-associated cognitive decline. [49] *Bacopa monnieri*, a traditional Ayurvedic memory-enhancing herb, has been investigated for its direct impact on synaptic plasticity, specifically long-term potentiation (LTP), **Table 3.** in acute hippocampal slices. In this study, adult male Wistar rats were orally administered either sterile water or an ethanolic extract of *Bacopa monnieri* for 60 days. The results revealed a significant increase in the magnitude of long-term potentiation in rats treated with *Bacopa monnieri* extract compared to the control group. Notably, there were no changes observed in basal synaptic transmission. This suggests that the mnemonic effects of *Bacopa monnieri* may be attributed to the enhancement of learning-associated synaptic mechanisms, leading to strengthened hippocampal synapses crucial for learning and memory formation. [50]

A study that aimed to investigate the impact of *Bacopa monnieri* (Brahmi), Ginkgo biloba, and donepezil on cerebral blood flow (CBF) in rats, comparing chronic and acute effects. Chronic oral administration of *Bacopa monnieri* (40 mg/kg) for 8 weeks resulted in a significant 25% increase in CBF compared to control rats. Ginkgo biloba (60 mg/kg) also increased CBF by 29%. Conversely, donepezil (1 mg/kg) did not show a clear effect on CBF. Importantly, chronic administration of these herbal preparations did not

affect blood pressure. In contrast, acute intravenous infusion of these herbs had dose-dependent hypotensive effects, reducing CBF. The findings suggest that the increased CBF observed with *Bacopa monnieri* may contribute to its reported cognitive benefits, warranting further exploration as a potential nootropic drug. **Table 3.** [52]

Bacopa monnieri (Brahmi), a herb traditionally used for cognitive benefits, was investigated for its cardiovascular effects. Intravenous administration of Brahmi extract (20-60 mg/kg) reduced systolic and diastolic pressures in anaesthetised rats without affecting heart rate. In isolated arteries, Brahmi exhibited vasodilator effects, with varying potency in different artery types. Two saponins from Brahmi, bacoside A3 and bacoside II, also demonstrated vasodilator actions. The vasodilation was attributed, in part, to the release of nitric oxide from the endothelium, and additional actions on vascular smooth muscle Ca^{2+} homeostasis. The study suggests that some components of Brahmi may have antihypertensive effects, and the observed vasodilation could contribute to its medicinal actions. [53] **Table 3.**

Table 3. *Bacopa monnieri* as a therapy for the treatment of related neurological disorders.

References	Study on key research area	Objective and key findings
[48] [46]	Relationship Between SCD and Repetitive Negative Thinking (RNT)	Investigated the relationship between Subjective Cognitive Decline (SCD) and Repetitive Negative Thinking (RNT) alongside other psychological risk/protective factors for dementia and cognitive decline. Cross-sectional online survey with 491 older adults. RNT was the only psychological variable associated with lower self-perceived cognitive function and a higher likelihood of memory complaints in the final prediction models. Suggests a theoretical relationship between SCD and RNT, emphasising the need for longitudinal studies to establish RNT as a prodromal symptom or an independent risk factor.
[5] [77] [63] [40] [66] [70] [44]	Cognitive Training and <i>Bacopa monnieri</i> Synergy for Age-Associated Cognitive Decline	Proposed a hypothesis that combining cognitive training with <i>Bacopa monnieri</i> supplementation could synergistically enhance cognitive outcomes in addressing age-associated cognitive decline. Cognitive training improves brain connectivity, and <i>Bacopa monnieri</i> 's neuro-molecular effects on synaptogenesis may strengthen and optimise synaptic changes facilitated by cognitive training. Synergistic effect proposed as a potential treatment for age-associated cognitive decline.
[5] [77] [63] [40] [66] [70] [44]	<i>Bacopa monnieri</i> and Long-Term Potentiation (LTP)	Investigated <i>Bacopa monnieri</i> 's impact on synaptic plasticity, specifically long-term potentiation (LTP), in acute hippocampal slices of adult male Wistar rats. Oral administration of <i>Bacopa monnieri</i> extract for 60 days significantly increased the magnitude of LTP compared to the control group. Mnemonic effects of <i>Bacopa monnieri</i> attributed to the enhancement of learning-associated synaptic mechanisms, leading to strengthened hippocampal synapses crucial for learning and memory formation.
[5] [77] [63] [40] [66] [70] [44] [52]	Impact of <i>Bacopa monnieri</i> , Ginkgo biloba, and Donepezil on Cerebral Blood Flow (CBF)	Investigated the impact of chronic and acute administration of <i>Bacopa monnieri</i> , Ginkgo biloba, and donepezil on cerebral blood flow (CBF) in rats. Chronic oral administration of <i>Bacopa monnieri</i> (40 mg/kg) for 8 weeks resulted in a significant 25% increase in CBF. Ginkgo biloba (60 mg/kg) also increased CBF by 29%. Donepezil (1 mg/kg) did not show a clear effect on CBF. Acute intravenous infusion had dose-dependent hypotensive effects, reducing CBF. Increased CBF with <i>Bacopa monnieri</i> may contribute to reported cognitive benefits.
[5] [77] [63] [40] [66] [70] [44] [53]	Cardiovascular effects of <i>Bacopa monnieri</i> (Brahmi)	Investigated the cardiovascular effects of intravenous administration of <i>Bacopa monnieri</i> extract (20-60 mg/kg) in anaesthetised rats. <i>Bacopa monnieri</i> reduced systolic and diastolic pressures without affecting heart rate. Isolated arteries showed vasodilator effects of <i>Bacopa monnieri</i> , attributed to the release of nitric oxide and actions on vascular smooth muscle Ca^{2+} homeostasis. Components of Brahmi may have antihypertensive effects, and vasodilation could contribute to its medicinal actions.

Examining the efficacy and mechanisms of *Bacopa monnieri*: insights into vasorelaxation, neuroprotection, cognitive enhancement, and safety in older adults

The vasorelaxant effects and mechanisms of action of specific compounds found in *Bacopa monnieri* extract (BME) on rat isolated mesenteric arteries. Saponins (bacoside A and bacoside I) and flavonoids (luteolin and apigenin) were investigated for their vasorelaxation potential. Both saponins and flavonoids induced concentration-dependent vasorelaxation, with flavonoids exhibiting higher efficacy and potency compared to saponins. The relaxant effects were partially mediated through the endothelial nitric oxide synthase (eNOS) pathway, as inhibition of eNOS or endothelial removal reduced the effects. The compounds also demonstrated inhibitory effects on calcium-induced and phenylephrine-induced contractions, suggesting actions on both endothelial and vascular smooth muscle cells. Overall, flavonoids were found to be more potent, but due to higher concentrations in BME, saponins were considered more effective vasodilators. [54]

The neuroprotective effects of *Bacopa monnieri* (Brahmi) extract against beta-amyloid and glutamate-induced neurotoxicity in primary cortical cultured neurons. The results indicated that Brahmi extract protected neurons specifically from beta-amyloid-induced cell death but not from glutamate-induced excitotoxicity. The neuroprotective mechanism involved the suppression of acetylcholinesterase activity, which contributed to cell survival. *Bacopa monnieri* extract also exhibited antioxidant properties by reducing intracellular oxidative stress and inhibiting lipid peroxidation. Overall, the findings suggested that Brahmi extract could be a potential alternative for treating neurodegenerative disorders associated with oxidative stress, such as Alzheimer's disease. [55]

In Ayurvedic medicine, *Bacopa* is primarily recommended for enhancing memory, alleviating insomnia, managing epilepsy, and acting as an anxiolytic. Numerous clinical investigations have shown positive outcomes, including enhanced verbal learning, improved delayed word recall, increased memory acquisition, and reduced anxiety, associated with the use of *Bacopa*.

Bacopa monnieri, commonly known as Brahmi, is a botanical frequently utilised in Ayurvedic medicine. Its primary applications in Ayurvedic practice include enhancing memory, addressing insomnia, managing epilepsy, and serving as an anxiolytic. Numerous clinical studies have highlighted the positive effects of *Bacopa*, showcasing improvements in verbal learning, delayed word recall, memory acquisition, and anxiety reduction. Regarded as a calming cognitive enhancer, the herb's pharmacological actions are largely attributed to triterpenoid saponins. *Bacopa* generally boasts a high therapeutic index and is well-tolerated, with common side effects centered around the gastrointestinal system, such as: increased stool frequency, nausea, and abdominal cramps. [63]

The safety and effectiveness of herbal and nutritional medicines in enhancing cognitive function among older adults, both with and without subjective cognitive impairment (SCI). SCI is recognised as a significant factor elevating the risk of dementia and is often seen as the preclinical, asymptomatic phase of cognitive decline. Given the limited availability of pharmaceutical interventions for treating SCI and reducing dementia risk, coupled with the widespread use of herbal and nutritional medicines, the primary objective of this study was to assess the impact on cognitive function and safety of such interventions in comparison to control groups.

The secondary objectives encompass detailing study characteristics and evaluating the methodological quality of the included studies. Notably, the current body of evidence presents a low quality regarding the efficacy of cognitive function and safety associated with herbal and nutritional medicines for older adults with and without SCI. This limitation is attributed to a high risk of bias observed across various studies. Additionally, a critical need exists for refining the classification and comprehension of SCI, along with the identification of appropriate primary outcomes in trials. Addressing these challenges is crucial to establishing a more accurate understanding of the effectiveness of interventions for this population, emphasising the importance of further research in this domain. [1]

A study sought to evaluate the scientific evidence regarding the traditional belief that *Bacopa monnieri* enhances cognitive performance. Despite some indications that *Bacopa* may improve memory free recall, the available evidence for its enhancement in other cognitive abilities is limited, possibly due to inconsistencies in the measures employed by studies across these cognitive domains. Research on the nootropic effects of *Bacopa* is in its early stages, and there is a need for further investigation into the effects of *Bacopa* on various cognitive abilities. Additionally, future research should explore the nootropic effects of *Bacopa* at different dosages and with different extracts to provide a more comprehensive understanding of its cognitive-enhancing potential. [12]

Bacosides, the primary bioactive constituents extracted from *Bacopa monnieri*, a plant traditionally utilised in Indian medicine as a nootropic, have gained significant attention in recent years due to their diverse neurobiological effects. These compounds exhibit neuroprotective properties by mitigating damage to brain neurons caused by various detrimental factors such as: neurotoxins, oxidative stress, beta-amyloid deposition, and cigarette smoke, due cannabis as toxicants. Notably, bacosides have been found to lower inflammatory cytokine levels and impede the demyelination processes in neurons.

Further, bacosides demonstrate anticonvulsant effects and enhance cognitive functions, including memory and learning capabilities. Their impact on the dopaminergic and serotonergic systems in the striatum is particularly intriguing for potential applications in addressing morphine addiction. Theoretical foundations are provided to support the future utilisation of bacosides as a versatile therapeutic approach for complex neurological and psychiatric conditions. [2]

The study explores the impact of a 12-week chronic supplementation with a multi-ingredient herbal supplement, comprising: *Bacopa monnieri*, Cardamom, Gotu kola leaf, Green Tea & Seagreens, Holy Basil, Reishi full spectrum, Rosemary, Turmeric whole powder, Turmeric Wholistic™ extract, on cognitive function in cognitively intact older adults with subjective memory decline. Unlike previous investigations focusing on individual herbs, this research addresses the effects of a complex herbal combination targeting widespread mechanisms. [3]

Bacopa monnieri, commonly known as Brahmi, is a plant frequently utilised in Ayurvedic medicine. It is primarily recommended for memory enhancement, addressing insomnia, managing epilepsy, and acting as an anxiolytic. Numerous clinical studies have evidenced its positive impact on verbal learning, delayed word recall, memory acquisition, and anxiety reduction. *Bacopa* is recognised as a calming cognitive enhancer, with triterpenoid saponins believed to contribute significantly to its pharmacological effects. Notably, *Bacopa* exhibits a high therapeutic index and is generally well-tolerated, with gastrointestinal side effects like increased stool frequency, nausea, and abdominal cramps being the most common. Explores the indications, contraindications, mechanisms of action, adverse events, and other essential aspects of using *Bacopa monnieri* in managing patients with cognitive decline and anxiety. **Table 4.** [39]

Table 4. Therapeutic study of the *Bacopa monnieri*.

References	Study	Objective/key findings
[5] [77] [63] [40] [66] [70] [44] [54]	Vasorelaxant effects of <i>Bacopa monnieri</i> compounds	Explored vasorelaxant effects and mechanisms of action of specific compounds in <i>Bacopa monnieri</i> extract (BME) on rat isolated mesenteric arteries. Saponins (bacoside A and bacopaside I) and flavonoids (luteolin and apigenin) induced concentration-dependent vasorelaxation. Flavonoids exhibited higher efficacy and potency compared to saponins. Relaxant effects partially mediated through the endothelial nitric oxide synthase (eNOS) pathway. Inhibitory effects on calcium-induced and phenylephrine-induced contractions observed, suggesting actions on both endothelial and vascular smooth muscle cells.
[77] [14] [55] [38] [41] [42] [57] [58] [59] [60] [61] [2]	Neuroprotective effects of <i>Bacopa monnieri</i> extract	Investigated neuroprotective effects of <i>Bacopa monnieri</i> extract against beta-amyloid and glutamate-induced neurotoxicity in primary cortical cultured neurons. Brahmi extract protected neurons specifically from beta-amyloid-induced cell death. Neuroprotective mechanism involved suppression of acetylcholinesterase activity, reduction of oxidative stress, and inhibition of lipid peroxidation. Suggested potential alternative for treating neurodegenerative disorders associated with oxidative stress, such as Alzheimer's disease.
[5] [77] [63] [40] [66] [70] [44] [39]	Clinical outcomes and positive effects of <i>Bacopa monnieri</i>	Explored the primary applications of <i>Bacopa monnieri</i> in Ayurvedic medicine, including enhancing memory, addressing insomnia, managing epilepsy, and serving as an anxiolytic. Numerous clinical studies highlighted positive effects of <i>Bacopa</i> , such as: enhanced verbal learning, improved delayed word recall, increased memory acquisition, and reduced anxiety. Considered a calming cognitive enhancer, primarily attributed to triterpenoid saponins.
[1]	Safety and effectiveness of herbal and nutritional medicines for cognitive function	Investigated safety and effectiveness of herbal and nutritional medicines in enhancing cognitive function among older adults with and without subjective cognitive impairment (SCI). Current evidence presents low quality regarding efficacy and safety, attributed to a high risk of bias in various studies. Emphasised the need for refining classification of SCI and identification of appropriate outcomes in trials.
[5] [77] [63] [40] [66] [70] [44]	<i>Bacopa monnieri</i> 's cognitive performance enhancement	Evaluated scientific evidence regarding the traditional belief that <i>Bacopa monnieri</i> enhances cognitive performance. Limited evidence for enhancement in cognitive abilities other than memory free recall. Need for further research on different dosages and extracts to provide a more comprehensive understanding of its cognitive-enhancing potential.
[5] [77] [63] [40] [66] [70] [44]	Neurobiological effects of bacosides from <i>Bacopa monnieri</i>	Explored neurobiological effects of bacosides, primary bioactive constituents from <i>Bacopa monnieri</i> . Bacosides exhibited neuroprotective properties by mitigating damage to brain neurons caused by various detrimental factors. Lowered inflammatory cytokine levels, impeded demyelination processes, demonstrated anticonvulsant effects, and enhanced cognitive functions. Considered as versatile therapeutic approach for neurological and psychiatric conditions.
[5] [77] [63] [40] [66] [70] [44] [3]	Impact of multi-ingredient herbal supplement on cognitive function	Investigated the impact of a 12-week chronic supplementation with a multi-ingredient herbal supplement, including <i>Bacopa monnieri</i> , on cognitive function in cognitively intact older adults with subjective memory decline. Addressed effects of a complex herbal combination targeting widespread mechanisms. Provided a holistic perspective on the potential cognitive benefits of <i>Bacopa monnieri</i> in combination with other herbs.
[5] [77] [63] [40] [66] [70] [44] [39]	Overview of <i>Bacopa monnieri</i> in ayurvedic medicine	Explored indications, contraindications, mechanisms of action, adverse events, and other essential aspects of using <i>Bacopa monnieri</i> in managing patients with cognitive decline and anxiety. Highlighted positive impact on verbal learning, delayed word recall, memory acquisition, and anxiety reduction. Considered a calming cognitive enhancer with a high therapeutic index and generally well-tolerated.

Investigating the cognitive and therapeutic potential of *Bacopa monnieri*: effects on processing speed, gut microbiome, stress-related memory deficits, and antioxidant activity

In a randomised, placebo-controlled, parallel groups investigation involving 128 participants aged 55-75, the herbal supplement was associated with improved speed of cognitive task performance. Notably, deficits in memory were observed, but the positive effects were concentrated on processing speed, with an additional reduction in false alarms on the rapid visual information processing task. The enhancements correlated with an elevated presence of tyrosine in the urinary metabolome, suggesting a potential role of dopamine in these cognitive improvements. [3]

Further, the multi-ingredient herbal supplement led to a significant reduction in the levels of three bacterial species in the gut microbiome, particularly *Sutterella*, coinciding with reported lower levels of constipation in the herbal supplement condition. The study highlights that while the herbal supplement positively influences cognitive function and dopaminergic activity, the interpretation of memory-related effects is complicated by uneven randomisation of participants pre- and post-COVID-19. The clinical trial registration identifier is NCT05504668. [3]

Chronic stress often leads to memory deficits, and the cholinergic system plays a crucial role in memory modulation, influencing not only neuronal cells but also interacting with non-neuronal cells like microglia. These microglia can impact synaptic function and plasticity, influencing cognition and memory. *Withania somnifera* (WS) and *Bacopa monnieri* (BM) are traditional herbal remedies used to alleviate stress symptoms temporarily. Explore whether choline (CLN) activity could be enhanced by combining it with adaptogens like WS and BM extracts.

Initially, the study optimised an *in vitro* model using corticotropin-releasing hormone (CRH) to induce oxidative stress in microglial BV2 cells. CRH at 100 nM adversely affected BV2 cell viability, induced morphological changes, and triggered neurotoxicity after 24 hours of stimulation. It also led to increased production of reactive oxygen species (ROS) and dysregulated antioxidant proteins like SIRT-1 and NRF-2. The combination of choline with adaptogens (CBW) at 10 µg/mL counteracted the effects of CRH on BV2 cells and reduced neurotoxicity caused by BV2 CRH-conditioned medium in SH-SY5Y cell lines. In mice, CBW at 200 mg/kg demonstrated a positive effect on recognition memory in the novel object recognition test (NORT).

In summary, the study suggests that combining choline with adaptogen plant extracts may offer a promising intervention for memory disturbances associated with chronic stress by mitigating microglia-induced oxidative stress. [4]

The isolation and identification of phenyl glycosides from *Bacopa monnieri*, including a newly discovered compound named bacomoside D3, along with seven known phenyl glycosides.

The compounds were then evaluated for their antioxidant and anti-inflammatory activities. Notably, these compounds demonstrated robust DPPH radical scavenging activity, with IC_{50} values of 9.77 ± 0.08 and 3.50 ± 0.04 µM, respectively. Compounds 2 and 5 exhibited significant inhibition of TNF-α production in LPS-stimulated RAW264.7 cells, with IC_{50} values of 40.60 ± 3.05 and 38.19 ± 1.75 µM, respectively. **Table 11.** Additionally, *in silico* studies suggested that these active compounds could efficiently act as inhibitors of oxidants by interfering with DPPH activity.

The antioxidant and anti-inflammatory potential of phenyl glycosides from *Bacopa monnieri*, with specific compounds showing promising activities in scavenging radicals and inhibiting inflammatory responses. [5]

Evaluating the antioxidant, anti-inflammatory, and cognitive benefits of *Bacopa monnieri*: insights from *in vitro* studies, clinical trials, and metabolite analysis

The antioxidant, anti-inflammatory, and anti-obesity potential of extracts containing phenols, chlorophyll, and carotenoids from wild populations of *Bacopa monnieri* (L.) Wettst. While certain *Bacopa* species are recognised in global pharmacopoeias, *Bacopa monnieri* has not been extensively cultivated, studied, or utilised in traditional medicine in Mexico. The primary objectives of this study include taxonomic verification of *B. monnieri*, analysis of their pigment and phenol content, and an assessment of their potential bioactivity.

The validation of *B. monnieri* wild populations in Mexico is achieved through molecular markers. High-performance liquid chromatography with a photodiode array detector (HPLC-PDA) reveals a complex profile comprising 21 compounds, including 12 chlorophylls and nine carotenoids. Notably, major carotenoids include lutein and β-carotene. The total phenolic content, determined by the Folin-Ciocalteu assay, ranges from 54.8 ± 5.8 to 70.3 ± 2.2 µg of gallic acid equivalents (GAE)/mg. The extracts exhibit significant free radical scavenging activity against DPPH, with IC_{50} values ranging from 130.6 ± 3.0 to 249.9 ± 12.1 µg dry extract/mL. In terms of anti-inflammatory potential, the most effective extract, derived from a soil-based plant in Jalisco (BS), demonstrates notable inhibition of nitric oxide in a RAW 264.7 culture medium.

Moreover, the BS extract displays significant activity in reducing neutral lipid levels in a zebrafish model, suggesting anti-obesity potential. These findings, presenting the antioxidant, anti-inflammatory, and anti-obesity properties of these extracts for the first time, indicate their promising potential for future applications. [6]

In vitro cultures of *Bacopa monnieri* L. Pennell, a significant plant in Ayurveda, to optimise its growth for efficient metabolite accumulation. The biomass growth is achieved through liquid cultures on Murashige & Skoog medium. Methanol extraction of powdered shoots from these *in vitro* cultures allows for the analysis of indole compounds, phenolic compounds, and bacosides using RP-HPLC. Gas chromatography is employed for fatty acid analysis. The anti-inflammatory effects of *B. monnieri* extracts are evaluated in A549 cells, with the analysis of COX-2 and cPGES expression via Western blots. [7]

The study reveals the presence of l-tryptophan and serotonin in the biomass from *in vitro* cultures of *B. monnieri* on MS medium. Additionally, these compounds are found in biomass from MS mediums enriched with various additions, such as: magnesium sulfate, zinc hydroaspartate, l-tryptophan, serine, and anthranilic acid. The highest content of l-tryptophan and serotonin is observed in biomass from the medium with the addition of zinc hydroaspartate. Phenolic compounds identified in biomass from the same variants of MS medium include chlorogenic acid, neochlorogenic acid, and caffeic acid. The main group of fatty acids in the biomass is saturated fatty acids, with palmitic acid being the predominant fatty acid. [7]

Notably, it provides the first analysis of indole compounds and phenolic acids in *Bacopa monnieri*. The multi-therapeutic effect of the plant is attributed to the activity of bacosides, and the presence of indole and phenolic compounds, along with fatty acids, may contribute to the physiological activity of *Bacopa monnieri*. **Table 5.** [7]

A research focuses on optimising the content of essential elements for bioaccumulation in *Bacopa monnieri* (L.) through *in vitro* shoot cultures. *Bacopa monnieri* holds significance in Ayurveda, and the objectives of this study involve determining and assessing the impact of crucial metabolites on the accumulation of selected bioelements in the biomass.

The most notable increase in biomass production occurs in the culture medium enriched with 0.5 mg/L of anthranilic acid. This medium also exhibits the highest accumulation of Mg. The highest concentration of iron is found in the *in vitro* culture of *B. monnieri* enriched with 0.25 g/L of serine. L-tryptophan, magnesium sulfate, and zinc hydroaspartate additions result in a modest increase in copper accumulation in *B. monnieri*. Zn accumulation increases in biomass from *in vitro* cultures with the addition of magnesium sulfate and zinc hydroaspartate. For Na, the maximum level is observed in biomass from the medium enriched with zinc hydroaspartate. A twofold increase in K concentration is achieved in biomass from cultures on a medium with the addition of serine and magnesium sulfate. The concentrations of Ca in the biomass from all studied media are comparable.

In summary, to optimise the medium content for bioelement accumulation in *Bacopa monnieri in vitro* cultures, providing valuable insights into the influence of specific metabolites on the accumulation of essential elements in the plant biomass. [8]

Supplementation with *Bacopa monnieri*, an Ayurvedic herb known for its cognitive enhancement properties, was investigated in a 3-month open-labeled study involving cognitively healthy subjects. The study aimed to explore the effects on cognition, mood, and serum biomarkers, with a focus on brain-derived neurotrophic factor (BDNF) levels and intracellular signaling processes.

Bacopa administration to 35 subjects was generally well-tolerated, with only 11% experiencing reversible gastrointestinal side effects leading to early termination. The study assessed cognition and mood using the Montreal Cognitive Assessment (MoCA) and geriatric depression scale (GDS). While the GDS and total MoCA scores showed no significant changes over 3 months, the delayed-recall subscale demonstrated improvement.

Serum levels of mature (mBDNF) and proBDNF, associated with neurotrophic effects, did not significantly change. However, intracellular signaling processes analysis revealed a significant increase in cyclic AMP response element-binding protein (CREB) phosphorylation (associated with synaptogenesis) and a significant decrease in p65 nuclear factor kappa B (NF-κB) phosphorylation (indicative of an anti-inflammatory effect). **Table 5.**

These findings suggest that *Bacopa monnieri* may exert anti-inflammatory effects through NF-κB modulation and enhance intracellular signaling processes related to synaptogenesis via CREB. The study recommends future placebo-controlled trials to further investigate these effects. [9]

A randomised, double-blind, placebo-controlled clinical trial aimed to assess the effects of a standardised *Bacopa monnieri* whole plant dry extract on cognitive function, mood, and safety in healthy elderly participants. The study involved a 6-week placebo run-in followed by a 12-week treatment period. Fifty-four participants aged 65 or older, without clinical signs of dementia, were recruited and randomised into *Bacopa* or placebo groups, with 48 participants completing the study. Participants received either 300 mg/day of standardised *B. monnieri* extract or a similar placebo for 12 weeks. The primary outcome measure was the delayed recall score from the Rey Auditory Verbal Learning Test (AVLT). Other cognitive measures included the Stroop Task, Divided Attention Task (DAT), and Wechsler Adult Intelligence Scale (WAIS) letter-digit test. Affective measures comprised the State-Trait Anxiety Inventory, Center for Epidemiologic Studies Depression scale (CESD)-10, and Profile of Mood States. Vital signs were also monitored.

After controlling for baseline cognitive deficit, *Bacopa* participants showed enhanced AVLT delayed word recall memory scores compared to placebo. Stroop results similarly favoured the *Bacopa* group, with improvement observed compared to the unchanged placebo group. CESD-10 depression scores, combined anxiety scores, and heart rate decreased over time in the *Bacopa* group but increased in the placebo group. No effects were found on the DAT, WAIS digit task, mood, or blood pressure. The dose was well-tolerated with few adverse events, primarily stomach upset. Study contributed further evidence supporting the potential of *Bacopa monnieri* for safely enhancing cognitive performance in aging individuals. **Table 5.** [10]

Table 5. Further therapeutic emphasis on *Bacopa monnieri*.

References	Study	Objective and key findings
[3]	Herbal supplement and cognitive task performance	Randomised, placebo-controlled investigation involving 128 participants aged 55-75. Herbal supplement associated with improved speed of cognitive task performance. Positive effects concentrated on processing speed with a reduction in false alarms on rapid visual information processing task. Correlation with elevated tyrosine in urinary metabolome, suggesting a potential role of dopamine. Significant reduction in levels of three bacterial species in the gut microbiome. Uneven randomisation of participants pre- and post-COVID-19 complicates interpretation of memory-related effects.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Choline activity enhancement with adaptogens	Explored enhancing choline (CLN) activity by combining it with adaptogens <i>Withania somnifera</i> (WS) and <i>Bacopa monnieri</i> (BM) extracts. <i>In vitro</i> model with CRH-induced oxidative stress in microglial BV2 cells. Combination of choline with adaptogens (CBW) counteracted effects of CRH on BV2 cells and reduced neurotoxicity. CBW demonstrated positive effect on recognition memory in mice. Suggested promising intervention for memory disturbances associated with chronic stress.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	<i>Bacopa monnieri</i> in ayurvedic medicine	Explored traditional uses, pharmacological investigations, and clinical studies of <i>Bacopa monnieri</i> in Ayurvedic medicine. Highlighted positive effects on memory, learning, concentration, anxiety, and depression. Key active compounds include saponins (bacoside A and B), alkaloids, and sterols.

		Initial clinical studies suggest favourable outcomes and good tolerability. Emphasised the need for further research to validate medical indications.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [34] [5]	Phenyl Glycosides from <i>Bacopa monnieri</i>	Investigated phenyl glycosides from <i>Bacopa monnieri</i> for antioxidant and anti-inflammatory activities. Identified eight compounds, with compounds showed robust DPPH radical scavenging activity. Compounds also exhibited significant inhibition of TNF- α production in LPS-stimulated cells. <i>In silico</i> studies suggested efficient inhibition of oxidants by these active compounds.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [6]	Bioactivity of <i>Bacopa monnieri</i> extracts in Mexico	Explored antioxidant, anti-inflammatory, and anti-obesity potential of <i>Bacopa monnieri</i> extracts from wild populations in Mexico. Validated <i>B. monnieri</i> populations through molecular markers. Complex profile comprising 21 compounds, including chlorophylls and carotenoids. Significant free radical scavenging activity against DPPH observed. Extract from Jalisco demonstrated notable inhibition of nitric oxide and anti-obesity potential.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [8]	<i>In Vitro</i> cultures of <i>Bacopa monnieri</i>	Optimised <i>in vitro</i> cultures of <i>Bacopa monnieri</i> for growth and metabolite accumulation. Analysis of indole compounds, phenolic compounds, and bacosides using RP-HPLC. Identified presence of l-tryptophan, serotonin, and phenolic compounds. Provided first analysis of indole compounds and phenolic acids in <i>Bacopa monnieri</i> . Indole and phenolic compounds, along with fatty acids, may contribute to physiological activity.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Optimisation of bioelement accumulation in <i>Bacopa monnieri</i>	Investigated optimisation of essential bioelement accumulation in <i>Bacopa monnieri</i> in <i>in vitro</i> cultures. Examined impact of specific metabolites on accumulation of bioelements. Medium enriched with anthranilic acid led to notable increase in biomass and Mg accumulation. Various additions influenced accumulation of elements such as: iron, copper, zinc, Na, and K. Study provides insights into influence of metabolites on bioelement accumulation.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [39] [10] [69] [68] [3]	<i>Bacopa monnieri</i> supplementation in elderly	Explored effects of standardised <i>Bacopa monnieri</i> extract on cognition, mood, and safety in healthy elderly participants. 12-week treatment with 300 mg/day <i>Bacopa</i> improved delayed recall memory scores. Improved performance in Stroop Task and reduction in depression scores compared to placebo. No significant changes in total MoCA scores or affective measures. Generally well-tolerated with few adverse events, primarily stomach upset.

Efficacy of *Bacopa monnieri* on memory performance and cognitive function: insights from clinical trials, cognitive training, and neurodegeneration studies

An examination of the effectiveness of *Bacopa monnieri* Linn. in improving memory performance among healthy older individuals in a randomised, double-blind, placebo-controlled trial conducted in Lismore, NSW, Australia, between February and July 2005. Ninety-eight healthy participants aged over 55 were recruited from the general population and were randomly assigned to receive either a daily dose of 300 mg of *Bacopa monnieri* extract (BacoMind™) or an identical placebo. Neuropsychological and subjective memory assessments were conducted at baseline and after 12 weeks. The Rey Auditory Verbal Learning Test (AVLT), Rey-Osterrieth Complex Figure Test (CFT), and Reitan Trail Making Test (TMT) were used to measure audioverbal and visual memory performance. **Table 13.** Subjective memory performance was evaluated using the Memory Complaint Questionnaire (MAC-Q). Of the 136 initial volunteers, 103 met entry criteria, 98 began the trial, and 81 completed it. *Bacopa* demonstrated significant improvements in verbal learning, memory acquisition, and delayed recall based on AVLT results. However, there were no significant differences in CFT, MAC-Q, and TMT scores between the *Bacopa* and placebo groups. *Bacopa* did cause gastrointestinal side effects, including increased stool frequency, abdominal cramps, and nausea. **Table 13.**

In conclusion, *Bacopa monnieri* significantly enhanced memory acquisition and retention in healthy older Australians, aligning with previous findings and traditional uses. The study emphasised the potential cognitive benefits of *Bacopa* while noting the occurrence of gastrointestinal side effects. [11]

As the elderly population continues to grow, the prevalence of age-associated cognitive decline and neurodegenerative diseases like Alzheimer's and dementia becomes increasingly impactful. Aging often leads to consistent cognitive impairments in areas such as: processing speed, memory, executive function, and learning, all of which are crucial for overall well-being and participation in society. Recent research efforts have focused on finding ways to enhance cognitive function in older individuals, with cognitive training showing promise in improving performance in various cognitive domains.

Cognitive training has demonstrated efficacy in areas like: memory, processing speed, executive function, and attention in older adults, with improvements linked to enhanced brain connectivity and neural circuitry. *Bacopa monnieri*, a herbal supplement, has also exhibited positive effects on specific cognitive domains sensitive to age-related decline, particularly in processing speed and memory. The improvements attributed to *Bacopa monnieri* may be linked to its ability to enhance neuro-molecular mechanisms associated with synaptogenesis, the formation of connections between neurons.

Animal studies have shown that *Bacopa monnieri* consumption can upregulate calcium-dependent kinases in synapses and post-synaptic cells, crucial for strengthening and growing neuronal connections, particularly in regions important for cognitive processes like the hippocampus. Given that *Bacopa monnieri* promotes synaptogenesis and cognitive training enhances brain connectivity, there is a theoretical basis to suggest that combining these interventions could synergistically improve cognitive outcomes. The hypothesis presented in this study work proposes that the joint administration of cognitive training and *Bacopa monnieri* supplementation may be more effective in ameliorating age-associated cognitive decline than administering these interventions independently. [13]

Bacopa monnieri (L.) Wettst., a plant with a history of use in Ayurvedic medicine for enhancing intelligence and memory, has been considered for its potential in protecting against Alzheimer's disease. However, there is limited documented support for this claim. The study aimed to investigate the impact of the alcoholic extract of *Bacopa monnieri* on cognitive function and neurodegeneration in an Alzheimer's disease animal model induced by ethylcholine aziridinium ion (AF64A).

Male Wistar rats received the alcoholic extract of *Bacopa monnieri* orally at doses of 20, 40, and 80 mg/kg body weight for two weeks before and one week after the intracerebroventricular administration of AF64A. Spatial memory was assessed using the Morris water maze test, and histological techniques were employed to determine the density of neurons and cholinergic neurons seven days after AF64A administration. *Bacopa monnieri* extract significantly improved the escape latency time in the Morris water maze test. Additionally, it mitigated the reduction in neuron and cholinergic neuron densities. In conclusion, these findings suggest that *Bacopa monnieri* has the potential to enhance cognitive function and provide neuroprotection against Alzheimer's disease. [14]

Evaluating the neuroprotective and cognitive enhancement potential of *Bacopa monnieri*: insights from animal models, clinical trials, and meta-analysis

Bacopa monnieri (L.) Wettst. (BM), traditionally used for its memory and intelligence-enhancing properties, has been explored for its potential benefits in dementia. BM's anti-dementia effects using a mouse model of vascular dementia induced by transient 2 vessels occlusion (T2VO). Additionally, the study aimed to identify the constituent(s) responsible for BM's actions using an *in vitro* model of ischemia with oxygen- and glucose-deprivation (OGD).

In vivo experiments involved treating T2VO mice with a standardised BM extract (50mg/kg, p.o.) one week before and continuously for three days after surgery. The BM treatment significantly improved T2VO-induced impairments in non-spatial short-term memory performance. In *in vitro* experiments using organotypic hippocampal slice cultures (OHSCs), triterpenoid saponins from BM (bacosides) were tested, revealing that bacopaside I exhibited potent neuroprotective effects against OGD-induced neuronal cell damage. Bacopaside I demonstrated the ability to attenuate necrosis and apoptosis caused by OGD. The neuroprotective effects were found to be mediated through PKC and PI3K/Akt mechanisms, as inhibitors of these pathways blocked the effects of bacopaside I. OGD-induced reduction in phospho-Akt (p-Akt) levels in OHSCs was reversed by bacopaside I treatment. Moreover, bacopaside I itself elevated the levels of p-Akt in OHSCs.

In conclusion, BM is beneficial in preventing cognitive deficits associated with cerebral ischemia, and bacopaside I, acting through PKC and PI3K/Akt pathways, plays a key role in the observed neuroprotective effects of BM in the mouse model. [15]

Bacopa monnieri (L.) WETTST. is traditionally used as a nerve tonic in Indian medicine. This study aimed to investigate the neuropharmacological properties of bacopaside I, a key component of *B. monnieri*, in a rat model of transient focal ischemia induced by middle cerebral artery occlusion (MCAO). **Table 6.**

Adult male Sprague-Dawley rats were divided into five groups, including a sham-operated group, an ischemia group, and three groups treated with different doses of bacopaside I (3, 10, and 30 mg/kg). Bacopaside I or the vehicle was administered orally for 6 days, with rats subjected to 2 hours of right MCAO on the third day, followed by 70 hours of reperfusion. Behavioral deficits were assessed at 22 and 70 hours, and various parameters were measured at 70 hours post-MCAO reperfusion. Bacopaside I treatment (10 and 30 mg/kg) significantly reduced neurological deficits at 22 and 70 hours, decreased cerebral infarct volume and edema at 70 hours, and improved cerebral energy metabolism. **Table 6.** It increased brain ATP content, energy charge, total adenine nucleotides, nitric oxide (NO) level, $\text{Na}^+\text{K}^+\text{ATPase}$, and $\text{Ca}_2^+\text{Mg}_2^+\text{ATPase}$ activity. Bacopaside I treatment also enhanced antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), while inhibiting malondialdehyde (MDA) content in the brain. In conclusion, bacopaside I demonstrated neuroprotective effects against cerebral ischemia, possibly through improving cerebral energy metabolism and increasing antioxidant levels. [16]

Bacopa monnieri, a herb with historical use in Ayurvedic medicine for neurological and behavioural issues, has been investigated for its potential to enhance cognitive function.

Randomised, placebo-controlled human intervention trials, involving chronic dosing of standardised *Bacopa monnieri* extracts for at least 12 weeks without co-medication, were included. The methodological quality of studies was assessed, and a meta-analysis was performed using the random-effects model. Nine studies meet the criteria included 518 subjects. Overall, the quality of these trials was assessed as having a low risk of bias, and the reported information quality was high. The meta-analysis, involving 437 eligible subjects, revealed improved cognition, particularly in the speed of attention, as demonstrated by a shortened Trail B test (-17.9 ms; 95% CI -24.6 to -11.2; $p < 0.001$) and decreased choice reaction time (10.6 ms; 95% CI -12.1 to -9.2; $p < 0.001$). **Table 6.**

In conclusion, findings suggests that *Bacopa monnieri* has the potential to enhance cognition, specifically in attention speed. However, the need for a large, well-designed "head-to-head" trial against an existing medication is emphasised to provide definitive data on its efficacy for healthy individuals or those with dementia using standardised preparations. **Table 6.** [17]

Table 6. Pharmacological aspect of the plant extract *Bacopa monnieri*.

References	Study	Objective and key findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	<i>Bacopa monnieri</i> in memory improvement	Randomised, double-blind, placebo-controlled trial in healthy older individuals (98 participants over 55). <i>Bacopa</i> (300 mg/day) significantly enhanced verbal learning, memory acquisition, and delayed recall based on AVLT results. No significant differences in CFT, MAC-Q, and TMT scores between <i>Bacopa</i> and placebo groups. Gastrointestinal side effects observed, including increased stool frequency, abdominal cramps, and nausea. <i>Bacopa</i> significantly improved memory acquisition and retention.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Cognitive training and <i>Bacopa monnieri</i> synergy	Proposal for joint administration of cognitive training and <i>Bacopa monnieri</i> supplementation for age-associated cognitive decline. Cognitive training has demonstrated efficacy in improving various cognitive domains in older adults. <i>Bacopa monnieri</i> has positive effects on processing speed and memory, linked to enhanced brain connectivity and neural circuitry. Suggested theoretical basis for synergistic improvement in cognitive outcomes with combined interventions.
[77] [14] [55] [38] [41] [42]	<i>Bacopa monnieri</i> in Alzheimer's Disease Model	Investigated the impact of <i>Bacopa monnieri</i> extract on cognitive function and neurodegeneration in an Alzheimer's disease animal model. Improved spatial memory in rats treated with <i>Bacopa</i> after AF64A-induced damage. Mitigated reduction in neuron and cholinergic neuron densities. Suggested potential neuroprotective effects against Alzheimer's disease.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [15]	<i>Bacopa monnieri</i> in Vascular Dementia Model	Explored anti-dementia effects of <i>Bacopa monnieri</i> in a mouse model of vascular dementia induced by transient 2 vessels occlusion (T2VO). <i>Bacopa</i> treatment improved T2VO-induced impairments in non-spatial short-term memory performance. <i>In vitro</i> , bacopaside I exhibited neuroprotective effects against OGD-induced neuronal cell damage. Bacopaside I acted through PKC and PI3K/Akt pathways, playing a key role in neuroprotective effects.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [16]	Neuropharmacological properties of Bacopaside I	Investigated neuropharmacological properties of bacopaside I, a key component of <i>Bacopa monnieri</i> , in a rat model of transient focal ischemia (MCAO). Bacopaside I treatment reduced neurological deficits, cerebral infarct volume, and edema. Improved cerebral energy metabolism, increased ATP content, and enhanced antioxidant enzyme activities. Bacopaside I demonstrated neuroprotective effects against cerebral ischemia.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Meta-Analysis on <i>Bacopa monnieri</i> efficacy	Meta-analysis of randomised, placebo-controlled human intervention trials on <i>Bacopa monnieri</i> 's cognitive performance. Nine studies (518 subjects) included, showing improved cognition, especially in attention speed. <i>Bacopa</i> demonstrated positive effects on Trail B test and choice reaction time. Emphasised the need for large, well-designed trials against existing medications for definitive efficacy data.

Clinical and preclinical evaluations of *Bacopa monnieri*: efficacy, safety, and mechanisms in cognitive enhancement and neuroprotection.

The outcomes and safety of *Bacopa monnieri* in clinical trials focusing on cognition and behaviour in children and adolescents. Cognitive and behavioural outcomes were categorised into validated constructs, and effect sizes were calculated for significant data to facilitate direct comparisons.

Five studies meeting the inclusion criteria were analysed. The findings consistently revealed significant improvements in the language behaviour cognitive domain and several memory sub-domains. Positive effects were also observed in hyperactivity and attention-deficit domains. Overall outcome data indicated small to medium effect sizes (mean $d=0.42$). Safety and tolerability were well-documented in 80% of studies, with only 2.3% of participants reporting mild side effects.

The safe use of *Bacopa monnieri* in children and adolescents, showing enhancements in aspects of cognition, behaviour, and attention-deficit domains. However, the need for replicated study designs and rigorous statistical analysis is emphasised to validate these outcomes. [18]

Clinicians rely on critical research to enhance their understanding when prescribing both standard and alternative therapies for developmental disorders. Recent research has indicated that *Bacopa monnieri*, a traditional Ayurvedic medicine, may enhance cognitive outcomes in adult populations. However, there is limited exploration of its benefits in younger age groups. A thoroughly assessed and summarised clinical trial outcomes and safety aspects of *Bacopa* in children and adolescents' cognition and behaviour. Five studies met the inclusion criteria, revealing consistent and significant improvements in the language-behavioural cognitive domain and various memory sub-domains. Notable enhancements were also observed in the hyperactivity and attention-deficit domains. The overall outcome data indicated small to medium effect sizes (mean $d=0.42$). Safety and tolerability data were well-documented for 80% of the studies, with only 2.3% of participants reporting mild side effects.

It had emphasised the safe use of *Bacopa monnieri* in child and adolescent populations, showcasing its potential to improve cognitive elements, behaviour, and attention-deficit domains. However, it emphasises the need for replicated study designs and rigorous statistical analysis to validate these outcomes. [19]

A critically summarised clinical trials investigating *Bacopa monnieri* (*B.monnieri*)-dominant poly-herbal formulas and their impact on cognition, memory, learning, and behaviour in children and adolescents within the Ayurvedic medicinal system. Effect sizes were calculated for significant findings to facilitate direct comparisons, and each study was evaluated for design quality. For cross-study comparison, cognitive and behavioural outcomes were categorised into validated categories. Nine trials met inclusion criteria, and five studies provided sufficient data for effect size analysis, with most improvements reported in behavioural outcomes. Cognitive abilities and behavioural constructs were reviewed in six studies, showing the greatest improvements in visual perception, impulsivity, and attention. The evidence for the formulations reviewed is compromised by inconsistent statistical design and under-reporting of safety and tolerability data (44%).

In conclusion, this study extends support for *B.monnieri* as a cognitive enhancer and offers modest evidence for its use in poly-herbal preparations to improve cognitive and behavioural outcomes in children and adolescents. Emphasising statistical rigour and reporting tolerability data are crucial for future trials to effectively document the efficacy of poly-herbal treatments. [20]

A randomised controlled trial is set to investigate the impact of a specialised extract of *Bacopa monnieri*, known as CDRI 08, on hyperactivity and inattention in male children and adolescents. With the increasing diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) and concerns about traditional treatments involving amphetamine-type substances, alternative pharmacological approaches are sought. CDRI 08, backed by numerous scientific studies and human randomised controlled trials, has demonstrated improvements in memory, attention, and mood. The hypothesis posits that the chronic administration of CDRI 08 will enhance attention, concentration, and behaviour in children exhibiting high levels of hyperactivity and/or inattention. The protocol for the first 16-week, randomised, placebo-controlled, double-blind trial, focusing on male children aged 6-14 with elevated inattention and hyperactivity. The primary outcome will be measured by the Conners' Parent Rating Scale (CPRS), assessing hyperactivity and inattention. Secondary outcomes include cognition, mood, sleep, and EEG. The trial is registered with the Australia and New Zealand Clinical Trials Register (ANZCTR) under ACTRN12612000827831. [21]

The study aimed to assess the effectiveness of *Bacopa monnieri* extract (CDRI 08®) in reducing inattention and hyperactivity levels in young children. While BM has shown cognitive improvements in adults, limited research exists on its impact in younger populations. This 14-week randomised, double-blind, placebo-controlled trial, featuring placebo run-in and run-out phases, examined the effects of BM on behavioural, cognitive, mood, and sleep aspects in male children aged 6 to 14 years compared to placebo. Out of 112 participants, 93 datasets were available for analysis. Behavioural differences between treatment groups were not significant. However, cognitive outcomes revealed reduced error rates in children on CDRI 08® ($p = .04$) and increased reaction time speed in those on placebo ($p = .04$) by the study's end. Children consuming CDRI 08® exhibited enhancements in cognitive flexibility ($p = .01$), executive functioning ($p = .04$), interpersonal problems ($p = .02$), and sleep routine ($p = .04$) compared to the placebo group. While CDRI 08® did not significantly improve behavioural outcomes, it may offer cognitive, mood, and sleep benefits in children aged 6 to 14 years. Further investigation is required to bolster these conclusions. [22]

This double-blind, placebo-controlled cross-over study aimed to investigate the acute effects of *Bacopa monnieri* (BM) on multitasking stress reactivity and mood in healthy individuals. The study utilised a specific BM extract, KeenMind® - CDRI 08. Seventeen participants completed a multitasking framework at baseline, 1 hour, and 2 hours after consuming a placebo, 320 mg BM, and 640 mg BM. **Table 11. Table 12.** Cognitive outcomes from the multitasking framework, mood, and salivary cortisol levels were measured. The results indicated positive cognitive effects, especially at 1 hour and 2 hours post-BM consumption on tasks such as: Letter Search and Stroop, suggesting an earlier nootropic impact than previously explored. Positive mood effects and reduced cortisol levels were also observed, indicating potential adaptogenic and stress-reducing effects associated with BM consumption. The study concluded that acute BM supplementation demonstrated adaptogenic and nootropic effects, suggesting the need for further research in a larger sample and under less stressful conditions to quantify these effects accurately. The Australian and New Zealand Clinical Trials Registry (ACTRN12612000834853) has the trial registered. [23]

A double-blind, placebo-controlled crossover study aimed to investigate the acute effects of specific *Bacopa monnieri* (BM) extract, KeenMind®-CDRI 08, on sustained cognitive performance in healthy individuals. **Table 11. Table 12.** Twenty-four participants completed a series of cognitively demanding tests, the Cognitive Demand Battery (CDB), after consuming a placebo, 320 mg BM, or 640 mg BM in a cross-over design. Cardiovascular and mood assessments were conducted before and after treatment. The results indicated that the 320 mg dose of BM improved performance at the first, second, and fourth repetitions post-dosing on the CDB. No significant effects were observed on cardiovascular activity or in mitigating task-induced stress and fatigue. Exploring an earlier pharmacological window, using less memory-specific cognitive tests, and employing more temporally sensitive measures of brain activity could enhance understanding of the acute neurocognitive properties of BM. [24]

A randomised, double-blind, placebo-controlled trial investigated the neurocognitive effects of *Bacopa monnieri* (BM) and cognitive training (CT) on brain microstructure markers in healthy older adults. Twenty-eight participants over 55 years engaged in CT for 12 weeks, with 15 taking a standardised BM extract, and 13 a placebo daily. Cognitive tasks, mood, life satisfaction, and memory complaints were assessed, along with serum brain-derived neurotrophic factor (BDNF) levels. Neuroimaging analysis revealed increased white matter mean diffusivity (MD) and gray matter dispersion of neurites (orientation dispersion index, ODI) in the BM group, along with decreased white matter fractional anisotropy (FA) and gray matter neurite density (ND). These outcomes, conflicting with behavioural results, may suggest increased network complexity and dendritic branching accompanied by pruning for enhanced efficiency. However, due to exploratory nature and inconsistent findings, larger studies are needed to confirm BM's synaptogenic mechanisms. [25]

Bacopa monnieri extracts exhibit chemical-genetic interactions with cells deficient in the DNA repair endonuclease RAD1, linked to vacuolar disruption. In a yeast model of colorectal cancer lacking RAD1, *B. monnieri* extracts induce mutations and disrupt the vacuole, similar to mammalian lysosomes. RAD1 deficiency sensitises cells to vacuole disruption, leading to an apoptosis-like event dependent on the meta-caspase Yca1p. The toxicity of *B. monnieri* extracts is associated with sterol content, suggesting saponins may limit yeast cell proliferation. Bacopasaponin C, a major constituent, interacts with rad1Δ yeast, indicating its potential as a drug candidate for colorectal cancer treatment or a model for analog development. **Table 7.** [26]

Bacopa monnieri (L.) extract (BME) has demonstrated cognitive enhancement in dementia models by promoting synaptic plasticity signaling and protecting cholinergic neurons. In a trimethyltin (TMT)-induced neurotoxicity model in mice, where TMT impairs hippocampus-dependent spatial and fear-motivated memory, BME administration significantly prevented cognitive deficits. The protective effects of BME were confirmed through histological analyses of hippocampal tissues and organotypic hippocampal slice cultures. BME not only shielded hippocampal neurons from TMT-induced lesions but also stimulated neuroregeneration in the dentate gyrus region. **Table 13.** BME mitigates TMT-induced cognitive dysfunction by preventing damage and promoting neuroregeneration in relevant brain regions. **Table 7. Table 8. Table 9.** [27]

Table 7. Comprehensive analysis of *Bacopa monnieri* in Young People includes: children and adolescents.

References	Study	Main results
[5] [77] [63] [40] [66] [70] [44] [8] [7] [18] [19]	Study 1	Evaluate and summarise <i>Bacopa monnieri</i> outcomes in clinical trials for cognition and behaviour in children and adolescents. 5 studies analysed showed. Significant improvements in language behaviour cognitive domain and memory sub-domains. Positive effects observed in hyperactivity and attention-deficit domains. Small to medium effect sizes (mean d=0.42). Safety and tolerability well-documented (2.3% mild side effects). Emphasised the need for replicated study designs and rigorous statistical analysis.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [18] [19]	Study 2	Assess clinical trial outcomes and safety of <i>Bacopa monnieri</i> in children and adolescents' cognition and behaviour. 5 studies analysed outcomes. Consistent and significant improvements in language behaviour cognitive domain and memory sub-domains. Enhancements in hyperactivity and attention-deficit domains. Small to medium effect sizes (mean d=0.42). Safety and tolerability well-documented (2.3% mild side effects). Emphasised the need for replicated study designs and rigorous statistical analysis.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Study 3	Evaluate <i>Bacopa monnieri</i> -dominant poly-herbal formulas in Ayurvedic medicine for cognition, memory, learning, and behaviour in children and adolescents. 9 trials analysed results in outcomes: Inconsistent statistical design and under-reporting of safety data (44%). Modest evidence for cognitive and behavioural improvements. Emphasised the importance of statistical rigour and reporting tolerability data in future trials.

Table 8. Studies on *Bacopa monnieri* mechanisms and specific extracts.

References	Study	Objective and key findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Yeast Model Study	Explore chemical-genetic interactions of <i>Bacopa monnieri</i> extracts with RAD1-deficient cells in a yeast model. <i>B. monnieri</i> extracts induce mutations and disrupt vacuole in RAD1-deficient cells. RAD1 deficiency sensitises cells to vacuole disruption, leading to apoptosis-like event. Toxicity associated with sterol content, suggesting potential for colorectal cancer treatment.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	TMT-Induced Neurotoxicity Model	Investigate <i>B. monnieri</i> extract's protective effects in a TMT-induced neurotoxicity model in mice. BME prevented cognitive deficits and hippocampal neuron damage induced by TMT. BME stimulated neuroregeneration in the dentate gyrus region. Suggested BME mitigates TMT-induced cognitive dysfunction through damage prevention and neuroregeneration.

Table 9. Clinical trials on *Bacopa monnieri* in children and adolescents.

References	Study	Objective and key findings
[21]	CDRI 08 Trial	Investigate CDRI 08's impact on hyperactivity and inattention in male children and adolescents. 16-week, randomised, placebo-controlled, double-blind trial. Primary outcome: Conners' Parent Rating Scale (CPRS) for hyperactivity and inattention. Secondary outcomes: Cognition, mood, sleep, EEG. Registered with ANZCTR (ACTRN12612000827831).
[5] [77] [63] [40] [66] [70] [44] [8] [7]	BM Extract Trial	Assess effectiveness of <i>Bacopa monnieri</i> extract (CDRI 08) in reducing inattention and hyperactivity in young children. 14-week, randomised, double-blind, placebo-controlled trial. Reduced error rates in CDRI 08 group, increased reaction time speed in placebo group. CDRI 08 group exhibited enhancements in cognitive flexibility, executive functioning, interpersonal problems, and sleep routine.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [23] [24] [36]	Multitasking Stress Reactivity Trial	Investigate acute effects of <i>Bacopa monnieri</i> (KeenMind® - CDRI 08) on multitasking stress reactivity and mood. Positive cognitive effects at 1 and 2 hours post-BM consumption. Positive mood effects and reduced cortisol levels observed. Acute BM supplementation demonstrated adaptogenic and nootropic effects.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [23] [24] [36]	Sustained Cognitive Performance Trial	Explore acute effects of specific <i>Bacopa monnieri</i> extract (KeenMind®-CDRI 08) on sustained cognitive performance. 320 mg dose improved performance on Cognitive Demand Battery (CDB). No significant effects on cardiovascular activity or mitigating task-induced stress and fatigue.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Neurocognitive Effects Trial	Investigate neurocognitive effects of <i>Bacopa monnieri</i> and cognitive training on brain microstructure markers in older adults. 28 participants over 55 engaged in CT for 12 weeks. BM group showed increased white matter mean diffusivity and gray matter dispersion of neurites. Inconsistent findings suggested increased network complexity and dendritic branching.

Investigating *Bacopa monnieri*: cognitive, neuroprotective, anti-inflammatory, and anti-tumor properties across preclinical and clinical studies

The impact of *Bacopa monnieri* (BM) alcoholic extract on cognitive deficits in olfactory bulbectomised (OBX) mice **Table 10.** and the underlying molecular mechanisms. OBX mice, which exhibited impaired memory, were treated with BM, showing improvements in non-spatial short-term memory, spatial working memory, and long-term fair memory. The beneficial effects on short-term memory were blocked by a muscarinic receptor antagonist. BM treatment reversed OBX-induced neurochemical and histological alterations, enhanced synaptic plasticity-related signaling and brain-derived neurotrophic factor transcription, and protected cholinergic systems from OBX-induced damage. Hence, BM ameliorates cognitive dysfunction in OBX mice through various neuroprotective and neuroenhancing mechanisms. [28]

Bacopa monnieri L. Wettst. (BM) extract improves spatial working memory in adolescent mice, with sustained benefits even after discontinuation of the treatment. The administration of BM extract enhances hippocampal neurogenesis, as evidenced by increased BrdU incorporation and altered gene expression related to neurogenesis. Notably, the active component, bacopaside I, promotes the proliferation of neural progenitor cells *in vitro* by facilitating Akt and ERK1/2 signaling. These findings suggest that BM extract's positive effects on spatial working memory in adolescent mice are linked to the promotion of hippocampal neurogenesis, particularly through bacopaside I. [29]

Three newly identified saponins, bacopasides IX-XI (1-3), along with known analogues (4-7), were isolated from *Bacopa monnieri*. Compounds 3, 4, and 6 demonstrated nootropic effects in tests for scopolamine-induced memory impairment in mice, specifically in the Morris water maze test and step-down test. [30]

Three recently identified triterpene glycosides, bacopasides VI-VIII (1-3), along with three known analogues, were obtained from *Bacopa monnieri*. Compounds exhibited antidepressant effects in mice, as demonstrated in forced swimming and tail suspension tests. [31]

The anti-tumour potential of bacopaside II, a purified extract from *Bacopa monnieri*, in colon cancer cells. Provided data that bacopaside II significantly reduced the growth of colon cancer cells by inducing cell cycle arrest and apoptosis. Higher expression of the transmembrane molecule Aquaporin-1 (AQP1) **Table 11.** was observed in HT-29 cells compared to SW480, SW620, and HCT116 cells. Bacopaside II demonstrated growth inhibition, primarily through G0/G1 cell cycle arrest in HT-29 cells and G2/M arrest along with apoptosis in SW480, SW620, and HCT116 cells. This study provides novel insights into the potential anti-tumour effects of bacopaside II in colon cancer cells. [32]

The neuropharmacology of *Bacopa monnieri* (BM), a nootropic herb recognised for its cognitive-enhancing properties and traditional use as a neural tonic. The study explored behavioural research alongside potential neuromolecular mechanisms underlying BM's low-toxicity cognitive benefits. With roots in Ayurvedic medicine, BM has been subject to various animal and *in vitro* studies, demonstrating medicinal potential. Human trials have further substantiated its nootropic effects, and there's emerging evidence for its impact on conditions like dementia, Parkinson's disease, and epilepsy. Study identifies multiple mechanisms through which BM may act, including antioxidant neuroprotection, acetylcholinesterase inhibition, β -amyloid reduction, enhanced cerebral blood flow, and modulation of neurotransmitters (acetylcholine, 5-hydroxytryptamine, dopamine). Despite displaying low toxicity

in models and humans, long-term studies on human toxicity are still pending, making this study an integration of molecular neuroscience and behavioural research. [33]

The anti-inflammatory properties of *Bacopa monnieri* (*Bacopa*), an Ayurvedic medicinal plant recognised for its nootropic benefits. While traditionally used to enhance cognitive functions, *Bacopa* has also been employed in Ayurveda to address inflammatory conditions such as: arthritis. *Bacopa*'s potential to inhibit the release of pro-inflammatory cytokines from microglial cells in the brain, crucial contributors to central nervous system inflammation.

Various *Bacopa* extracts were tested on N9 microglial cells to assess their impact on inhibiting the release of inflammatory cytokines, specifically TNF- α and IL-6. **Table 5. Table 12.** Additionally, the study examined the extracts' effects on signaling enzymes associated with inflammatory pathways in the central nervous system (CNS).

The results indicated that *Bacopa* extracts, including tea, infusion, and alkaloid extracts, as well as Bacoside A, effectively suppressed the release of TNF- α and IL-6 **Table 11. Table 12.** from activated microglial cells. Additionally, these extracts demonstrated inhibitory effects on enzymes related to inflammation in cell-free assays, targeting caspase-1, caspase-3, and matrix metalloproteinase-3.

Hence, *Bacopa* exhibits anti-inflammatory properties by limiting the release of inflammatory cytokines from microglial cells and inhibiting enzymes associated with brain inflammation. [Thus the potential of *Bacopa* as a valuable source for novel therapeutics in treating various CNS disorders characterised by inflammation. [34]

Bacopa monnieri (BM), an integral part of traditional Ayurvedic medicine, has been renowned for its diverse therapeutic properties, including memory enhancement, anti-inflammatory, analgesic, antipyretic, sedative, and antiepileptic effects, and has been used for centuries. Extensive research has been conducted on the plant, its extracts, and the major active components known as bacosides, revealing their neuropharmacological benefits, particularly in terms of nootropic action. Several studies have explored additional pharmacological effects such as: anti-inflammatory and cardiogenic properties associated with BM preparations. Given the significant activities demonstrated by this plant, it is imperative to further investigate recently observed actions. Additionally, encouraging additional clinical studies is crucial to uncover any potential side effects and interactions between this herbal medicine and synthetic drugs. **Table 10.** [35]

Exploring the cognitive impacts of a unique extract from *Bacopa monnieri* (CDRI08: KeenMind): a comprehensive study spanning a decade of research at Swinburne University. **Table 11.** *Bacopa monnieri* (BM), a water-dwelling herb from India, has a rich history in traditional Ayurvedic medicine, particularly in addressing memory and inflammation-related concerns. Certain BM extracts that have undergone extensive testing, including *in vitro*, animal, and human clinical studies, have been launched in recent advancements. Numerous research investigations have employed a specific BM extract (CDRI08) to investigate its processes and effectiveness. The results of these studies indicate that CDRI08 has diverse impacts on the human brain. Positive outcomes suggest that it may be useful in improving cognition in the elderly and those suffering from neurodegenerative diseases. [36]

Short-term enhancement of executive function in older adults through antioxidant supplementation: insights from the BLA twelve study

Enhancement of executive function following short-term intake of an antioxidant blend comprising *Bacopa*, Lycopene, Astaxanthin, and Vitamin B12: The BLA twelve investigation. Recent attention has been directed towards antioxidants as potential agents for preventing the onset and progression of cognitive decline. A double-blind, randomised, controlled study aimed to assess the impact of a daily antioxidant mixture on cognitive function in healthy older adults. After a one-week run-in period, 80 participants aged 60 or older, without signs of cognitive dysfunction, were randomly assigned to either a blend of four bioactive compounds (*bacopa*, lycopene, astaxanthin, and vitamin B12) or a matched placebo, taken orally once a day for 8 weeks. The primary objective was to evaluate changes in trail making test (TMT) scores from baseline to 8 weeks, with a hierarchical analysis of TMT-B, TMT-A, and TMT-B minus TMT-A. TMT-B increased in the control group (+3.46 s) but decreased in the active group (-17.63 s), with a treatment difference favouring the active group (-21.01 s, 95% C.I. -26.80 to -15.2, $p < 0.0001$). The decrease in TMT-A was significantly higher in the active group (-6.86 s) compared to the control group (-0.37 s). TMT-B minus TMT-A increased in the control group (+3.84 s) but decreased in the active group (-10.46 s). **Table 13.** Additionally, the increase in letter fluency in the verbal fluency test (VFT) was significantly higher in the active group and statistically significant (+5.28 vs. +1.07 words; $p < 0.001$). These findings suggest that regular dietary supplementation with *bacopa*, lycopene, astaxanthin, and vitamin B12 may be an effective approach to counteract cognitive changes associated with aging. **Table 10. Table 11. Table 12. Table 13.** [37]

Table 10. Studies on *Bacopa monnieri* and cognitive function in animal models.

References	Study	Objective and major findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	OBX Mice Study	Investigate the impact of <i>Bacopa monnieri</i> alcoholic extract on cognitive deficits in olfactory bulbectomised (OBX) mice. (Olfactory bulbectomy (OBX)) BM improved non-spatial short-term memory, spatial working memory, and long-term fair memory. Beneficial effects on short-term memory blocked by muscarinic receptor antagonist. BM reversed OBX-induced neurochemical and histological alterations. Enhanced synaptic plasticity-related signaling and brain-derived neurotrophic factor transcription. Protected cholinergic systems from OBX-induced damage.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Adolescent Mice Study	Explore the effects of <i>Bacopa monnieri</i> extract on spatial working memory in adolescent mice. BM extract improved spatial working memory with sustained benefits after treatment discontinuation. Increased hippocampal neurogenesis and altered gene expression related to neurogenesis observed. Bacopaside I, an active component, promoted proliferation of neural progenitor cells <i>in vitro</i> .

[5] [77] [63] [40] [66] [70] [44] [8] [7]	Saponins and Triterpene Glycosides studies	Identify and assess the effects of newly identified saponins and triterpene glycosides from <i>Bacopa monnieri</i> . Saponins (bacopasides IX-XI) and triterpene glycosides exhibited nootropic and antidepressant effects, respectively, in mice.
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Table 11. Studies on *Bacopa monnieri* and anti-tumour effects.

References	Study	Objective and major findings
[32]	Bacopaside II Study	Explore the anti-tumour potential of bacopaside II, a purified extract from <i>Bacopa monnieri</i> , in colon cancer cells. Bacopaside II significantly reduced the growth of colon cancer cells. Induced cell cycle arrest and apoptosis in different colon cancer cell lines. Higher expression of Aquaporin-1 (AQP1) observed in HT-29 cells. Potential implications for novel therapeutics in colon cancer treatment.

Table 12. Comprehensive, extensive research and analysis on *Bacopa monnieri*.

References	Study	Objective and major findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Neuropharmacology	Provide a comprehensive view of the neuropharmacology of <i>Bacopa monnieri</i> (BM). Explore behavioural research and potential neuromolecular mechanisms underlying BM's cognitive benefits. Highlight multiple mechanisms, including antioxidant neuroprotection, acetylcholinesterase inhibition, and modulation of neurotransmitters. Emphasise the need for further long-term studies on human toxicity.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [34] [5]	Anti-Inflammatory properties	Investigate the anti-inflammatory properties of <i>Bacopa monnieri</i> . Explore <i>Bacopa</i> 's potential to inhibit the release of pro-inflammatory cytokines from microglial cells. Various <i>Bacopa</i> extracts effectively suppressed release of TNF- α and IL-6. Inhibitory effects on enzymes related to inflammation in the central nervous system.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Therapeutic properties	Provide an overview of the diverse therapeutic properties of <i>Bacopa monnieri</i> . Highlight neuropharmacological benefits, including memory enhancement, anti-inflammatory, analgesic, and sedative effects. Emphasise the need for further clinical studies to uncover potential side effects and interactions.
[5] [77] [63] [40] [66] [70] [44] [8] [7] [36]	Cognitive impacts	The cognitive impacts of a unique <i>Bacopa monnieri</i> extract (CDRI08: KeenMind) based on a decade of research. Focus on mechanisms and effectiveness of CDRI08 in enhancing cognition among the elderly and individuals with neurodegenerative conditions.

Table 13. Antioxidant blend study on cognitive function in older adults.

References	Study	Objective and major findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Antioxidant blend study	Assess the impact of a daily antioxidant blend (<i>Bacopa</i> , Lycopene, Astaxanthin, and Vitamin B12) on cognitive function in healthy older adults. Significant improvements observed in trail making test (TMT) scores, particularly TMT-B. Decreased TMT-A and TMT-B minus TMT-A in the active group compared to the control group. Increased letter fluency in the verbal fluency test (VFT) in the active group. Suggested potential effectiveness in counteracting cognitive changes associated with aging.

Evaluating *Bacopa monnieri*'s cognitive enhancement and neuroprotective potential in schizophrenia models: insights from rat studies

Assessment of the effectiveness of *Bacopa monnieri* (Linn.) Wettst. as a nootropic, neuroprotective, or antidepressant supplement: examination of available clinical data. *Bacopa monnieri* (Linn.) Wettst. has a historical use in traditional medicine as a memory-enhancing remedy. *B. monnieri*'s efficacy as a neuroprotective and nootropic agent against various neurological conditions; a meta-analysis was conducted using Jamovi computer software for Mac. Selected studies suggested that *B. monnieri* extracts exhibited some improvements in healthy subjects, measured through tasks like the Auditory Verbal Learning Task, digit span-reverse test, inspection time task, and working memory. Although not always statistically significant, *B. monnieri* demonstrated modest enhancements in subjects with memory loss, with a few neuropsychological tests showing statistical significance. When combined with other plant extracts, *B. monnieri* significantly reduced the effects of Alzheimer's disease and depression. However, these effects cannot be solely attributed to *B. monnieri*. While in one study, *B. monnieri* potentiated the beneficial effects of citalopram, overall, there is limited evidence supporting the memory-enhancing and neuroprotective effects of *B. monnieri*. Future studies comparing its effects with standard drugs are necessary to clinically establish these effects and validate preclinical data. [38]

Potential toxic effects of *Bacopa monnieri* extract in rats, focusing on hematological, biochemical, and histopathological parameters. The acute toxicity test involved a single oral dose of *Bacopa monnieri* extract at 5,000 mg/kg in female rats, monitored for 14 days. A chronic toxicity test, both female and male rats received daily oral doses of *Bacopa monnieri* extract at 30, 60, 300, or 1,500 mg/kg for 270 days. The results indicated no significant adverse effects in the acute or chronic toxicity tests, with normal behaviour, health, and parameter values within the standard range. **Table 15.** Overall, the study suggests that *Bacopa monnieri* extract, even at high doses, did not induce serious undesirable effects or toxicity in rats. [51] The study aimed to investigate the potential cognitive enhancement effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. Rats were

administered PCP or vehicle, and a subset of the PCP group was treated with Brahmi. Cognitive abilities were assessed using the novel object recognition task, and NMDA receptor immunodensity was measured in various brain regions.

Results showed that the PCP group exhibited decreased discrimination ratio (DR), indicating cognitive deficits, along with increased NMDA receptor density in the prefrontal cortex and hippocampal regions (CA1-3). However, the PCP group treated with Brahmi showed a significant improvement in DR, and this was accompanied by a decrease in NMDA receptor immunodensity in the prefrontal cortex and CA1-3. Notably, there was no significant difference in cerebral NMDA immunodensity between the PCP with Brahmi group and the control group.

Thus, Brahmi appeared to mitigate cognitive deficits induced by PCP by normalising NMDA receptor density in specific brain areas, suggesting its potential as a treatment for cognitive impairment in schizophrenia. [56]

The potential cognitive enhancement effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia, focusing on vesicular glutamate transporter type 1 (VGLUT1) density in various brain regions. Rats were administered PCP or vehicle, with a subset of the PCP group receiving Brahmi treatment. Cognitive abilities were assessed using the novel object recognition test, and VGLUT1 density was measured in the prefrontal cortex, striatum, hippocampal regions (CA1 and CA2/3), and dentate gyrus.

Results revealed that the PCP group exhibited decreased discrimination ratio (DR), indicative of cognitive deficits, along with reduced VGLUT1 density in the prefrontal cortex, striatum, CA1, and CA2/3. However, the PCP group treated with Brahmi showed a significant improvement in DR, accompanied by an increase in VGLUT1 density specifically in CA1 and CA2/3. This suggested that Brahmi could alleviate cognitive deficits induced by PCP by normalising VGLUT1 density in these hippocampal regions. [57]

The preventive effects of *Bacopa monnieri* (Brahmi) on cognitive deficits and vesicular glutamate transporter type 1 (VGLUT1) density in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. Rats were divided into three groups: Control, PCP administration, and Brahmi + PCP. Cognitive abilities were assessed using the Discrimination Ratio (DR) from the novel object recognition test, and VGLUT1 optical density was measured in various brain regions.

Results indicated that the PCP group exhibited a significantly decreased DR, indicative of cognitive deficits, along with reduced VGLUT1 density in the prefrontal cortex and CA2/3. The Brahmi + PCP group showed a significant improvement in DR compared to the PCP alone group, alongside a significant increase in VGLUT1 density specifically in CA2/3. This suggested that Brahmi could prevent cognitive deficits induced by PCP by maintaining VGLUT1 density in CA2/3 at a normal level. [58]

The cognitive enhancement and neuroprotective effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. Rats were divided into different groups based on the administration of PCP and Brahmi. Cognitive abilities were assessed using the Discrimination Ratio (DR) from the novel object recognition task, and vesicular glutamate transporter type 2 (VGLUT2) immunodensity was measured in various brain regions.

Results indicated that the PCP group exhibited significantly reduced DR and decreased VGLUT2 density in the prefrontal cortex. Both groups receiving Brahmi, either after PCP administration or before, showed an increased DR score, restoring it to normal levels. This improvement was accompanied by a significant increase in VGLUT2 immunodensity in the prefrontal cortex, suggesting that Brahmi could enhance cognitive function and prevent cognitive impairment by elevating VGLUT2 density in the prefrontal cortex. Therefore, highlights Brahmi as a potential intervention for restoring and preventing cognitive deficits in schizophrenia. [59]

Neuroprotective and cognitive enhancement effects of *Bacopa monnieri* in pcip-induced schizophrenia models: implications for VGLUT3, NMDAR1, and GABAergic neuronal density

The cognitive enhancement and neuroprotective effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. Rats were divided into groups based on PCP administration and Brahmi treatment. Cognitive abilities were assessed using the Discrimination Ratio (DR) from the novel object recognition task, and vesicular glutamate transporter type 3 (VGLUT3) immunodensity was measured in different brain regions.

Results revealed a reduced DR in the PCP group, accompanied by decreased VGLUT3 in all brain areas studied. Both groups receiving Brahmi, either after PCP administration or before, exhibited higher DR scores along with increased VGLUT3 immunodensity in the prefrontal cortex, striatum, and *cornu ammonis* fields 1-3 (CA1-3). **Table 14.** The findings suggest that reduced cerebral VGLUT3 is associated with cognitive deficits in PCP-administered rats. Brahmi administration, either as a restoration or prevention strategy, was linked to increased VGLUT3, indicating its potential as a novel intervention for cognitive deficits in schizophrenia. [60]

The study aimed to investigate the neuroprotective effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia by assessing novel object recognition and cerebral glutamate/N-methyl-D-aspartate receptor subtype 1 (NMDAR1) immunodensity. Rats were divided into groups receiving PCP, Brahmi, or a combination of both.

Results showed a significant reduction in the Discrimination Ratio (DR), indicating cognitive deficit in the PCP group, accompanied by an up-regulation of NMDAR1 in CA2/3 and dentate gyrus (DG). However, Brahmi administration alongside PCP restored the DR to normal levels, concomitant with a significant decrease in NMDAR1 immunodensity in CA2/3 and DG compared to the PCP group.

The findings suggest that cognitive deficits induced by PCP are associated with NMDAR1 up-regulation in specific brain regions, and Brahmi administration before PCP treatment can effectively prevent this cognitive deficit by modulating NMDAR1 levels. Brahmi may serve as a novel neuroprotective agent for preventing cognitive deficits in schizophrenia. **Table 14.** [61]

The study aimed to investigate the cognitive enhancement and neuroprotective effects of *Bacopa monnieri* (Brahmi) in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. The focus was on GABAergic neuronal density, identified by calcium binding proteins (CBPs) calbindin (CB), parvalbumin (PV), and calretinin (CR). Rats were assigned to groups receiving PCP, Brahmi, or a combination of both.

Results revealed a reduced discrimination ratio (DR) in the PCP group, indicating cognitive deficit, alongside decreased CB, PV, and CR in various brain regions. Administration of Brahmi alongside PCP led to increased DR, with elevated CB in the prefrontal cortex and striatum, increased PV in the prefrontal cortex and CA1-3, and increased CR in the prefrontal cortex. The Brahmi+PCP group exhibited a higher DR score with increased CB in all areas, increased PV in the striatum, and increased CR in the prefrontal cortex and striatum.

The study demonstrated the partial restoration of cognitive deficit and neuroprotection by Brahmi in a PCP-induced schizophrenic-like model, suggesting a mechanism involving the augmentation of GABAergic neurons. **Table 14.** [62] **Table 15.**

Table 14. Cognitive enhancement and neuroprotective effects in PCP rat model studies.

References	Study	Objective and major findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - NMDA Receptor Density	Investigate cognitive enhancement effects of <i>Bacopa monnieri</i> in a sub-chronic phencyclidine (PCP) rat model of schizophrenia. Brahmi mitigated cognitive deficits induced by PCP, normalised NMDA receptor density in specific brain areas. Potential treatment for cognitive impairment in schizophrenia.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - VGLUT1 Density	Explore cognitive enhancement effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model of schizophrenia. Brahmi alleviated cognitive deficits induced by PCP, normalised VGLUT1 density in specific hippocampal regions.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - VGLUT1 and Cognitive Enhancement	Investigate preventive effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model of schizophrenia. Brahmi prevented cognitive deficits induced by PCP, maintained VGLUT1 density in specific hippocampal regions.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - VGLUT2 Density	Explore cognitive enhancement and neuroprotective effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model. Brahmi enhanced cognitive function and prevented cognitive impairment, elevated VGLUT2 density in the prefrontal cortex.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - VGLUT3 Density	Investigate cognitive enhancement and neuroprotective effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model. Brahmi restored and prevented cognitive deficits, increased VGLUT3 density in various brain regions.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - NMDAR1 Immunodensity	Explore neuroprotective effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model. Brahmi prevented cognitive deficits induced by PCP, modulated NMDAR1 levels in specific brain regions.
[5] [77] [63] [40] [66] [70] [44] [8] [7]	PCP Rat Model - GABAergic Neuronal Density	Investigate cognitive enhancement and neuroprotective effects of <i>Bacopa monnieri</i> in a sub-chronic PCP rat model. Brahmi partially restored cognitive deficit and neuroprotection, involved augmentation of GABAergic neurons.
[77] [14] [55] [38] [41] [42]	Meta-analysis	Evaluate <i>Bacopa monnieri</i> 's efficacy as a neuroprotective and nootropic agent against various neurological conditions. <i>B. monnieri</i> extracts showed improvements in healthy subjects, measured through tasks like Auditory Verbal Learning Task and working memory. Modest enhancements observed in subjects with memory loss. Significant reduction of Alzheimer's disease and depression effects when combined with other plant extracts. Limited evidence supporting memory-enhancing and neuroprotective effects. Future studies comparing effects with standard drugs are necessary for clinical validation.

Table 15. Toxicity assessment of *Bacopa monnieri* extract in rats.

References	Study	Objective and major findings
[5] [77] [63] [40] [66] [70] [44] [8] [7]	Acute and chronic toxicity tests	Investigate potential toxic effects of <i>Bacopa monnieri</i> extract in rats. No significant adverse effects in acute or chronic toxicity tests. Normal behaviour, health, and parameter values within standard range. <i>Bacopa monnieri</i> extract, even at high doses, did not induce serious undesirable effects or toxicity in rats.

Impact of *Bacopa monnieri* and bacosides on cytochrome P450 enzymes: implications for drug interactions and metabolism

Bacopa monnieri and its constituents, particularly bacosides, possess diverse neuropharmacological properties. Similar to pharmaceutical drugs, certain herbal extracts and their components can impact cytochrome P450 (CYP) enzymes, leading to potential interactions with drugs. The impact of *Bacopa monnieri* standardised extract and its bacosides on five major CYP isoforms was investigated *in vitro* using a luminescent CYP recombinant human enzyme assay. The extract exhibited non-competitive inhibition of CYP2C19, CYP2C9, and CYP1A2, competitive inhibition of CYP3A4, and weak inhibition of CYP2D6. In contrast, the bacosides displayed negligible inhibition of these isoforms. Since *Bacopa monnieri* is orally administered and has a higher concentration in the gut than the liver, it could exert stronger inhibition of intestinal CYPs than hepatic CYPs. At an estimated gut concentration of 600 µg/mL (based on a daily dosage of 300 mg/day), *Bacopa monnieri* reduced the catalytic activities of CYP3A4, CYP2C9, and CYP2C19 to less than 10% compared to total activity. These findings suggest that *Bacopa monnieri* extract may

contribute to herb-drug interactions when co-administered orally with drugs metabolised by CYP1A2, CYP3A4, CYP2C9, and CYP2C19. [39] Interactions between drugs can result in severe adverse events or a reduction in drug effectiveness. These interactions may arise from the inhibition or induction of enzymes involved in drug metabolism in the liver and intestines, such as: cytochrome P450 enzymes (CYPs), as well as transporters like p-glycoprotein. [71] Considering that the concentration of orally ingested *B. monnieri* is expected to be greater in the gastrointestinal tract than in the liver, it has been aimed at assessing the inhibitory impact of this extract on intestinal CYPs, specifically CYP3A4, CYP2C9, and CYP2C19, at a gut concentration. [73] CYP2C19 plays a role in the breakdown of centrally acting antidepressants like: citalopram, clomipramine, and imipramine, as well as anxiolytics such as: diazepam and alprazolam. Additionally, it is involved in the metabolism of anticonvulsants like phenobarbital. [74] Medications metabolised by CYP2C9, such as: the antidepressants amitriptyline and fluoxetine, as well as antiepileptics like phenytoin, can be affected by this enzyme. CYP1A2, another enzyme, is responsible for metabolising antidepressants (amitriptyline, clomipramine, fluvoxamine, imipramine) and antipsychotic drugs (clozapine, chlorpromazine, haloperidol). CYP3A4, the most abundant enzyme, plays a role in the metabolism of around 50% of clinically available drugs, including psychotropics and anticonvulsants. The inhibitory effect of *B. monnieri* extract on CYP2C19, CYP2C9, CYP1A2, and CYP3A4 suggests that co-administration with drugs metabolised by these enzymes could lead to elevated drug plasma levels, potentially causing adverse reactions or toxicities. Additionally, genetic polymorphisms in CYP2C19 and CYP2C9 may further impact individual responses. [75] Cytochrome P450 enzymes play a crucial role in the metabolism of various medications and endogenous substances. Among the CYP isoforms, the CYP3A family is the most prevalent in the liver, comprising at least four isoforms: 3A4, 3A5, 3A7, and 3A43, with 3A4 being the most significant. CYP3A4 is involved in processes such as: detoxification of bile acids, termination of the effects of steroid hormones, and the elimination of phytochemicals found in food as well as the majority of pharmaceutical drugs. [79] [80] [81] **Figure 3. Figure 4. Figure 5. Figure 6. Table 16. Table 17. Table 18. Table 19. Table 20.**

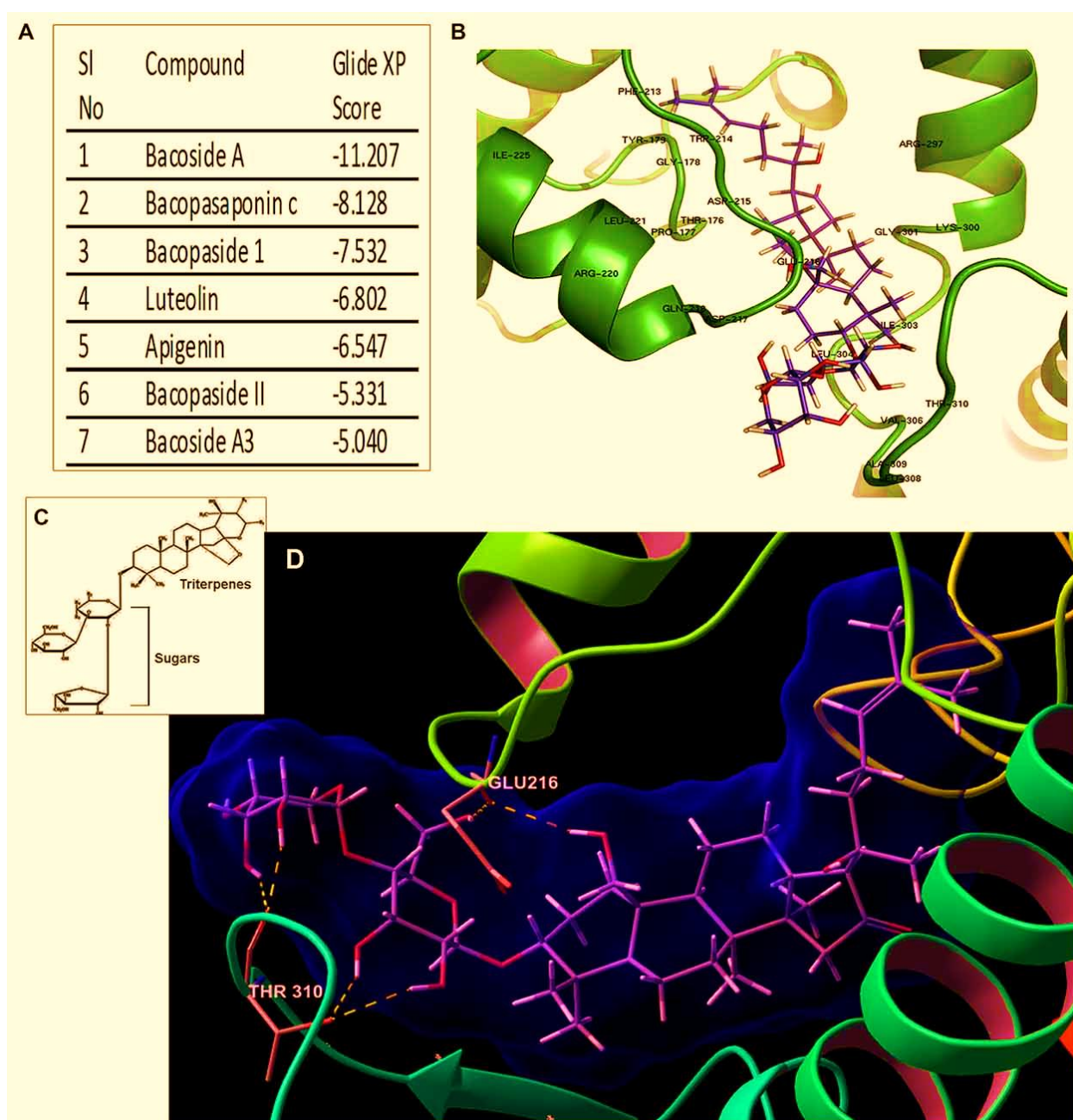


Figure 3. Molecular docking of Bacoside A, Bacopasaponin c, Bacopaside 1, etc. [83]

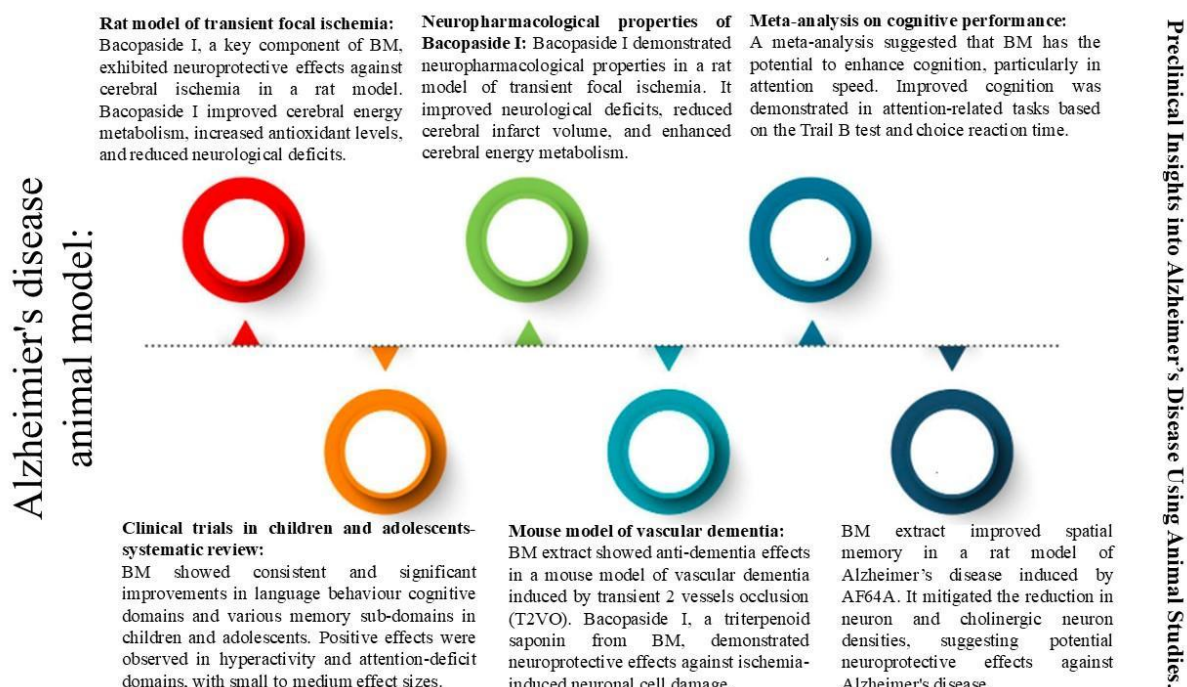


Figure 4. Understanding Alzheimer's disease mechanisms via animal studies.

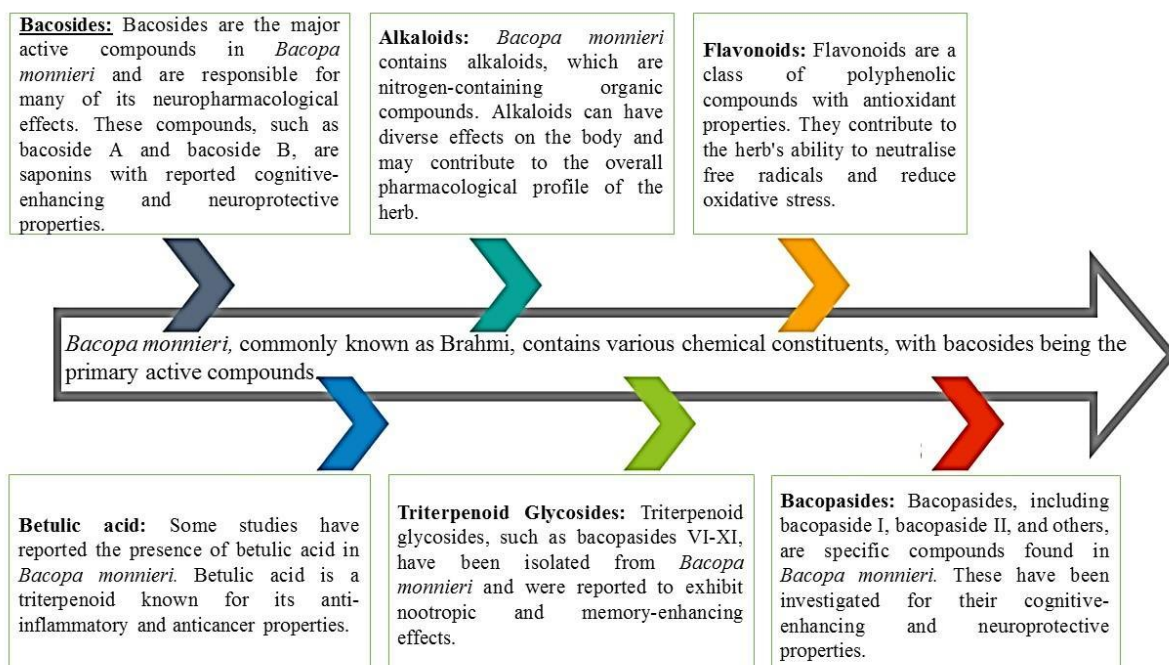


Figure 5. Chemical composition of *Bacopa monnieri*.

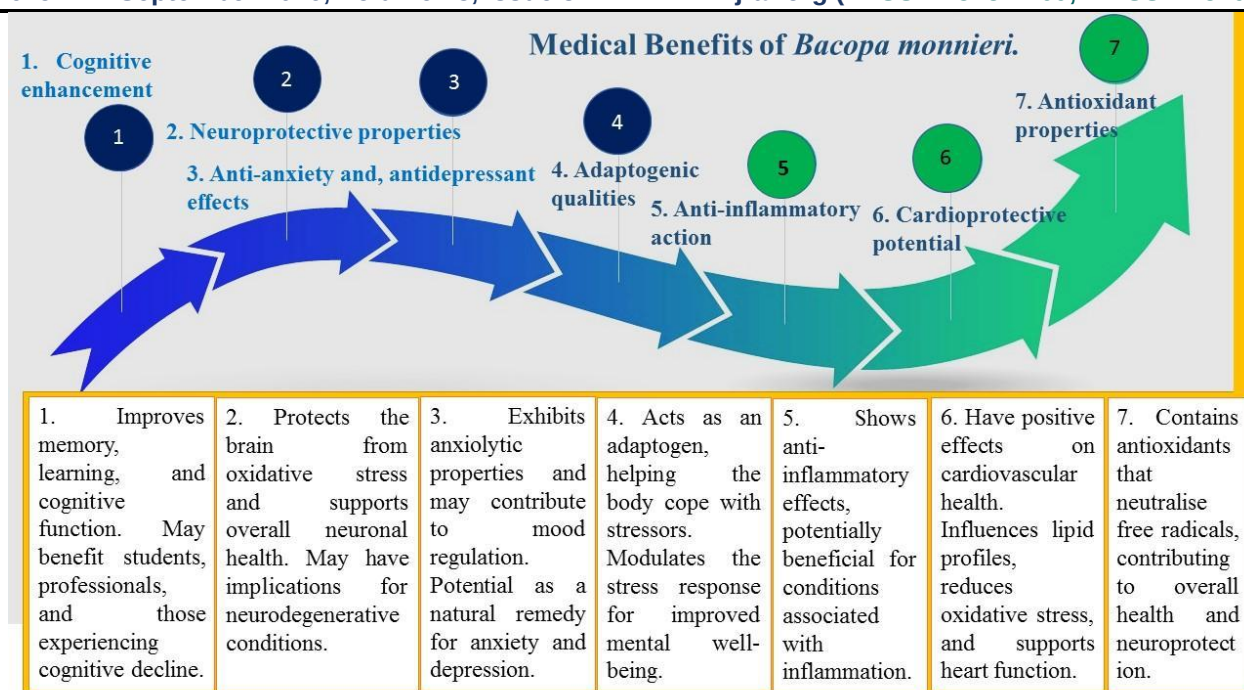


Figure 6. Therapeutics utilisation of *Bacopa monnieri*.

Table 16. *In Vitro* inhibition of Cytochrome P450 (CYP) isoforms by *Bacopa monnieri* extract and Bacosides.

References	CYP isoform	Inhibition type	<i>Bacopa monnieri</i> extract	Bacosides
[39] [73] [75]	CYP2C19	Non-competitive	Inhibited	Negligible
[39] [73] [74] [75]	CYP2C9	Non-competitive	Inhibited	Negligible
[39] [75]	CYP1A2	Non-competitive	Inhibited	Negligible
[39] [73] [75] [79] [80] [81]	CYP3A4	Competitive	Inhibited	Negligible
[39]	CYP2D6	Weak Inhibition	Inhibited	Negligible

Table 17. Estimated inhibition of CYP isoforms by *Bacopa monnieri* extract in the gut at 600 µg/mL.

References	CYP isoform	Estimated inhibition (%)
[39] [73] [75]	CYP2C19	>90
[39] [73] [74] [75]	CYP2C9	>90
[39] [75]	CYP1A2	>90
[39] [73] [75] [79] [80] [81]	CYP3A4	>90

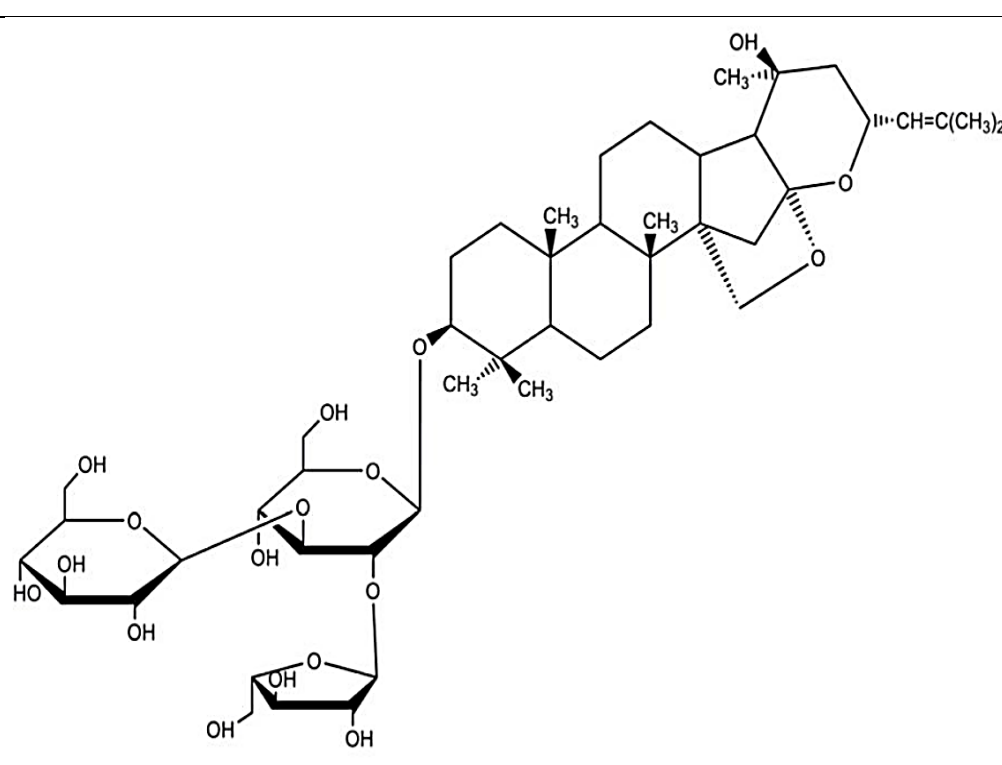
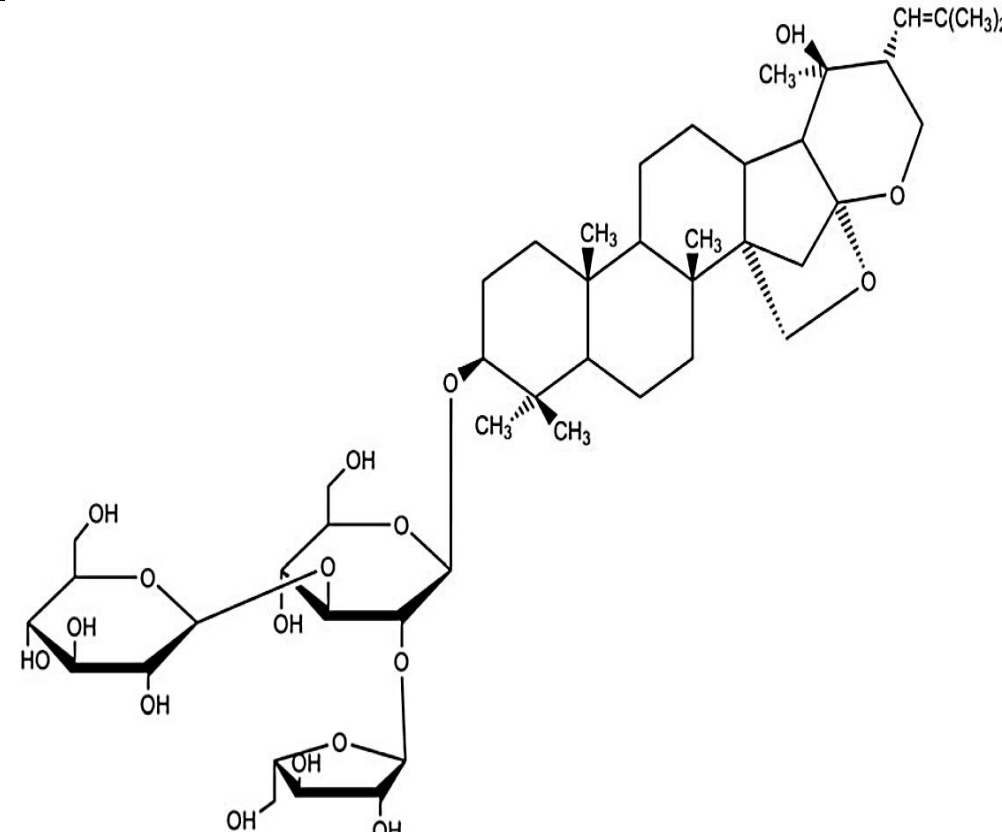
Table 18. Medications metabolised by inhibited CYP isoforms.

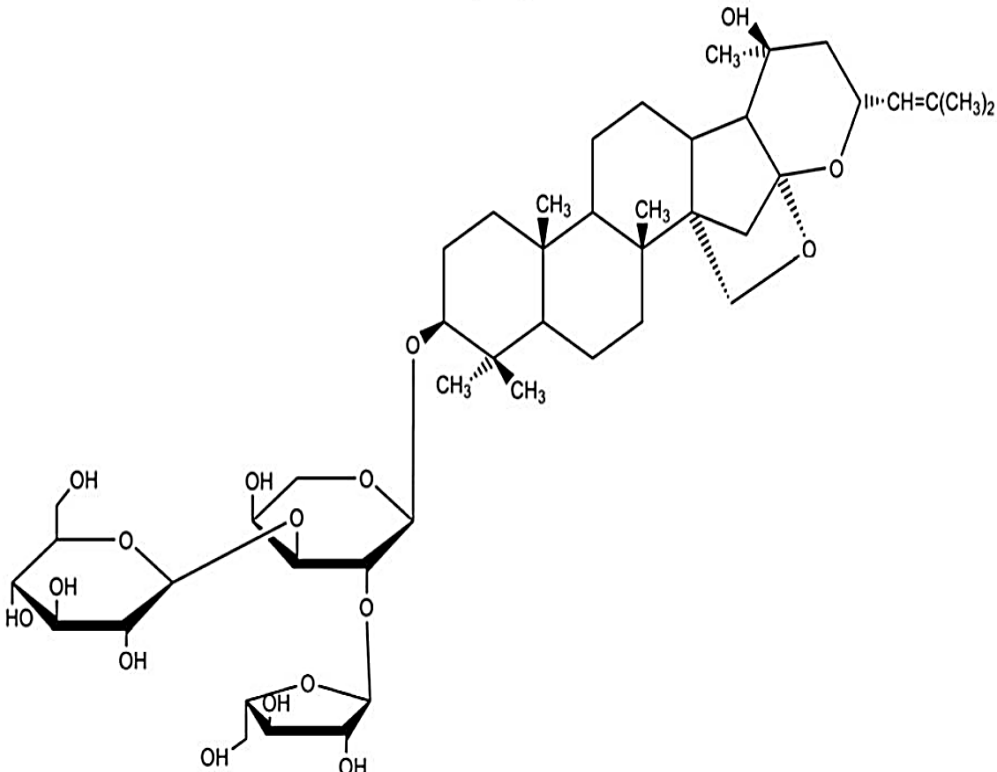
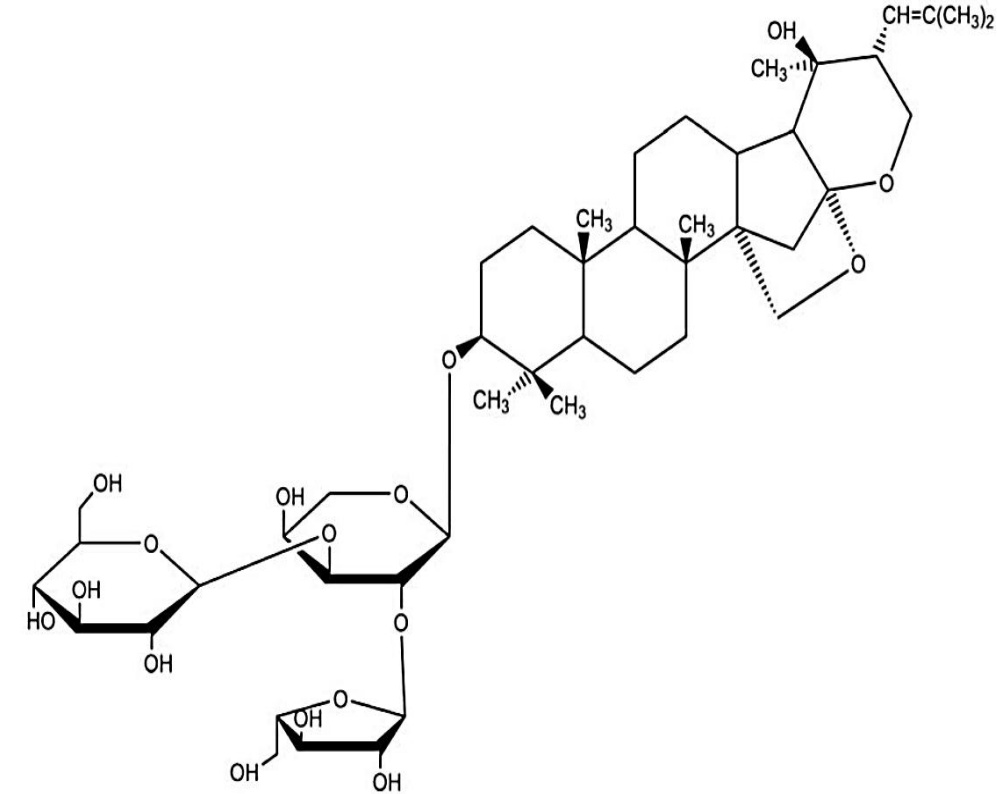
References	CYP Isoform	Medications metabolised
[39] [73] [74] [75]	CYP2C19	Centrally acting antidepressants, anxiolytics, anticonvulsants
[39] [73] [74] [75]	CYP2C9	Antidepressants, antiepileptics
[39] [75]	CYP1A2	Antidepressants, antipsychotic drugs
[39] [73] [75] [79] [80] [81]	CYP3A4	Approximately 50% of clinically available drugs, including psychotropics and anticonvulsants

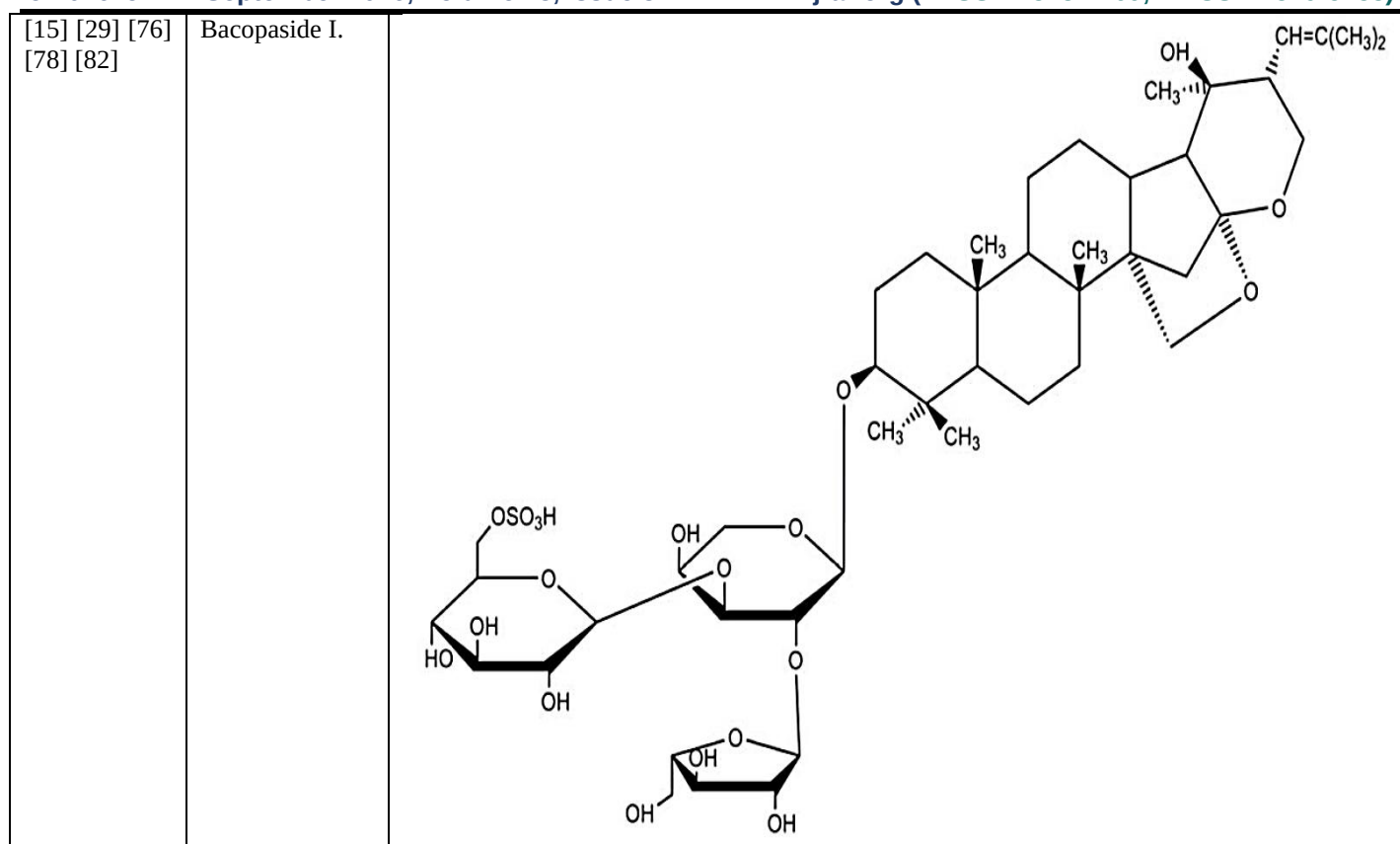
Table 19. Implications of *Bacopa monnieri* extract inhibition on drug metabolism.

References	Implications	Potential consequences
[75]	Elevated drug plasma levels	Adverse reactions or toxicities
[39] [71] [73]	Interaction with drugs metabolised by inhibited CYPs	Altered drug effectiveness, potential side effects
[39] [73] [74] [75]	Genetic polymorphisms in CYP2C19 and CYP2C9	Variable individual responses

Table 20. Chemical constituents present in the *Bacopa monnieri*: [76] [78] [82]

References	Chemical constituents	Structure
[78] [76] [82]	Bacoside A ₃ .	
[32] [76] [78] [82]	Bacopaside II	

[76] [78] [82]	Bacopaside X	 The chemical structure of Bacopaside X is a complex molecule. It features a central steroid-like core with several methyl groups (CH₃) and a side chain containing an ether linkage. Attached to this core are two sugar moieties: a glucose unit (a six-membered ring with multiple hydroxyl groups) and a rhamnose unit (a five-membered ring with a hydroxyl group and a methyl group). The structure is highly detailed, showing stereochemistry with wedges and dashes.
[26] [83] [76] [78] [82]	Bacopasaponin C	 The chemical structure of Bacopasaponin C is very similar to Bacopaside X. It has the same central steroid-like core and side chain. However, the sugar moieties are different: it features a glucose unit and a rhamnose unit, but the stereochemistry and specific substituents differ from those in Bacopaside X. The structure is also highly detailed, showing stereochemistry with wedges and dashes.



Discussion

Cognitive enhancement and neuroprotective effects of *Bacopa monnieri*

The comprehensive data presented highlight *Bacopa monnieri* (BM) as a significant herb with potential cognitive and neuroprotective benefits. Various studies have demonstrated that BM and its constituents, particularly bacosides, offer promising therapeutic effects for cognitive enhancement and neuroprotection.

- I. **Cognitive enhancement:** Clinical and preclinical studies reveal that BM extract and its active components can improve cognitive functions, including memory and executive functions. The efficacy of BM in enhancing non-spatial short-term memory, spatial working memory, and long-term memory is notable. The fact that these cognitive improvements are blocked by muscarinic receptor antagonists suggests that BM's effects might involve cholinergic pathways. Further, BM has been shown to enhance spatial working memory in adolescent mice, with sustained benefits even after treatment discontinuation. The involvement of Bacopaside I in promoting neural progenitor cell proliferation and hippocampal neurogenesis supports the notion that BM's cognitive benefits are linked to neurogenesis.
- II. **Neuroprotective and antidepressant effects:** BM exhibits neuroprotective properties, which are evident in its ability to reverse OBX-induced neurochemical and histological alterations and protect cholinergic systems. BM's antidepressant effects have also been documented, with studies showing that BM or its constituents can reduce symptoms of depression in animal models. The ability of BM to mitigate cognitive deficits in models of schizophrenia, including those induced by phencyclidine (PCP), emphasises its potential as a neuroprotective agent. The restoration of cognitive functions and normalisation of NMDA receptor and vesicular glutamate transporter (VGLUT) densities in these models further supports BM's neuroprotective role.
- III. **Mechanisms of action:** BM's beneficial effects are mediated through several mechanisms, including modulation of neurotransmitter systems (e.g., cholinergic, GABAergic), enhancement of synaptic plasticity, and neurogenesis. Significantly, BM's ability to inhibit inflammatory cytokines and enzymes linked to central nervous system (CNS) inflammation highlights its anti-inflammatory properties, which complement its neuroprotective and cognitive-enhancing effects.
- IV. **Toxicity and safety:** Toxicological studies have shown that high doses of BM extract do not induce significant adverse effects in rats, suggesting a favourable safety profile. However, while BM has demonstrated low toxicity, the need for long-term studies in humans remains crucial to fully understanding its safety profile and potential interactions.
- V. **Drug interactions and cytochrome P450 enzymes:** The impact of BM on cytochrome P450 (CYP) enzymes raises important considerations regarding herb-drug interactions. BM extract exhibits non-competitive inhibition of several major CYP isoforms, including CYP2C19, CYP2C9, and CYP1A2, with competitive inhibition of CYP3A4 and weak inhibition of CYP2D6. This inhibition suggests that BM could influence the metabolism of drugs processed by these enzymes, potentially leading to elevated drug plasma levels and an increased risk of adverse reactions. The finding that BM may exert stronger inhibition of intestinal CYPs than hepatic CYPs is particularly relevant for drugs metabolised in the gut.

Clinical implications

The findings signify that BM's potential as a therapeutic agent for cognitive enhancement and neuroprotection. The herb's diverse effects on memory, neuroprotection, and mood disorders suggest it could be beneficial for managing conditions such as: dementia, Alzheimer's disease, and depression. However, the potential for drug interactions necessitates caution when BM is co-administered with medications metabolised by CYP enzymes. Clinicians should consider this interaction risk, especially in patients taking drugs that are substrates of CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Future directions

Further research is warranted to validate BM's clinical efficacy, explore its mechanisms of action in greater depth, and assess its long-term safety and interaction profile. Clinical trials comparing BM with standard pharmacological treatments will be essential for establishing its therapeutic potential and ensuring safe integration into treatment regimens. Investigating BM's impact on genetic variations in CYP enzymes and its potential interactions with other commonly used drugs will also provide valuable insights for personalised medicine approaches.

In summary, *Bacopa monnieri* shows considerable promise as a nootropic and neuroprotective agent, with various studies supporting its cognitive and mood-enhancing effects. Its potential for drug interactions emphasises the need for careful consideration in clinical use, highlighting the importance of ongoing research to optimise its therapeutic benefits while minimising risks.

Future scope

Future studies may focus on the development of suitable and rapid-release formulations of the drug to achieve improved therapeutic performance and patient compliance. In addition, the design and optimisation of **transdermal drug delivery systems (TDDS)** represents a promising area for future research, with the potential to enhance drug permeation, provide sustained and controlled drug release, and improve overall therapeutic efficacy. Further investigations may explore various formulation approaches and delivery platforms to identify an optimised system with desirable physicochemical, pharmacokinetic, and therapeutic characteristics. Further to this, future research may explore the incorporation of **natural bioenhancers and functional ingredients** into different drug formulations to investigate their potential role in enhancing drug activity, absorption, bioavailability, and metabolism, particularly in the management of cognitive disorders. Natural ingredients such as: **mango, banana, strawberry, honey, tamarind, moringa leaves, pineapple, and lemon, rose sharbat (sherbet)** may be investigated as potential supportive agents based on their reported nutritional, antioxidant, and bioactive properties. The synergistic potential of such natural components with the herbal drug may be evaluated through appropriate formulation development, *in-vitro*, *ex-vivo*, pharmacokinetic, and *in-vivo* studies. Such investigations could provide a novel approach toward developing multifunctional drug delivery systems with improved therapeutic potential for cognitive diseases.

Potential Herbal and Pharmacological Combinations of *Bacopa monnieri* with Similar-Acting Drugs.

1. *Centella asiatica* (Gotu Kola/Mandukaparni) [88] [92].

Centella asiatica (L.) Urban is an important medicinal herb traditionally used in the Indian system of medicine and commonly known as Gotu Kola or Mandukaparni. It belongs to the family Apiaceae and is frequently associated with the name "Brahmi" in traditional literature, although the botanical identity of Brahmi is also attributed to *Bacopa monnieri*. Other botanical names historically associated with the plant include *Hydrocotyle asiatica*. The herb is widely distributed in moist environments, particularly near ponds, streams, riverbanks, and other areas with adequate soil moisture. In Ayurveda, Mandukaparni is regarded as a Medhya Rasayana, a category of medicinal substances traditionally associated with intellect, memory, mental performance, and rejuvenation.

The traditional Ayurvedic description of Mandukaparni emphasises its potential effects on cognition, vitality, complexion, digestion, and general physiological strength. The Charaka Samhita-India describes the juice of Mandukaparni among the Medhya Rasayana preparations and attributes to it properties related to longevity, disease resistance, strength, digestive capacity, complexion, and intellectual function. The classical description is given as follows:

मण्डूकपर्णः स्वरसाः प्रयोज्यः... आयुःप्रदानायामयनाशनानि बलाग्निवर्णस्वरवर्धनानि।
मेध्यानी चैतानि रसायनानि... ॥३१॥

According to the classical interpretation, the fresh juice of Mandukaparni is traditionally used as a rejuvenative preparation and is associated with the maintenance of intellectual function, physical strength, digestive capacity, skin health, and voice. These traditional attributes have contributed to the continued interest in *C. asiatica* as a medicinal plant with potential neurological, dermatological, and systemic applications.

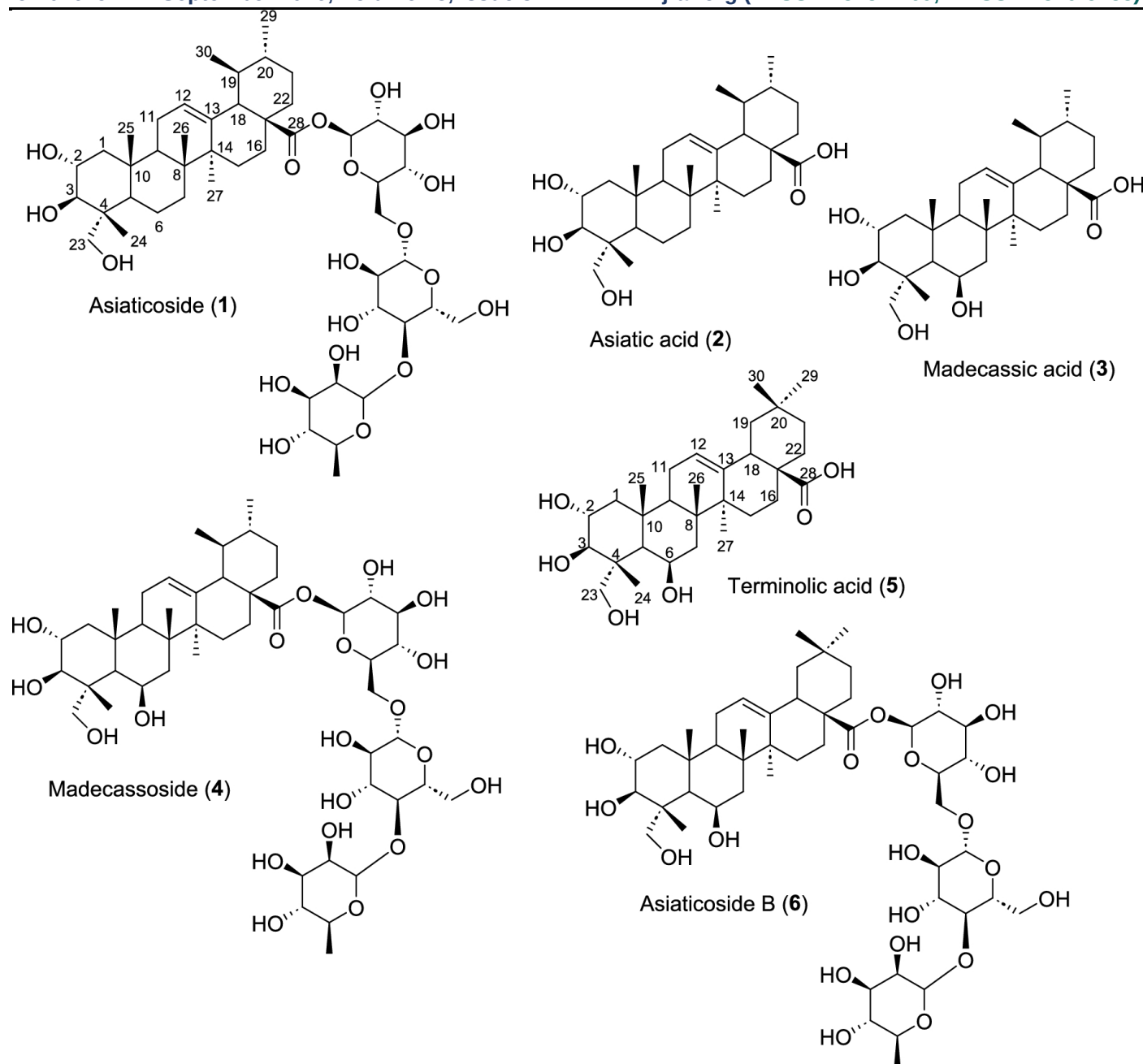


Figure 7. Phytochemical structures of the major bioactive triterpenoids of *Centella asiatica*. Chemical structures of madecassic acid, asiatic acid, madecassoside, and asiaticoside, the principal pentacyclic triterpenoid constituents associated with the pharmacological and dermatological activities of *C. asiatica* along with other [93] [94] [95].

Traditional respiratory applications

Mandukaparni has also been described in Ayurvedic literature in relation to respiratory disorders, including Kasa (cough) and conditions associated with persistent respiratory symptoms. A traditional formulation involving the juice of Mandukaparni with milk is described in classical literature. The relevant textual passage is:

पिबेन्नागबलामूलस्यार्धकर्षाभिवर्धितम् ॥ ११८ ॥

पलं क्षीरयुतं मासं क्षीरवृत्तिरनन्नभुक् ।

एष प्रयोगः पुष्ट्यायुर् बलवर्णकरः परम् ॥ ११९ ॥

मण्डूकपर्ण्याः कल्पोऽयं यष्ट्या विश्वौषधस्य च ॥

pibennāgabalāmūlasyardhakarṣābhivardhitam ॥ 118 ॥

palaṃ kṣīrayutaṃ māsaṃ kṣīravṛttiranannabhuk ।

eṣa prayogaḥ puṣṭyāyurbalavarṇakaraḥ param ॥ 119 ॥

This classical formulation is traditionally regarded as a nourishing and rejuvenating intervention. Such descriptions should be understood within the context of Ayurvedic therapeutic practice and should not be interpreted as evidence of established treatment efficacy for chronic respiratory diseases.

Dermatological and wound-healing relevance

The traditional use of *C. asiatica* extends considerably to skin health and wound management. Ayurvedic texts describe Mandukaparni in the context of Kushta and other dermatological conditions. Its traditional applications have subsequently attracted pharmacological interest because extracts of the plant contain several bioactive constituents that may influence connective-tissue formation, inflammatory responses, and tissue repair.

Experimental investigations have particularly focused on the wound-healing properties of *C. asiatica*. Constituents such as asiaticoside and related triterpenoids have been investigated for their effects on fibroblast activity, collagen synthesis, extracellular-matrix organisation, and repair of damaged tissue. Consequently, the plant has been studied in relation to wound healing, scar formation, burns, and other conditions involving abnormal or delayed tissue repair. Traditional topical preparations may involve the herb alone or its incorporation into herbal oils, ghee-based preparations, or other formulations.

Ayurvedic pharmacodynamic profile

From an Ayurvedic perspective, Mandukaparni is characterised by Tikta rasa (bitter taste), Laghu guna (light quality), Sheeta virya (cool potency), and Madhura vipaka (sweet post-digestive effect). These characteristics are traditionally considered relevant to its effects on Pitta and Kapha and to its rejuvenative and cognitive properties. Its distinctive Prabhava is described as Medhya, reflecting its traditional association with intellectual and cognitive functions.

The herb is traditionally classified as a Rasayana, indicating its use in approaches aimed at maintaining vitality and supporting healthy aging. Traditional indications include conditions involving impaired memory, reduced digestive function, inflammatory disorders, respiratory complaints, dermatological disorders, urinary disturbances, and general weakness. It has also been described as Hrudya (supportive of cardiovascular health), Smrutiprada (associated with memory), and Shothahara (traditionally used for reducing inflammatory manifestations).

Phytochemical constituents and pharmacological interest

Phytochemical investigations have identified several characteristic constituents in *C. asiatica*, including asiaticoside, centelloside, brahmoside, brahmic acid, hydrocotylin, and related triterpenoid compounds. These constituents are considered important contributors to the biological activity of the plant. Modern experimental research has investigated: antioxidant, anti-inflammatory, neuroprotective, anxiolytic, antidepressant, wound-healing, and hepatoprotective activities associated with *C. asiatica* extracts and their constituents.

Of particular interest is the plant's potential influence on the central nervous system. Experimental studies suggest that certain preparations of *C. asiatica* may affect pathways involved in learning, memory, oxidative stress, neuronal survival, and neuroinflammation. These observations provide a pharmacological basis for continued investigation of the traditional Medhya Rasayana classification of the plant. However, findings from experimental models should be distinguished from demonstrated clinical efficacy in humans.

Botanical morphology

Centella asiatica is a small, creeping herbaceous plant that generally develops along the ground and can propagate through stolon-like stems that root at the nodes. Its roots are relatively slender and branched, while the stems are weak, green, and prostrate. The leaves are simple, smooth, and generally borne on elongated petioles. They possess characteristic venation and are frequently described as kidney-shaped to rounded, with shallow lobing. The flowers occur in small umbels and are relatively inconspicuous. Fruits are laterally compressed and characteristically divided into two mericarps.

The morphology of the leaves has contributed to several traditional names of the plant. The Sanskrit name Mandukaparni is commonly interpreted in relation to the resemblance of its leaves to the shape associated with a frog. Other traditional names, including Manduki and Sarasvati, reflect its habitat and its traditional association with intellect and cognition.

Traditional therapeutic applications

In India; Ayurvedic practice, the whole plant is used medicinally, although preparations may vary according to the intended application. Fresh juice, dried powder, decoctions, and formulated preparations are among the traditional dosage forms. Mandukaparni has traditionally been employed for cognitive support, digestive complaints, respiratory symptoms, skin disorders, inflammatory conditions, and general rejuvenation. It has also been incorporated into several classical and proprietary Ayurvedic formulations.

Its traditional action has been described across multiple physiological systems. With respect to the nervous system, it is primarily valued for its association with memory and intellectual performance. Within the digestive system, its bitter taste is traditionally considered supportive of digestive function. In respiratory disorders, it has been traditionally used in conditions characterised by cough and accumulated Kapha. In relation to the skin, it has been employed both internally and externally in traditional approaches to dermatological disorders and wound care.

Potential neuropharmacological significance

The cognitive applications of *C. asiatica* have generated substantial scientific interest. Preclinical studies have explored its possible role in learning and memory, neuronal protection, oxidative-stress regulation, and modulation of neuroinflammatory pathways. Antioxidant activity is considered one possible contributor to its neuroprotective effects, while other investigations have examined its influence on neuronal signaling and synaptic function.

The traditional designation of Mandukaparni as a Medhya Rasayana therefore provides an important conceptual basis for modern research into its neuropharmacological properties. Nevertheless, differences in plant material, extraction procedures, phytochemical composition, dosage, experimental models, and study duration can influence observed outcomes. Standardisation of extracts and well-controlled clinical investigations remain important for establishing the therapeutic relevance of these findings.

Safety and dosage considerations

Traditional dosage recommendations vary according to the preparation, plant material, and therapeutic purpose. Fresh juice and powdered plant material have historically been administered in different quantities, while standardised extracts are available in modern formulations. Because preparations may differ substantially in phytochemical concentration, traditional doses should not automatically be equated with doses of standardised extracts.

Excessive intake has been traditionally associated with symptoms such as drowsiness, fatigue, headache, dizziness, or other unwanted effects. Particular caution may be appropriate when *C. asiatica* is used concurrently with medicines that produce central nervous system depression or sedation. Individuals receiving prescription medicines, pregnant or breastfeeding women, children, and patients with underlying medical conditions should seek professional medical advice before using concentrated preparations.

Conclusion

Centella asiatica (Gotu Kola/Mandukaparni) represents an important medicinal herb with a long history of use in Ayurveda. Its traditional identity as a Medhya Rasayana has stimulated modern research into its potential cognitive, neuroprotective, antioxidant, anti-inflammatory, dermatological, and wound-healing properties. Its phytochemical profile, particularly the presence of triterpenoid constituents such as asiaticoside, provides a basis for investigating several of these biological activities. Although traditional knowledge and experimental findings indicate considerable therapeutic potential, further standardised pharmacological and clinical studies are necessary to establish dose-response relationships, mechanisms of action, efficacy, and long-term safety. Thus, *C. asiatica* remains a promising subject for interdisciplinary research integrating Ayurvedic pharmacology with contemporary neuropharmacological and phytochemical approaches [88] [92].

Nutritional and Therapeutic Significance of *Centella asiatica* [87] [92]

Centella asiatica (L.) Urban, commonly referred to as Gotu Kola, is an important medicinal and edible herb that has been traditionally utilised throughout South and Southeast Asia. In addition to its established position in traditional healthcare systems, the plant is consumed as a leafy vegetable and incorporated into a variety of dietary preparations. Its nutritional and pharmacological importance has been attributed largely to its diverse phytochemical profile, particularly the presence of pentacyclic triterpenoids and other biologically active constituents.

The aerial parts of *C. asiatica* are consumed in several forms, including: fresh leaves, juices, beverages, salads, and other food preparations. The plant provides a range of nutritional components, including vitamins, proteins, minerals, and various secondary metabolites. Phytochemically, it contains: triterpenoid saponins, carotenoids, flavonoids, tannins, polyphenolic compounds, and volatile constituents. The concentration and distribution of these compounds may contribute to the broad biological activities reported for the plant and have stimulated considerable interest in its potential as both a functional food and a source of therapeutic compounds.

Experimental research conducted using cellular and animal models has reported several potentially beneficial biological activities of *C. asiatica*. These include: antioxidant, antimicrobial, antidiabetic, wound-repair, memory-supporting, and neuroprotective effects. The reported neurobiological properties are of particular interest because they suggest possible applications in maintaining cognitive function and protecting neuronal tissues against various forms of cellular stress. Similarly, its effects on wound repair and oxidative balance have encouraged investigation of *C. asiatica* constituents as potential candidates for pharmaceutical and nutraceutical development.

Despite the extensive experimental literature, evidence from well-designed human clinical studies remains comparatively limited for several of the proposed therapeutic applications. Consequently, the precise mechanisms underlying many of the reported effects, appropriate therapeutic doses, long-term safety, and potential toxicity require further systematic investigation. Translation of findings from experimental models into clinically relevant applications will require standardised plant material, chemically characterised extracts, reproducible processing methods, and adequately controlled clinical trials.

Processing and preparation methods can also influence the nutritional and phytochemical characteristics of *C. asiatica*. Factors such as drying, heating, extraction, storage, and other food-processing procedures may alter the concentration or stability of biologically active compounds. Further to this, the chemical profile of the plant can vary according to genetic characteristics, geographical origin,

environmental conditions, soil composition, cultivation practices, maturity, and other biotic and abiotic factors. Comprehensive evaluation of these variables is therefore essential for establishing consistent quality and maximising the nutritional and therapeutic potential of *C. asiatica*. Further multidisciplinary research integrating: phytochemistry, nutrition, pharmacology, toxicology, and clinical science may facilitate the development of standardised *C. asiatica*-based functional foods and therapeutic preparations [87].

Pharmacological and Dermatological Potential of *Centella asiatica* [89] [90][92]

Centella asiatica (L.) Urban is a widely recognised medicinal plant that has been extensively used in traditional systems of medicine, particularly across Asian countries, and has gained increasing scientific and therapeutic interest in Western countries. The growing global attention toward medicinal plants has encouraged extensive investigation into the pharmacological properties, bioactive constituents, molecular mechanisms, therapeutic applications, and safety profile of *C. asiatica*. Among its major phytochemicals, triterpenoid saponins and their corresponding aglycones are considered key contributors to the plant's biological activities. Important constituents include asiaticoside, madecassoside, asiatic acid, and madecassic acid, which have demonstrated considerable pharmacological relevance, particularly in the management of skin disorders.

Accumulating preclinical evidence indicates that *C. asiatica* and its principal triterpenes possess significant dermatological activities, including anti-inflammatory, antioxidant, antimicrobial, and wound-healing effects. Experimental studies conducted using cellular and animal models suggest that these compounds can influence several molecular pathways involved in skin inflammation, tissue repair, extracellular matrix remodeling, and cellular proliferation. In particular, modulation of the NF- κ B, TGF- β /Smad, MAPK, Wnt/ β -catenin, and STAT signaling pathways has been associated with the protective and regenerative effects of *C. asiatica*. Such mechanisms may contribute to its reported therapeutic benefits in conditions including: acne, atopic dermatitis, burns, impaired wound healing, and other inflammatory or degenerative skin disorders.

Beyond dermatological applications, *C. asiatica* has traditionally been employed for a broad range of health conditions, including: chronic ulcers, eczema, psoriasis, leprosy, lupus, varicose ulcers, gastrointestinal disturbances, fever, menstrual disorders, and certain female genitourinary conditions. The plant has also attracted attention for its potential effects on the nervous system, particularly in relation to anxiety reduction, cognitive function, and neuroprotective activity. These diverse applications reflect the multifunctional pharmacological properties of its bioactive constituents and support continued investigation of the plant as a source of therapeutically relevant compounds.

Despite the promising findings from experimental and preliminary clinical studies, important gaps remain in establishing the clinical efficacy and long-term safety of *C. asiatica*. Well-designed, adequately powered, randomised, and long-duration clinical trials are required to determine appropriate therapeutic doses, treatment duration, efficacy across specific dermatological conditions, and potential adverse effects. Further, systematic evaluation of herb–drug and herb–herb interactions is essential because concomitant use of botanical preparations with conventional medicines may influence therapeutic outcomes or safety. Therefore, future research should integrate mechanistic pharmacology with rigorous clinical evaluation to clarify the therapeutic potential, pharmacokinetic characteristics, safety considerations, and clinical applicability of *C. asiatica* and its major triterpenoids. Altogether, current evidence provides a strong foundation for further development of *C. asiatica*-derived compounds as potential therapeutic agents in dermatology and other areas of medicine.

Dermatological and Cosmeceutical Potential of *Centella asiatica* [91] [92]

Centella asiatica (L.) Urb. has attracted considerable attention as a botanical ingredient for dermatological and cosmeceutical applications, particularly because of its reported effects on tissue regeneration, skin-barrier maintenance, scar remodeling, and age-associated cutaneous changes. Recent research published between 2016 and May 2025 has expanded the understanding of its pharmacological actions by examining the molecular pathways underlying skin protection and repair, together with evidence from experimental models, clinical investigations, and novel topical delivery technologies. The biological activity of *C. asiatica* is largely attributed to its triterpenoid constituents, notably asiaticoside and madecassoside, as well as their corresponding aglycones, asiatic acid and madecassic acid. Also, phenolic and other antioxidant constituents may contribute synergistically to its overall dermatological activity.

At the molecular level, *C. asiatica*-derived compounds appear to influence multiple interconnected processes involved in skin homeostasis and aging. Activation of the TGF- β /Smad axis can promote extracellular matrix synthesis and remodeling, thereby supporting tissue regeneration and potentially improving the structural characteristics of aged or damaged skin. Conversely, suppression of pro-inflammatory signaling mediated through NF- κ B and JAK/STAT3 may help reduce persistent cutaneous inflammation. The reported antioxidant and antiglycation properties of the plant may further protect cellular components and dermal macromolecules from oxidative damage and advanced glycation-associated alterations. Experimental evidence also suggests that its bioactive constituents can provide photoprotective effects, potentially limiting ultraviolet-induced cellular and structural damage. These complementary mechanisms may account for the observed improvements in skin integrity, elasticity, hydration, and age-related morphological changes. Transforming growth factor beta (TGF- β)/small mothers against decapentaplegic proteins (Smad)-driven extracellular matrix (ECM) anabolism; nuclear factor kappa B (NF- κ B) and Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) attenuation; mitigation of oxidative/glycation stress; and photoprotection to improve histologic and biophysical skin endpoints.

Clinical investigations, although generally limited by relatively small study populations, differences in formulations, and variation in study designs, provide encouraging evidence for the topical use of *C. asiatica*. Reported outcomes include enhanced skin hydration, reduced transepidermal water loss, improved elasticity, and attenuation of visible wrinkle characteristics. Beneficial changes in scar-related parameters have also been documented, suggesting that *C. asiatica* may have applications extending beyond routine moisturisation and barrier support. Available clinical observations additionally indicate favorable topical tolerability,

although larger randomised controlled trials with standardised preparations and longer follow-up periods are needed to establish definitive efficacy and safety.

A major challenge in utilising the triterpenoid constituents of *C. asiatica* is achieving adequate penetration, stability, and retention within the skin. Consequently, several advanced drug-delivery platforms have been investigated to improve the cutaneous availability of these phytochemicals. Vesicular and lipid-based systems, including transfersomes, liposomes, niosomes, and phytosomes, can facilitate dermal transport and protect unstable bioactive molecules. Similarly, nanoemulsions, hydrogels, microneedle-based systems, and nanofibrous formulations offer opportunities for controlled delivery, prolonged residence, and enhanced localisation within targeted skin layers. These formulation strategies may therefore increase the therapeutic and cosmeceutical value of *C. asiatica* by overcoming limitations associated with conventional topical preparations. On the whole, current evidence supports the potential of *C. asiatica* as a multifunctional botanical for skin repair and aging-related applications, while further standardised clinical research and formulation studies remain necessary to translate its promising pharmacological properties into well-established dermatological therapies [91] [92].

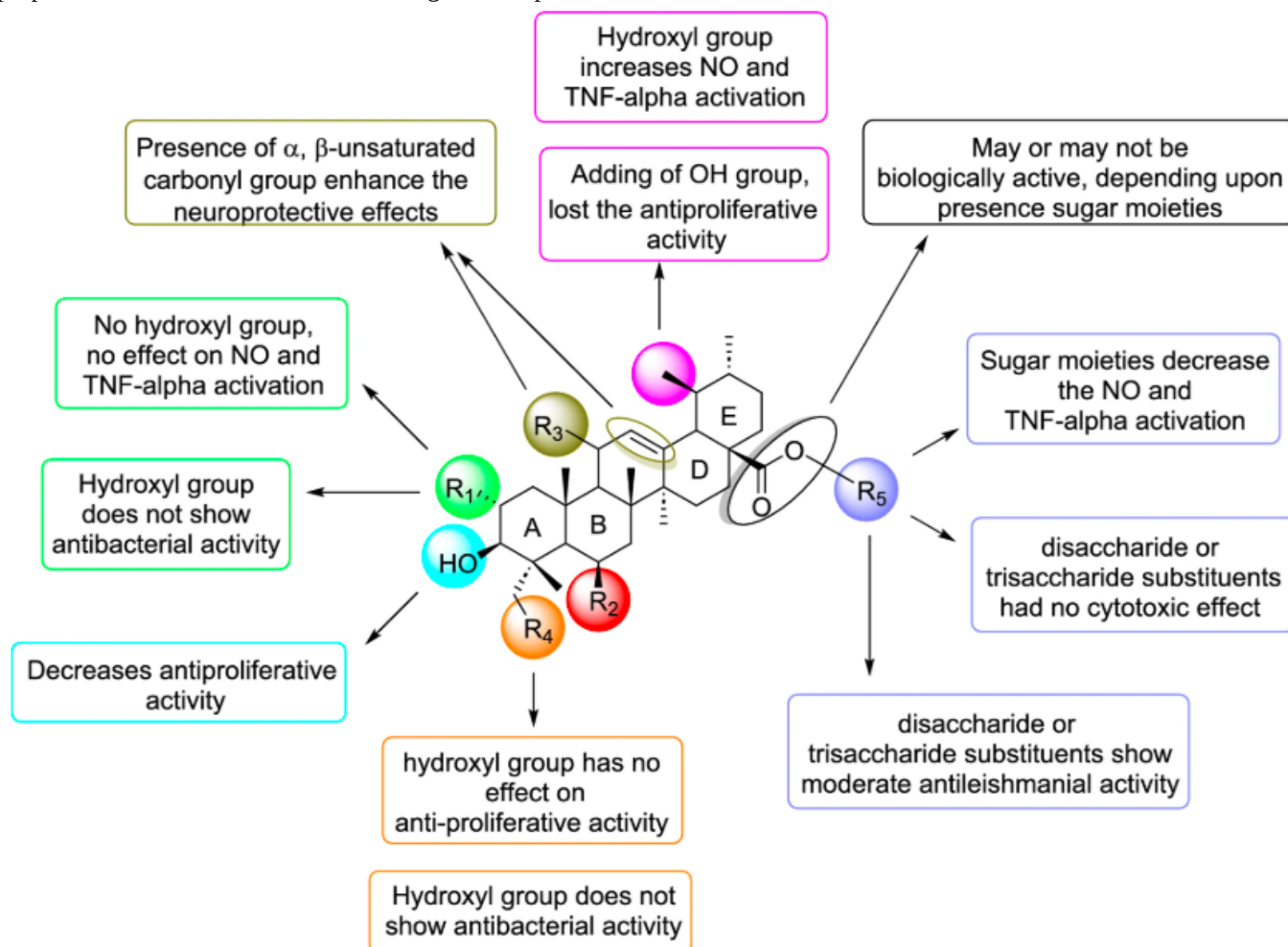


Figure 8. Structure–activity relationship of ursane-type pentacyclic triterpenoids derived from *Centella asiatica*. Representative chemical structures of *C. asiatica*-derived ursane-type triterpenoids highlighting structural features and functional groups that may contribute to their pharmacological and dermatological activities [96].

The major compounds identified in *Centella asiatica* include:

α -Humulene, Arjunolic acid, Asiatic acid, Asiaticoside, Asiaticoside B, Asiaticoside C, Asiaticoside D, Asiaticoside E, Asiaticoside F, Asiaticoside G, β -Caryophyllene, Bicyclogermacrene, Brahminoside B, Campesterol, Castillicetin, Castilliferol, Catechin, Centellasapogenol A, Centellasaponin A, Centellasaponin B, Centellasaponin C, Centellasaponin D, Centelloside E, Centelloside D, Chavicol, Chebuloside II, Chlorogenic acid, Corosolic acid, Cryptochlorogenic acid, 1,3-Dicaffeoylquinic acid, 1,5-Dicaffeoylquinic acid, 3,4-Dicaffeoylquinic acid, 3,5-Dicaffeoylquinic acid, 4,5-Dicaffeoylquinic acid, Epicatechin, 3-Epimaslinic acid, Eugenol acetate, Germacrene B, Kaempferol, Madecassic acid, Madecassoside, Methyleugenol, Myrcene, Myricetin, Naringin, Neochlorogenic acid, Patuletin, Pomolic acid, Quadranoside IV, Quercetin, Rutin, Scheffufoside B, Scheffufoside F, Sitosterol, Stigmasterol, Terminolic acid, and **Ursolic acid** [97].





Figure 9. *Bacopa monnieri* (Brahmi) plant showing its characteristic small leaves, foliage and white flowers [84] [85] [86].

Attention-Deficit/Hyperactivity Disorder: Clinical Features and Management

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition that typically emerges during childhood and may persist into adolescence and adulthood. It is characterised by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, which can interfere with academic performance, family relationships, social interactions, and everyday functioning. Based on the predominant symptom pattern, ADHD is clinically categorised into predominantly inattentive, predominantly hyperactive-impulsive, and combined presentations. Although occasional difficulties with attention or behavioural regulation are common during childhood, ADHD is distinguished by symptoms that are persistent, clinically significant, and associated with impairment across one or more settings. Symptom expression may also change throughout development and can become more apparent as environmental and academic demands increase [103].

The precise etiology of ADHD remains incompletely understood, although evidence indicates that genetic susceptibility has a substantial contribution. Several environmental and developmental factors have also been investigated, including exposure to environmental toxicants such as lead, prenatal exposure to alcohol or tobacco, pregnancy-related complications, childhood head injury, parental mental health, and characteristics of the family environment. ADHD diagnosis is based primarily on a comprehensive clinical assessment rather than a single diagnostic test. Evaluation generally involves assessment of symptom patterns, duration, developmental history, and functional impairment, while also considering alternative or coexisting conditions such as: anxiety, depression, sleep disturbances, and learning disorders [103].

Management of ADHD is individualised according to age, symptom severity, functional impairment, and family circumstances. Evidence-based approaches commonly include behavioural interventions and pharmacological treatment, with treatment plans requiring ongoing monitoring and periodic adjustment. For preschool children, particularly those between four and five years of age, behavioural interventions and parent-focused training are generally emphasised before medication is considered. In addition to formal treatment, healthy lifestyle practices, including regular physical activity, adequate sleep, balanced nutrition, and appropriate management of recreational screen exposure, may contribute to overall well-being and symptom management. Continued epidemiological surveillance and research into diagnosis, treatment patterns, comorbidities, and long-term outcomes remain important for improving the identification and management of ADHD in both children and adults [103].

Deanol (DMAE)

Deanol, also known as dimethylaminoethanol (DMAE), is chemically designated as 2-(dimethylamino)ethan-1-ol, with its molecular structure illustrated in Figure 10 below. This compound occurs naturally in the human brain and is also widely available as a dietary supplement marketed for its potential cognitive-related benefits. In commercial nutritional preparations, DMAE is frequently formulated as a salt of tartaric acid, commonly referred to as DMAE bitartrate [100].

Dietary sources provide relatively small quantities of DMAE, with being among the reported sources. Biochemically, DMAE is considered a precursor related to choline metabolism and may contribute to pathways involved in acetylcholine synthesis. Acetylcholine is an important neurotransmitter associated with several cognitive processes, including learning, memory, attention, and information processing. Through its influence on cholinergic pathways, DMAE has therefore been investigated for its possible role in supporting normal cognitive function [100].

For individuals presenting with ADHD symptoms in the absence of coexisting depression or anxiety, caffeine may be considered as an initial intervention. When the response is inadequate, pycnogenol may be considered as an alternative. If symptom improvement remains insufficient, omega-3 fatty acid supplementation may subsequently be explored, either alone or in combination with caffeine and/or pycnogenol [101].

In patients with ADHD accompanied by anxiety symptoms, inositol may be considered as an initial option, with DMAE or choline potentially incorporated as additional agents. When the clinical response is inadequate, omega-3 supplementation may be considered either as a standalone intervention or as an adjunct to inositol. Vitamin E and/or carnitine may also be incorporated depending on the therapeutic approach [101].

Rhodiola may be less suitable for individuals experiencing anxiety because of its potentially stimulating or activating effects, which could aggravate anxiety-related symptoms in some patients [101].

Dimethylaminoethanol (DMAE) and Choline

Choline, chemically referred to as trimethylaminoethanol, is an important precursor in the biosynthesis of acetylcholine, a neurotransmitter involved in several neurological processes. Dimethylaminoethanol (DMAE), also known as dimethylethanolamine, is metabolically related to choline and serves as a precursor in the pathway leading to its formation. Choline also contributes to the structural stability of cellular membranes and participates in the regulation of neuronal activity [101].

Although acetylcholine has not been directly established as a primary factor in the development of ADHD symptoms, the cholinergic system plays an important role in motor regulation. Interactions between dopaminergic and cholinergic signaling are particularly relevant to motor function, and disruption of this balance has been associated with motor-related adverse effects produced by certain medications, including some first-generation antipsychotic agents. Consequently, modulation of cholinergic activity has been investigated as a possible approach for influencing ADHD-related symptoms [101].

DMAE was previously marketed in the United States under the trade name Deaner for the management of conditions described at the time as minimal brain dysfunction. Its marketing was discontinued in 1980 after regulatory authorities required additional evidence supporting claims of therapeutic efficacy. Nevertheless, placebo-controlled investigations conducted during the 1960s and 1970s reported potential improvements in ADHD-related symptoms among children receiving DMAE at doses of approximately 500 mg/day or greater. DMAE is now less commonly available commercially, whereas choline-containing nutritional supplements are more readily accessible [101]. Because DMAE and choline are metabolically interconnected, supplementation with either compound has been proposed to influence related biochemical pathways [101].

Choline has also been investigated in combination with other nutritional compounds. The combined use of choline and inositol and reported beneficial effects on Attention-deficit/hyperactivity disorder ADHD symptoms. Given the generally favourable tolerability profile of choline, its addition to inositol has been proposed as a potential supplementation strategy in individuals for whom inositol is being considered [101].

Reported choline requirements and supplementation levels vary according to age and clinical context. Studies have examined relatively low doses in adults with limited adverse effects, while commonly cited supplemental amounts range from approximately 425–550 mg/day in adults and 250–350 mg/day in children. Choline is generally considered well tolerated, and adequate dietary intake is also regarded as important during pregnancy because of its role in foetal neurological development. At higher supplemental intakes, adverse effects may include gastrointestinal symptoms such as nausea, diarrhoea, and loose stools. Excessive intake has also been associated in some reports with reduced blood pressure and worsening of depressive symptoms. When choline is

administered together with inositol, conservative doses within the lower portion of the suggested therapeutic ranges may be preferable [101].

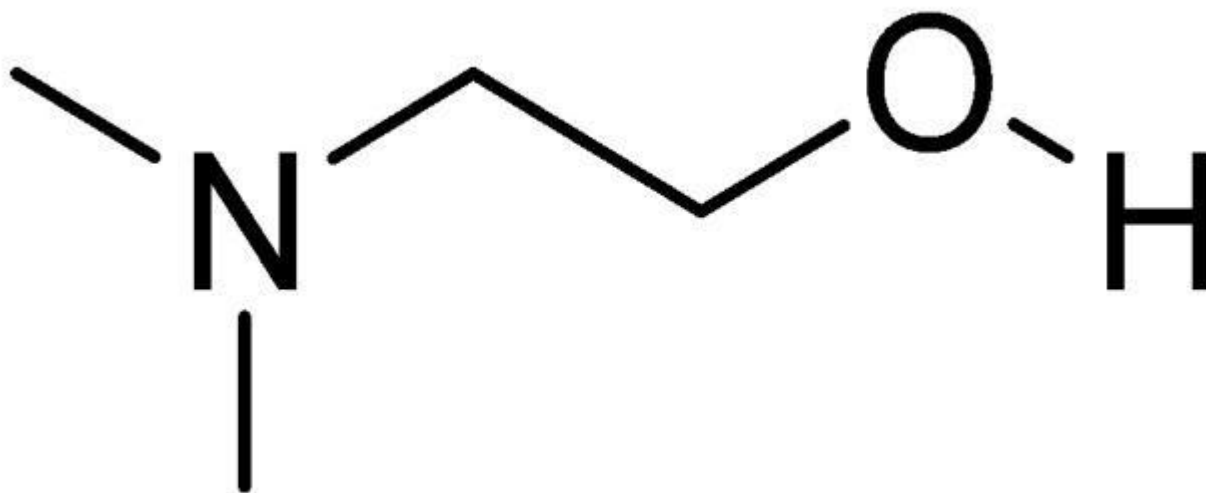


Figure 10. Chemical Structure of Deanol (DMAE) [102].

“Phytochemical Composition and Potential Health Benefits of Figs: A Review of Bioactive Compounds and Functional Properties”

Fig (*Ficus carica*) is a deciduous fruit-bearing tree belonging to the family Moraceae. It is widely cultivated for its edible and nutritionally valuable fruits and has a long history of culinary, traditional medicinal, and cultural significance. The fruit provides important nutrients, including vitamins, minerals, and dietary fibre, while its bioactive constituents have been associated with several pharmacological activities, particularly antioxidant and antibacterial effects.

Figs have been cultivated and consumed for thousands of years and are regarded as one of the earliest domesticated fruit crops. They hold an important place in the traditional Mediterranean diet and are valued for their considerable nutritional and phytochemical composition. Figs contain numerous biologically active compounds, including: flavonoids, phenolic compounds, carotenoids, tocopherols, and other antioxidants, which have historically been associated with their use in traditional medicine. These constituents have been investigated for their possible roles in supporting gastrointestinal, respiratory, metabolic, cardiovascular, and inflammatory health [104].

Recent research has examined the phenolic profile, antioxidant activity, and other functional characteristics of both fresh and dried figs produced in different geographical regions. The concentration and composition of these bioactive compounds can vary considerably depending on factors such as: cultivar, harvest period, degree of fruit maturity, processing conditions, and the specific part of the fig analysed. In addition, increasing attention has been given to the extent to which fig-derived bioactive compounds become accessible during digestion and are subsequently absorbed and utilised by the body [104].

Evidence from experimental studies indicates that fig-derived compounds may have beneficial effects on several aspects of health, including cardiovascular function, glucose regulation, body-weight management, and gastrointestinal health. Regular consumption of figs may also contribute to improved dietary quality and greater intake of certain essential micronutrients, particularly when figs are incorporated into the diet alongside other dried fruits. Nevertheless, although studies conducted in animal models and preliminary human investigations have reported potentially beneficial effects of figs and their extracts, the available evidence remains limited. Further well-designed clinical studies, particularly those evaluating the consumption of whole fig fruit, are needed to establish the extent to which regular dietary intake of figs can contribute to the prevention or management of contemporary health-related conditions [104].

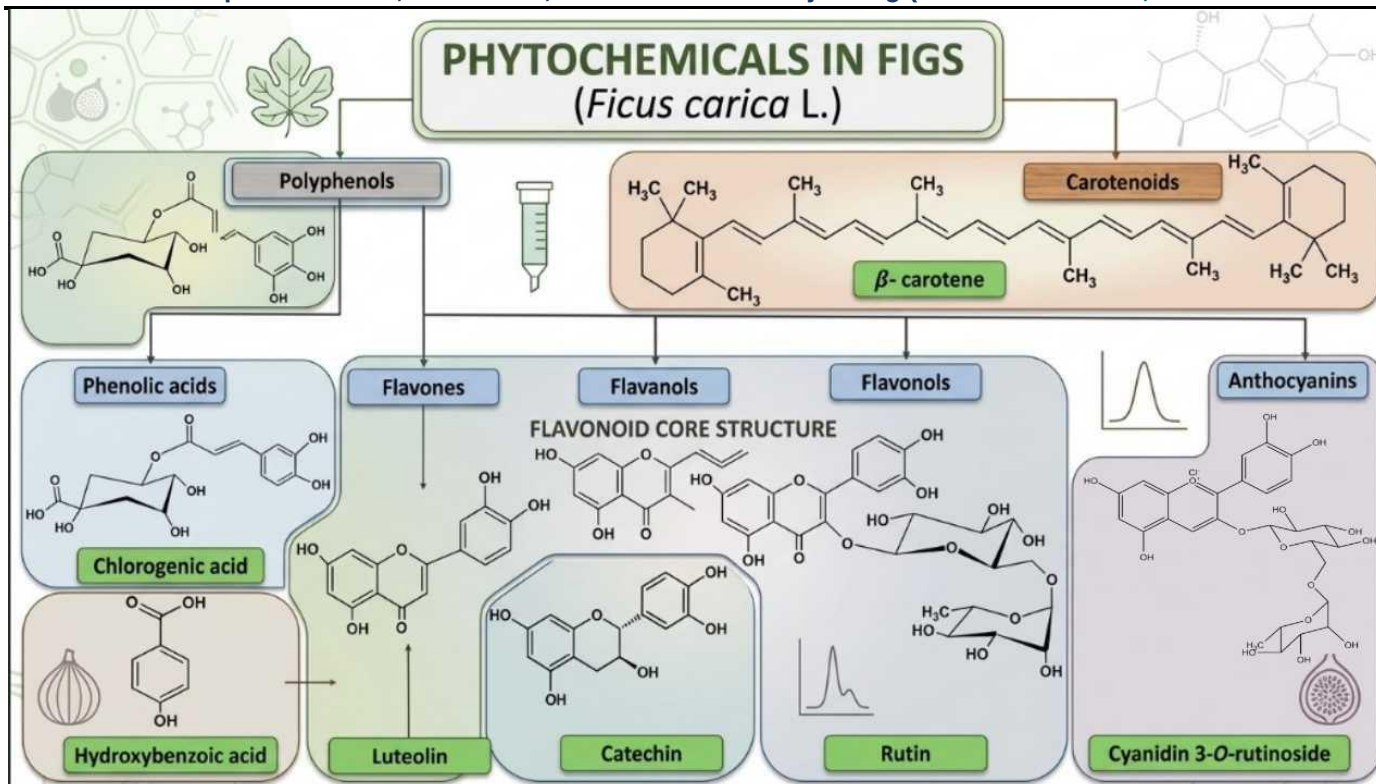


Figure 11. Structure of phytochemicals in fig [104].

Fig (*Ficus carica* L.) is a widely cultivated fruit crop in tropical and subtropical regions and has a long history of dietary and traditional use in the Mediterranean and Middle Eastern regions. Both fresh and dried figs contain a diverse range of phytochemicals, with **phenolic acids and flavonoids** representing the predominant bioactive groups. Important compounds reported in figs include: **gallic acid, chlorogenic acid, rutin, quercetin-3-O-rutinoside, and epicatechin**, which contribute substantially to their antioxidant potential. The concentration of these compounds varies according to fruit variety, colour, tissue type, maturity stage, and processing conditions. Dark-skinned cultivars generally contain greater amounts of phenolic compounds than light-coloured varieties, while the fruit peel is a particularly rich source compared with the pulp. Phenolic concentrations may also increase during ripening, although drying conditions can produce variable effects on individual phytochemicals and carotenoids. The antioxidant activity of figs is closely associated with their phenolic content, supporting their potential use as sources of natural antioxidants. In addition to the fruit, different plant parts, including leaves, roots, latex, and fruits, have demonstrated various biological activities, such as: **antifungal, anthelmintic, acetylcholinesterase-inhibitory, and potential anticancer effects**. Consequently, fig extracts and phytochemical-rich fractions may have applications as **functional food ingredients, natural antioxidant sources, nutraceutical components, and value-added products derived from fruit-processing by-products**. Further investigation, particularly through clinical studies, is needed to establish their health effects in humans and to explore the utilisation of fig-processing waste as a source of valuable bioactive compounds [106].

***Osmanthus fragrans* Fruit Peel: Phytochemicals and Functional Significance [105]**

The fruit peel of *Osmanthus fragrans* (OFF) represents a promising plant-derived source of anthocyanin pigments with potential applications in the food industry. Extraction with acidified ethanol followed by purification using macroporous resin produced an anthocyanin-rich fraction from the dried peel. Analytical characterisation using HPLC–MS/MS identified cyanidin-3-O-rutinoside (C3R) as the major anthocyanin present in the extract. The pigment exhibited pronounced pH-responsive coloration, with a relatively stable red appearance under strongly acidic conditions, particularly between pH 2.0 and 4.0. Its thermal stability was affected by both temperature and pH, while the degradation of C3R was described by first-order reaction kinetics. Further to this, the purified extract demonstrated antioxidant potential in DPPH radical-scavenging and FRAP assays. On the whole, *O. fragrans* fruit peel can be considered a valuable source of naturally occurring anthocyanins, especially C3R, and may have potential for development as a natural red colourant and antioxidant ingredient in acidic food formulations [105].

Scientific Name

The plant investigated is *Osmanthus fragrans*, specifically its **fruit peel (OFF peel)**.

Important Phytochemicals

The major bioactive compound identified in the fruit peel extract is:

Cyanidin-3-O-rutinoside (C3R) – the predominant anthocyanin responsible for much of the red colouration of the purified extract.

Anthocyanins – the principal class of pigments investigated and responsible for the pH-dependent color characteristics.

The extract also contains compounds contributing to **antioxidant activity**, demonstrated through DPPH and FRAP assays.

Uses and Potential Applications

The fruit peel of *Osmanthus fragrans* has potential as a **natural source of anthocyanin pigments**, particularly for use as a colourant in **acidic food products**. Its ability to produce a stable red colour under acidic conditions makes it potentially useful as an alternative to synthetic food colourants. Plus, its antioxidant properties may provide added functional value in food applications [105].

In brief: *Osmanthus fragrans* fruit peel → anthocyanins → mainly C3R → red natural pigment → pH-sensitive → antioxidant activity → potential acidic-food colourant [105].

Figs (*Ficus carica* L.) are nutritionally valuable fruits that can be utilised in both fresh and processed forms. Fresh figs are commonly consumed directly or incorporated into fruit preparations, salads, desserts, bakery products, beverages and cooked dishes, while dried figs are widely used as snacks and as ingredients in products such as jams, preserves, confectionery, cookies, energy bars and other bakery foods. Dried figs may also be processed into fig paste, puree and concentrated products, providing opportunities for value addition and extended storage. From a nutritional perspective, figs are notable for their dietary fibre, potassium, calcium and iron content, along with appreciable amounts of vitamins, amino acids and biologically active phytochemicals. They are naturally low in sodium and contain no cholesterol, while their fat content is also very low. The fruit, particularly its skin, contains phenolic compounds, flavonoids and anthocyanins that contribute to antioxidant activity. Dark-skinned fig cultivars generally contain greater concentrations of these phenolic constituents than lighter-skinned varieties. Thus, the combination of nutritional components and bioactive compounds makes figs a useful ingredient for developing nutrient-rich foods and value-added products [107].

Coconut (*Cocos nucifera* L.) is a multipurpose crop with considerable nutritional, economic and household importance. The tender fruit provides coconut water, which is consumed as a refreshing beverage, while the developing kernel serves as a source of nutrients and energy. Mature coconut kernel is processed to obtain coconut oil, which is widely used in food preparation and in the manufacture of products such as soaps and detergents. Owing to the extensive range of products obtained from different parts of the plant, coconut is often referred to as the “tree of life.” Traditionally, dried coconut kernel (copra) was an important commercial commodity and a major source of coconut oil. However, market demand was affected for several decades by concerns regarding the relatively high saturated fatty acid content of coconut oil, contributing to reduced consumption and lower commodity prices. In recent years, interest in coconut products has increased, particularly in virgin coconut oil and tender coconut, owing to their growing recognition as valuable food products [108].

Dates (*Phoenix dactylifera* L.) have served as an important food source for many civilisations for centuries and continue to be widely consumed, particularly across the Middle East and North Africa. Although date palms are cultivated in numerous countries, production and commercial activity remain largely concentrated in these regions. Global date production exceeds several million tonnes annually; however, only a relatively small proportion is traded internationally. Dates are energy-dense and nutritionally valuable fruits that may be consumed fresh, dried, or processed into a variety of food products. Fruits of dry cultivars generally have better keeping quality and can withstand transportation over long distances and extended storage. In contrast, soft and semi-moist cultivars are highly perishable and may have a short shelf life unless appropriate temperature-controlled handling is maintained from harvest through distribution. Significant postharvest losses can occur as a result of mechanical damage, physiological deterioration, microbial spoilage and insect infestation. Because dates tolerate low storage temperatures well, refrigerated storage and transportation are important approaches for preserving fruit quality. Maintaining suitable low temperatures helps retain colour, flavour and texture, while reducing sugar crystallisation or spotting, fungal and yeast growth, insect activity, syrup formation and undesirable souring in soft and moist cultivars [109].

Phoenix dactylifera L., commonly referred to as date palm, is an ancient fruit crop that has been cultivated for centuries., particularly in the desert oases region. Date fruits are nutritionally important because they provide substantial amounts of carbohydrates and dietary fibre, along with several vitamins and essential minerals. The seeds or pits, which are generally considered a by-product of date processing, also contain appreciable levels of dietary fibre, minerals, lipids and proteins, indicating their potential for value-added utilisation. Beyond their role as a food source, dates have a long history of use in traditional medicine for various health-related conditions. Phytochemical analyses have identified several biologically active constituents in date fruits, including: phenolic compounds, flavonoids, anthocyanins, carotenoids, sterols and procyanidins. Experimental studies have associated these constituents with various biological activities, including antioxidant and free-radical-scavenging effects, as well as: antimicrobial, anti-inflammatory, antimutagenic, gastroprotective, hepatoprotective and nephroprotective properties. Studies conducted under preclinical conditions have also reported potential anticancer and immunomodulatory effects of date fruit extracts, although these findings should not be interpreted as evidence of therapeutic efficacy in humans without appropriate clinical validation [110].

Culinary Uses and Nutritional Value of Figs:

Figs (*Ficus carica* L.) are nutritionally valuable fruits that can be consumed in both fresh and dried forms and are widely utilised in plant-based food preparations. Fresh figs may be eaten directly or incorporated into salads, fruit preparations, desserts, preserves and cooked dishes, while dried figs are commonly used as snacks and as ingredients in bakery products, confectionery, energy bars, breakfast foods, jams and fruit-based spreads. Figs can also be processed into paste, juice, concentrates and other value-added products, providing opportunities for their incorporation into diverse food formulations. Nutritionally, figs are notable for their dietary fibre, potassium, calcium and iron content, along with appreciable amounts of vitamins, amino acids and bioactive compounds. They are naturally low in sodium and contain no cholesterol, while their fat content is generally low. The fruit also contains phenolic compounds, flavonoids, anthocyanins and other antioxidant constituents, with darker-skinned cultivars generally exhibiting greater concentrations of these compounds than lighter-skinned varieties. Many of these phytochemicals are concentrated in the skin and contribute to the antioxidant potential of the fruit. Consequently, regular inclusion of figs as part of a balanced diet may contribute dietary fibre and essential minerals while increasing the intake of naturally occurring antioxidant compounds. Dried figs provide a concentrated source of nutrients and bioactive compounds because water removal increases the concentration of their constituents, although their energy and natural sugar content are also higher per unit weight than those of fresh figs [107].

Nutritional and Functional Importance of Fig Fruits

Fig (*Ficus carica* L.) is a nutritionally important fruit containing appreciable amounts of minerals such as iron, calcium and phosphorus, along with dietary fibre, particularly in the dried fruit. Fresh figs can be incorporated into a variety of plant-based foods, including seasonal fruit salads, smoothies and other fresh preparations. Both the fruits and leaves of *F. carica* contain diverse

bioactive constituents, including phenolic compounds, organic acids and volatile substances, which contribute to their functional and nutritional properties. Traditionally, fig preparations have been utilised in various systems of traditional medicine for managing gastrointestinal disturbances, inflammatory conditions and other health-related disorders. The presence of biologically active phytochemicals has generated scientific interest in the potential role of *F. carica* in supporting health and in the development of functional food products. However, traditional medicinal uses should be distinguished from clinically established therapeutic effects, and further scientific investigation is required to validate specific health claims [111].

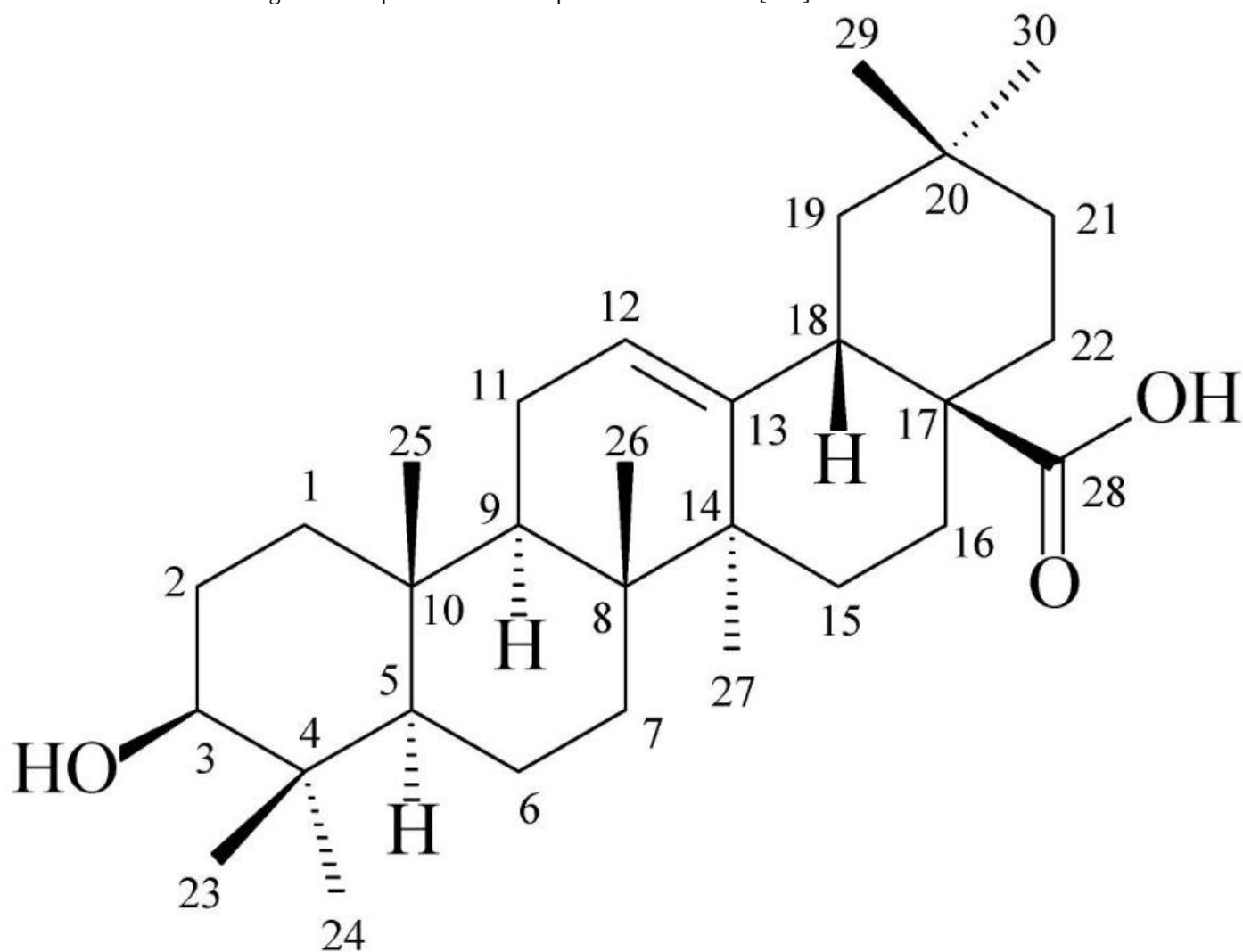


Figure 12. Structure of terpenic acid [112].

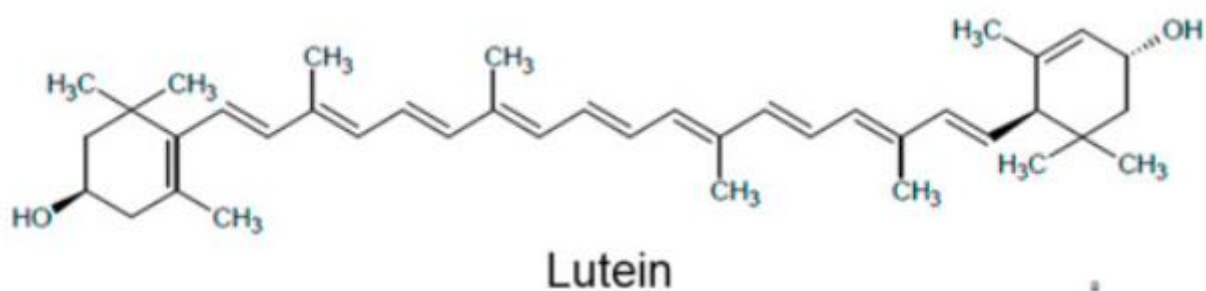


Figure 13. Structure of Lutein [112] [113].

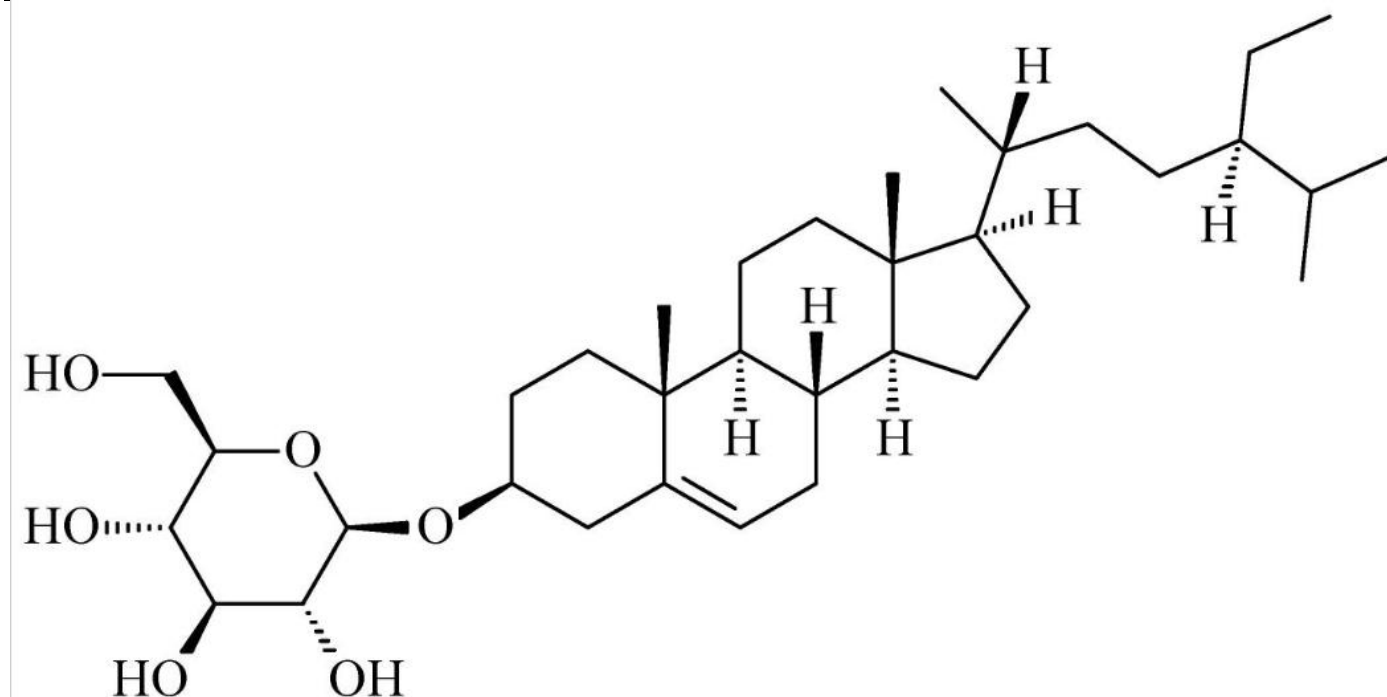


Figure 14. Structure of β -Sitosterol-3-O- β -D-Glucoside, (glycosidic sterol) [112] [114].

Botanical Description and Phytochemical Composition of Date Palm

The date palm (*Phoenix dactylifera* L.) is a dioecious, medium-sized perennial tree characterised by a stout trunk and pinnately compound leaves. Each leaf bears numerous narrow leaflets, with the basal portions of the petiole often modified into spines [115]. The plant produces small, yellowish flowers that are borne on branched spikelets and subsequently develop into date fruits. Depending on the cultivar and stage of maturity, the fruits are generally oval to cylindrical, contain a single seed, and may vary in colour from yellow to reddish shades during the immature stage [115].

Phytochemically, different parts of the date palm contain a diverse range of primary and secondary metabolites, including: carbohydrates, alkaloids, steroids, flavonoids, tannins, vitamins and other biologically active constituents [115]. The phenolic fraction is characterised predominantly by hydroxycinnamic acids, particularly ferulic, sinapic and p-coumaric acids, together with their derivatives, including 5-O-caffeoylshikimic acid (dactyliferic acid) [115]. Several flavonoid compounds and their glycosides, such as luteolin, methyl-luteolin, quercetin and methyl-quercetin, have also been reported, along with flavanols including catechin and epicatechin. Various phenolic acids have been identified in both free and bound forms, including: protocatechuic, vanillic, syringic, ferulic, gallic, p-hydroxybenzoic, caffeic, p-coumaric and o-coumaric acids. Phytochemical investigations have additionally detected several phytosterols, including cholesterol, stigmasterol, campesterol and α -sitosterol [115]. Anthocyanin pigments have been reported particularly in fresh date fruits, whereas lutein represents a major carotenoid constituent, followed by α -carotene [115].

Date seeds contain an appreciable oil fraction composed of several saturated and unsaturated fatty acids, including: oleic, lauric, palmitic, capric, myristic, myristoleic, palmitoleic, stearic, linoleic and linolenic acids. The fruit also provides several vitamins, including small quantities of vitamin C and members of the vitamin B group, such as thiamine, riboflavin and niacin, in addition to vitamin A-related compounds. Enzymatic constituents such as phytase, invertase and peroxidase have also been detected in dates [115]. Other reported phytochemicals include estrone in dried seeds and pollen, while date palm pollen contains compounds such as α -amyrin, triterpenoid saponins and gonadotropic substances. In addition, polysaccharide constituents, including α -D-glucan, heteroxylan and galactomannans, have been identified in different parts of the plant. The broad phytochemical diversity of *P. dactylifera* highlights its potential as a source of nutritionally and biologically relevant compounds [115].

Biological and Pharmacological Activities of *Phoenix dactylifera*

Biological and Pharmacological Activities

Recent experimental investigations have demonstrated that different parts of *Phoenix dactylifera* L., including the fruits, seeds, pits and pollen, possess a range of biological activities. These effects have largely been investigated using *in vitro* models and experimental animals, and the findings indicate that date palm contains several bioactive constituents with potential pharmacological significance [115].

- i. **Antiulcer activity:** Experimental studies have reported a protective effect of date fruit extracts against gastric ulceration. Oral administration of aqueous and ethanolic fruit extracts to rats before ethanol-induced gastric injury reduced the ulcer index and improved histological alterations, including necrosis, haemorrhage, congestion and oedema. Changes in gastric biochemical parameters, including mucin and histamine concentrations and plasma gastrin levels, were also observed. These findings provide experimental support for the traditional use of dates in the management of gastric disorders [115].
- ii. **Anticancer activity:** Polysaccharide fractions isolated from date fruits have demonstrated antitumour activity in experimental models. Date-derived glucans produced a dose-related reduction in tumour development in mice bearing transplanted Sarcoma-180 cells, with pronounced activity reported at the investigated optimum dose. Although these observations indicate potential

- antitumour properties, further mechanistic and clinical studies are required before therapeutic applications can be established [115].
- iii. **Antidiarrhoeal activity:** Aqueous extracts prepared from the spathes of *P. dactylifera* have exhibited antidiarrhoeal effects in experimental animals. Administration of different extract doses significantly reduced castor-oil-induced intestinal transit and the frequency of diarrhoeal episodes in rats. Such findings may contribute to the scientific basis for the traditional use of date palm preparations in gastrointestinal disorders [115].
 - iv. **Effects on gastrointestinal motility:** Extracts obtained from date pulp and pits have been reported to influence gastrointestinal transit in a dose-dependent manner. Water and ethanolic extracts produced changes in intestinal transit time at different concentrations, whereas a dialysed aqueous extract of date pulp produced an opposite response. These variations may be associated with differences in extraction procedures and the specific bioactive compounds present in individual fractions [115].
 - v. **Hepatoprotective activity:** Several experimental studies suggest that date fruit and seed extracts may exert protective effects on the liver. In rats exposed to carbon tetrachloride-induced hepatic injury, pretreatment and post-treatment with aqueous extracts of date pulp or pits reduced the elevation of serum hepatic enzymes, including AST, ALT and ALP, as well as bilirubin concentrations. Histological examination also indicated attenuation of liver tissue damage. Similar protective effects have been reported in thioacetamide-induced hepatic injury, where date extracts helped normalise biochemical markers associated with liver function and oxidative stress. Improvements in glutathione and malondialdehyde levels have further suggested a possible antioxidant component of this hepatoprotective action [115].
 - vi. **Antimutagenic activity:** Date fruit extracts have demonstrated inhibitory effects against chemically induced mutagenicity in bacterial test systems. In particular, the extracts reduced benzo[a]pyrene-induced mutations in *Salmonella typhimurium* strains TA98 and TA100 in a concentration-dependent manner. These observations indicate that compounds present in dates may possess antimutagenic potential under experimental conditions [115].
 - vii. **Antioxidant activity:** The antioxidant capacity of *P. dactylifera* has been associated with its phenolic compounds, flavonoids, vitamins and other phytochemicals. Investigations involving date fruits from different geographical regions have demonstrated a positive association between total phenolic content and antioxidant activity. Aqueous extracts have been reported to inhibit lipid and protein oxidation and to scavenge reactive oxygen species, including superoxide and hydroxyl radicals. Seed extracts have also demonstrated antioxidant effects in experimental models of inflammation, including reduction of elevated malondialdehyde and improvement of antioxidant vitamin levels. Further, date seed oil has shown protective effects against hydrogen-peroxide-induced oxidative damage in human skin tissue cultures. These findings suggest that date palm contains compounds capable of reducing oxidative stress in experimental systems [115].
 - viii. **Effects on the reproductive system:** Experimental research has investigated the influence of date fruits and pollen on male reproductive parameters. Administration of date fruit preparations to laboratory animals has been associated with improvements in sperm concentration, motility, morphology and DNA integrity, together with changes in reproductive organ weights. Other animal studies have reported effects of date extracts on spermatogenesis and reproductive hormone concentrations, including testosterone, follicle-stimulating hormone and luteinising hormone. Date palm pollen has also been investigated for its effects on hormonal and biochemical parameters in normal, castrated and ovariectomised animals. However, these experimental findings should not be interpreted as evidence of established fertility treatment in humans [115].
 - ix. **Anti-inflammatory activity:** Extracts from the edible portion of date fruits and from date seeds have exhibited anti-inflammatory effects in experimental models of arthritis. Methanolic and aqueous fruit extracts reduced inflammatory swelling, while seed extracts produced a lesser but significant reduction in inflammatory response. These effects were accompanied by changes in inflammatory and oxidative-stress-related biochemical parameters, including erythrocyte sedimentation rate, fibrinogen and antioxidant status. The findings suggest that phytochemicals present in date fruits and seeds may contribute to modulation of inflammatory responses [115].
 - x. **Antiviral and antimicrobial-related activity:** Extracts prepared from date pits have demonstrated antiviral-related activity in experimental bacteriophage systems. Acetone extracts inhibited the infectivity of *Pseudomonas phage*; virus (bacteriophage) to *Pseudomonas aeruginosa* in a concentration-dependent manner, apparently through interaction with the phage particles. Although such findings demonstrate biological activity against a specific phage model, they should not be directly extrapolated to treatment of human viral infections such as HIV without appropriate evidence from human studies. Date fruit extracts have also been investigated for their effects against *Streptococcus pyogenes*, where they reduced bacterial growth and substantially inhibited the haemolytic activity associated with streptolysin O [115].
 - xi. **Protection against cisplatin-induced genotoxicity:** Aqueous extracts of date palm pollen have demonstrated protective effects against cisplatin-associated reproductive toxicity in experimental mice. Oral administration of the pollen extract before cisplatin exposure reduced indicators of genotoxic damage and improved testicular histological changes. The treatment was also associated with fewer epididymal sperm abnormalities, while the higher investigated dose helped preserve sperm numbers. These results indicate a possible protective role of date palm pollen against chemotherapy-associated reproductive damage in experimental models [115].
 - xii. **Antihyperlipidemic activity:** Date fruit pulp, seed fibre and pollen have been investigated for their effects on lipid metabolism. In animals fed cholesterol-rich diets, supplementation with date fruit pulp reduced elevated plasma cholesterol, triglycerides and LDL cholesterol. Date seed fibre incorporated into the diet similarly decreased total cholesterol, triglycerides and LDL cholesterol while increasing HDL cholesterol. Dietary supplementation with date palm pollen has also been associated with reductions in plasma lipid fractions and improvements in selected liver-function parameters in experimental animals. These findings suggest that date palm-derived materials may influence lipid metabolism, although their effectiveness and safety for managing human dyslipidaemia require clinical evaluation [115].
 - xiii. **Nephroprotective activity:** Extracts obtained from date pulp and pits have shown protective effects against experimentally induced renal injury. In rats with gentamicin-associated nephrotoxicity, administration of date extracts reduced the increases in plasma creatinine and urea concentrations and lessened structural damage to the renal proximal tubules. The observed nephroprotective activity has been proposed to involve antioxidant constituents naturally present in dates, including vitamin E, ascorbic acid and melatonin. Nevertheless, further studies are necessary to establish the mechanisms and clinical relevance of these effects [115].

Broadly, experimental evidence indicates that *Phoenix dactylifera* contains a diverse range of phytochemicals with antioxidant, anti-inflammatory, gastroprotective, hepatoprotective, nephroprotective, antimicrobial and other biological activities. However, most reported effects have been demonstrated in laboratory or animal models. Therefore, these findings indicate pharmacological potential rather than established clinical efficacy, and well-designed human studies are necessary to determine appropriate doses, safety profiles and therapeutic applications [115].

Overview of *Morus alba* L.

Morus alba L., commonly known as white mulberry, belongs to the family Moraceae and has a long history of traditional use in several regions of Asia, Africa and Europe. The species possesses considerable economic importance because its sweet, nutrient-rich fruits are consumed fresh and are also incorporated into a variety of food products. Its leaves are particularly significant in sericulture, as they constitute the principal feed for silkworms and therefore contribute substantially to silk production. Beyond its nutritional and economic value, *M. alba* has been traditionally employed for medicinal purposes, with different plant parts, including the leaves, bark and fruits, being used in traditional healthcare practices for the management of various disorders [116].

Extensive research has investigated the phytochemical composition, ethnomedicinal applications, pharmacological properties and safety profile of *M. alba*. Investigations have identified numerous bioactive constituents that may contribute to its reported biological activities. Experimental evidence has indicated several potentially beneficial properties, including: antioxidant, antidiabetic, anti-inflammatory, hepatoprotective, immunomodulatory and antimicrobial effects, as well as possible anticancer and antiviral activities. Research conducted in different regions of India has also documented the diverse traditional applications of the plant and identified a wide range of phytochemicals of potential pharmacological importance. Nevertheless, much of the available evidence is derived from laboratory and animal studies, and comprehensive clinical investigations in humans remain limited. Further research is therefore necessary to establish the therapeutic efficacy, appropriate dosage, mechanisms of action and long-term safety of *M. alba*. Detailed toxicological evaluation is also essential before its bioactive preparations can be confidently developed for broader medicinal or health-promoting applications [116].

Botanical, Ethnomedicinal and Phytochemical Significance of *Morus alba* L.

Morus alba L., belonging to the family Moraceae, is widely referred to as white mulberry or Tut. The species originated in China, and particularly in the Himalayan and northern Chinese regions, and has subsequently been introduced and cultivated across numerous countries associated with sericulture. Although it is not indigenous to South Africa, the plant is now established in several parts of the country, where it is cultivated both for silkworm rearing and for traditional medicinal applications. *M. alba* is recognised as one of the principal species of the genus *Morus*, which comprises more than 150 species. Its importance in sericulture is primarily attributed to its leaves, which constitute the major dietary source for the silkworm, *Bombyx mori*. The widespread cultivation of mulberry along historical silk-producing regions contributed substantially to the development of the silk trade, particularly across Europe and Asia [116].

The geographical distribution and growth of *M. alba* are strongly influenced by environmental and soil conditions. The species is naturally associated with the Himalayan foothills and can grow at elevations of approximately 1200 m. It generally performs better in regions with adequate water availability and is less suited to dry sites or shallow soils where moisture is restricted. The plant can adapt to a broad range of soil textures, including sandy loam and clay loam, although deep, fertile, well-drained alluvial or loamy soils with adequate moisture are considered favourable for vigorous growth. It is relatively sensitive to alkaline soil conditions and develops well within a soil pH range of approximately 6.0–7.5. Soil depth and texture are important determinants of plant development. In seasonal climates, mature leaves are generally shed during November and December, resulting in a leafless period during winter, while new foliage develops during March and April depending on local climatic conditions [116].

In addition to its importance in silk production, *M. alba* has considerable nutritional and medicinal significance. The fruits are edible and are consumed fresh or incorporated into food and dietary preparations, while fruit-derived materials have also been investigated for use in pharmaceutical and nutraceutical products. Mulberry fruits contain several nutrients and biologically active substances, including: phenolic compounds, sugars, vitamins, minerals and other phytochemicals. Their antioxidant capacity is strongly associated with phenolic constituents. The leaves and fruits are also regarded as nutritionally valuable plant materials because they contain proteins and other nutrients. In India, mulberry foliage is used as livestock feed and may also be incorporated into dietary formulations in combination with cereal flours [116].

Different parts of *M. alba*, including the leaves, fruits, roots, bark and young twigs, have a long history of application in traditional healthcare systems. In Ayurveda and Traditional Chinese Medicine, preparations from these plant parts have traditionally been used for a wide range of conditions, including: fever, inflammatory disorders, digestive disturbances, constipation, diabetes, hypertension and other ailments. Traditional applications have also included the use of mulberry preparations to support liver function, promote urinary elimination and improve general health. Although these historical applications provide a basis for pharmacological investigation, traditional use alone does not establish clinical efficacy, and many reported therapeutic effects require confirmation through controlled human studies [116].

Phytochemical investigations have demonstrated that *M. alba* is a rich source of diverse secondary metabolites. The leaves contain sterols and triterpenoid compounds, including β -sitosterol, together with alkaloids, flavonoids such as rutin and quercitrin, coumarins, volatile constituents and various organic acids. The plant is also considered a source of natural antioxidant compounds, including ascorbic acid, with a substantial proportion reported to occur in its reduced form. One of the most extensively investigated constituents of mulberry leaves is 1-deoxynojirimycin (DNJ), a naturally occurring iminosugar that acts as an inhibitor of α -glucosidase and has therefore attracted considerable interest in research related to carbohydrate metabolism and type 2 diabetes [116].

The biological properties of *M. alba* have been investigated using different plant parts and extraction systems. Aqueous, ethanolic and methanolic extracts have demonstrated antioxidant, antidiabetic, hepatoprotective, nephroprotective, antimicrobial, anthelmintic, anticancer, antimutagenic and immunomodulatory activities in experimental studies. Additional investigations have reported potential anti-inflammatory, cholesterol-lowering, anxiolytic and antistress effects. Some studies have also examined the influence of mulberry extracts on inflammatory mediators and cellular responses, including the production of nitric oxide, prostaglandin E₂ and cytokines by macrophages. Traditional medicinal systems have similarly attributed diuretic, expectorant, anti-inflammatory and antidiabetic properties to the plant [116].

The nutritional, agricultural and pharmacological importance of *M. alba* makes it a valuable multipurpose plant. Its leaves have a central role in sericulture, while its fruits provide an edible source of nutrients and bioactive compounds. At the same time, its roots, bark, twigs and leaves represent important materials for traditional medicine and phytochemical research. The diversity of constituents identified from *M. alba* indicates considerable potential for the development of functional foods, nutraceutical preparations and plant-derived pharmaceutical products. Nevertheless, further research is required to isolate and characterise unexplored phytoconstituents, clarify their mechanisms of action, establish dose-response relationships and evaluate their safety and therapeutic efficacy through well-designed clinical investigations. Such studies could help determine the extent to which the pharmacological potential of *M. alba* can be translated into evidence-based applications [116].

Geographical Distribution of *Morus alba* L.

Morus alba L., commonly known as white mulberry, belongs to the family Moraceae and is considered native to China, particularly the central and northern regions. The species has subsequently been introduced and cultivated extensively in temperate and subtropical regions of Asia, Europe, Africa, North and South America, and Australia. Its wide geographical distribution is mainly associated with its adaptability to different environmental conditions and its economic importance in sericulture, as its leaves constitute the principal feed of *Bombyx mori* (silkworm). In India, *M. alba* is widely cultivated in areas associated with sericultural activities and is reported from several states, including: Andhra Pradesh, Haryana, Himachal Pradesh, Jammu and Kashmir, Karnataka, Kerala, Punjab, Tamil Nadu, Uttar Pradesh, Uttarakhand, West Bengal [116].

It is also found in other parts of the country to varying degrees depending on climatic and edaphic conditions. In the northwestern Himalayan region, the species is particularly distributed across Jammu and Kashmir, Himachal Pradesh and Uttarakhand; India, where suitable temperature, soil and moisture conditions support its growth and cultivation. The plant can tolerate a relatively broad range of environmental conditions, although adequate moisture and fertile soils favour healthy development. Its occurrence and cultivation in India are closely associated with the development of the sericulture industry, while its leaves, fruits, roots and bark have also contributed to its importance in traditional medicine and pharmacognosy. Thus, *M. alba* possesses a broad introduced and cultivated distribution beyond its native Chinese range and represents an economically and pharmacognostically significant plant species in India and other parts of the world [116].

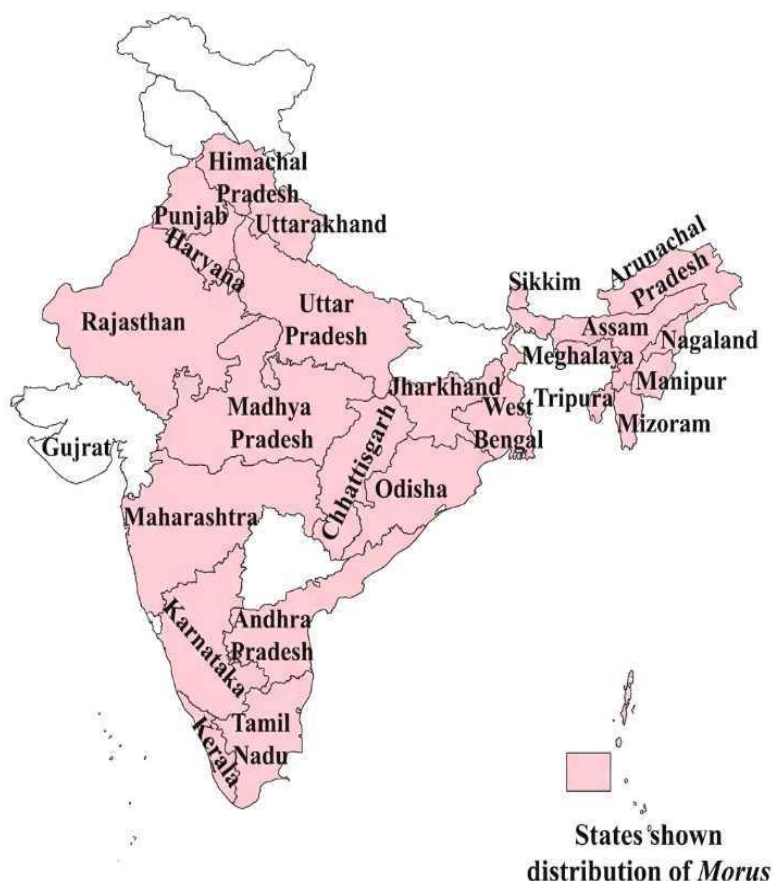
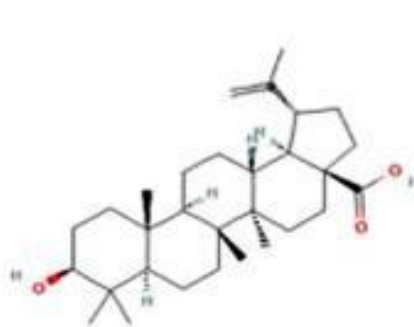
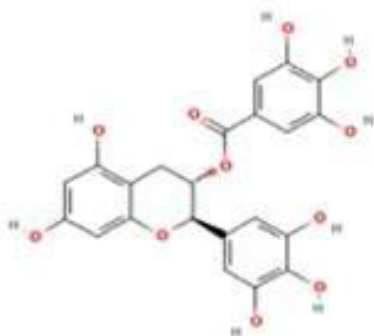
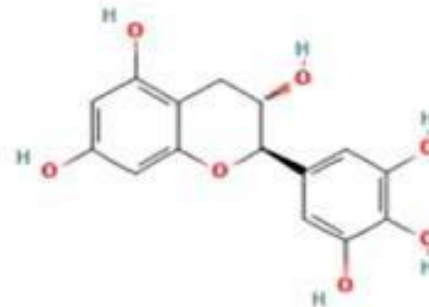
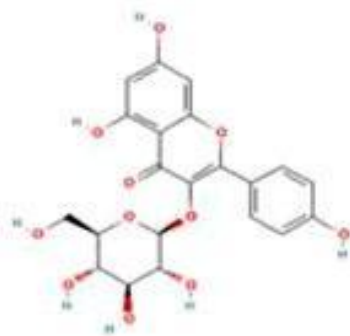
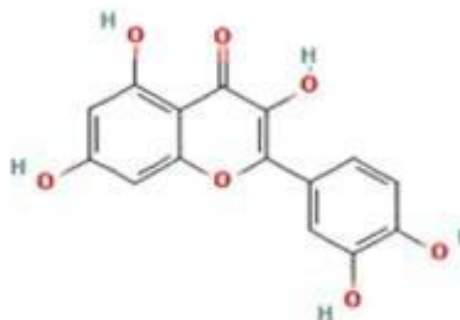
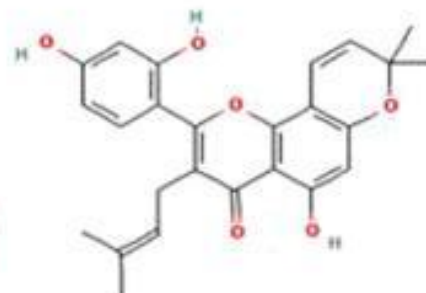
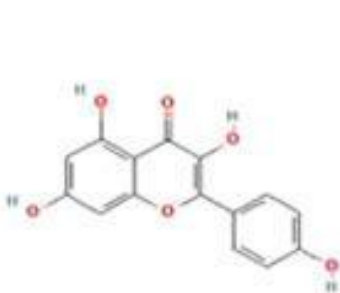
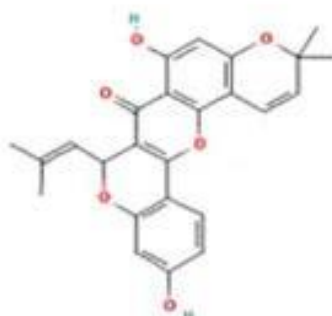
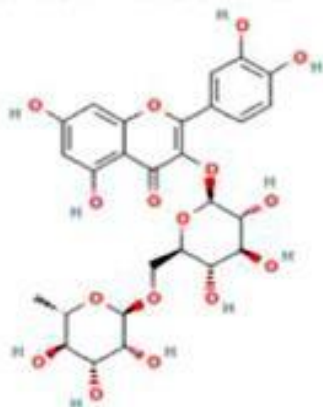
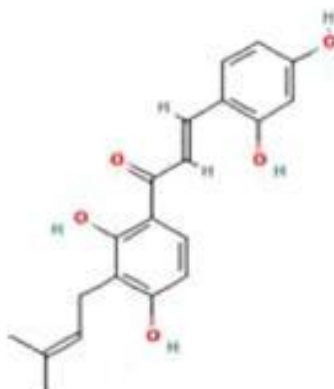
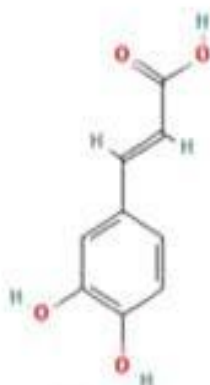


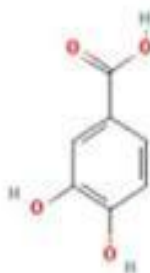
Figure 15. The map of India illustrating the Geographic Distribution of *Morus alba* L. in its regions of states [117].

FLAVONOIDS-**Betulinic acid****Galocatechin gallate****Galocatechin****Astragalin****Quercetin****Morusin****Kaempferol****Cyclomorusin****CHALCONES-****Rutin****Morachalcone A**

PHENOLIC ACIDS-



Caffeic Acid



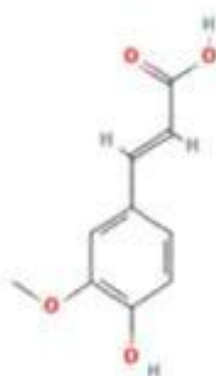
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Gallic Acid



Vanillic Acid

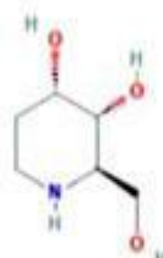


Ferulic acid

ALKALOIDS-

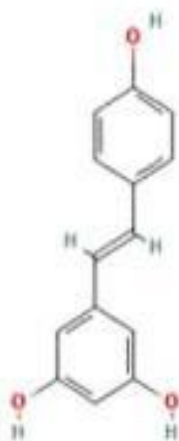


Fagomine

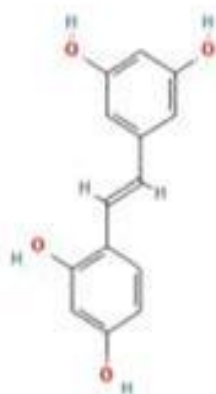


3-Epi-fagomine

STILBENOID-

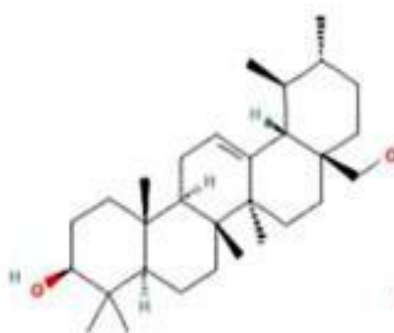


Resveratrol

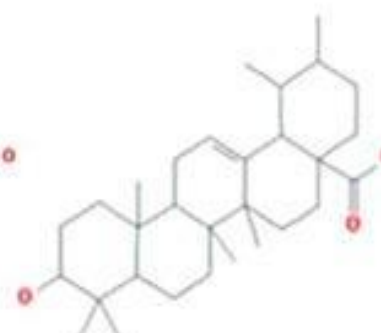


Oxyresveratrol

TERPENOID-



Uvaol



Urosolic Acid

Figure 16. Structural diversity of phytochemical constituents present in *Morus alba* L [118], [119].

Morus alba L. has demonstrated a broad spectrum of pharmacological activities, which can be attributed to its diverse array of bioactive phytochemicals. Different parts of the plant, including the leaves, fruits, stems, and root bark, have been investigated for their therapeutic potential. Its antidiabetic activity has been associated with compounds such as 1-deoxynojirimycin (DNJ), which inhibits carbohydrate-digesting enzymes including α -glucosidase, sucrase, and maltase, thereby contributing to the regulation of postprandial blood glucose levels. Mulberry extracts and anthocyanins such as cyanidin-3-glucoside, cyanidin-3-galactoside, and cyanidin-3-rutinoside exhibit considerable antioxidant activity through free-radical scavenging and protection against oxidative stress. Studies have also reported anti-obesity effects, with *M. alba* leaf extracts influencing hepatic lipid metabolism and reducing body weight and adiposity. In addition, several constituents, including: kuwanons, morusin, albanol compounds, and anthocyanins, have shown anticancer and antiproliferative effects in different cancer cell models by promoting apoptosis, inducing cell-cycle arrest, modulating caspase activity, and suppressing signalling pathways associated with tumour progression. Kuwanon M, in

particular, has been reported to inhibit proliferation and migration of lung cancer cells and to promote mitochondrial-mediated apoptotic mechanisms. The plant also possesses anti-inflammatory properties, with compounds such as oxyresveratrol and albanol B reported to interfere with inflammatory mediators and pathways, including NF- κ B, iNOS, COX-2, and CXCR4/MEK/ERK signalling. Further, *M. alba* has exhibited hepatoprotective, antimicrobial, antibacterial, neuroprotective, cardiovascular-protective, and tyrosinase-inhibitory activities in experimental models. Hepatoprotective effects have been associated with reductions in serum alanine and aspartate aminotransferase levels, while moracin C has demonstrated potential to regulate PCSK9 expression in HepG2 cells. Its antimicrobial potential has been observed against several pathogenic bacteria, whereas neuroprotective studies suggest possible improvements in memory performance and inhibition of acetylcholinesterase activity. Additionally, *M. alba* extracts and constituents have shown potential for skin-whitening applications through inhibition of tyrosinase activity and melanin synthesis. These findings indicate that *M. alba* is a rich source of pharmacologically active compounds with diverse biological effects, although further mechanistic and clinical studies are required to establish their therapeutic efficacy and safety [116].

Carissa lanceolata belongs to the family Apocynaceae, a diverse plant family comprising approximately 250 genera and numerous species distributed predominantly across tropical and subtropical regions of Africa, Asia, and Oceania. Commonly known as conkerberry, *C. lanceolata* is a woody, thorn-bearing shrub that has been traditionally utilised by several Indigenous communities, particularly in Australia and Queensland, for various medicinal purposes. In traditional healthcare practices, different parts of the plant have been employed for conditions such as toothache, respiratory disorders, and wound management [120].

Phytochemical investigations of *C. lanceolata* have revealed the presence of several classes of biologically active constituents, including volatile oils, flavonoids, phenolic compounds, and triterpenoids. These constituents may contribute to the diverse pharmacological properties reported for the plant. Extracts of *C. lanceolata* have demonstrated a range of biological activities, including: anti-inflammatory, antioxidant, antimicrobial, antibacterial, anticancer, antipyretic, anti-arthritic, analgesic, wound-healing, and anti-urinary tract infection effects. Such findings indicate that the plant may possess considerable therapeutic potential and provide a scientific basis for some of its traditional applications [120].

Morphologically, *C. lanceolata* is a small to medium-sized, spiny shrub that can grow to approximately 3 m in height. It generally possesses a bright-green appearance, while its fruits develop a bluish-black colouration upon maturity. The plant typically flowers from September to December, producing small, fragrant, star-shaped white flowers that resemble those of jasmine. The biological activities observed in different extracts of *C. lanceolata* suggest that its phytochemical constituents may have important roles in combating a variety of pathological conditions and support further investigation of the species for potential pharmacological applications [120].

Carissa lanceolata, a member of the family Apocynaceae, is commonly referred to as conkerberry. The species is primarily associated with tropical and subtropical regions and has a long history of use in traditional healthcare practices. The family Apocynaceae, commonly called the dogbane family, includes several medicinally important plants. Species belonging to the genus *Carissa* have traditionally been used for managing a variety of health conditions, including: headache, gastrointestinal discomfort, diabetes, cardiovascular disorders, asthma, rheumatism, syphilis, rabies, and gonorrhea [120].

Pharmacological investigations of *Carissa* species have provided scientific evidence for several biological activities, including: anti-inflammatory, antioxidant, antimicrobial, anticancer, antipyretic, cardioprotective, wound-healing, and antidiabetic effects. These activities are believed to be associated with the diverse phytochemical composition of the genus. Reported bioactive constituents include polyphenolic compounds, particularly flavonoids and phenolic acids, as well as: lignans, terpenoids, steroids, coumarins, and cardiac glycosides. Several individual compounds, including: lupeol, carrisol, naringin, carrissone, scopoletin, and ursolic acid, have been identified from *Carissa* species and may contribute to their reported pharmacological properties [120].

The fruits of *Carissa* also possess considerable nutritional value, containing proteins, carbohydrates, dietary fibre, vitamin C, and a range of macro- and micronutrients. Consequently, ripe fruits may have potential applications in food and nutraceutical products. However, attention should be given to the consumption of unripe fruits. Green or immature fruits have been reported to possess toxic properties, although detailed toxicological investigations remain limited. This toxicity has been associated with certain phytochemicals, including alkaloids and glycosides, which may produce adverse effects when immature fruits are consumed by humans or animals. As the fruit matures, it becomes edible and is generally considered to have reduced toxicity. Further toxicological and phytochemical studies are nevertheless required to clearly establish the safety profile of different developmental stages of *Carissa* fruits [120].

A. Anti-inflammatory activity

Investigations of *Carissa lanceolata* extracts have demonstrated notable anti-inflammatory potential, which may be attributed to the presence of bioactive constituents such as (+)-carrissone and dehydrocarrissone. These compounds have been reported to interfere with the synthesis or release of important inflammatory mediators, including bradykinin and prostaglandins, thereby contributing to the reduction of inflammatory responses. The anti-inflammatory effect may also involve inhibition of cyclooxygenase (COX) activity and suppression of nitric oxide production. Comparative investigations using conventional non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, have indicated promising anti-inflammatory activity of *C. lanceolata* extracts, suggesting their potential as a source of naturally derived anti-inflammatory agents [120].

B. Antioxidant activity

The antioxidant potential of *C. lanceolata* is associated mainly with its phenolic and flavonoid constituents, which are recognised for their ability to neutralise reactive free radicals and protect biological systems from oxidative damage. Various *in vitro* assays, particularly the DPPH [2,2-diphenyl-1-picrylhydrazyl] and ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] radical-scavenging methods, have been employed to assess the antioxidant capacity of the plant extracts. The reported IC₅₀ values indicate appreciable free-radical-scavenging activity, with the extracts demonstrating antioxidant effects in comparison with established standards such as ascorbic acid and Trolox. The persistence of antioxidant activity under different experimental conditions further suggests that *C. lanceolata* extracts may have potential applications in the food, pharmaceutical, and cosmetic sectors [120].

C. Antibacterial activity

Extracts prepared from the roots and wood of *C. lanceolata* have exhibited antibacterial activity against a range of both Gram-positive and Gram-negative microorganisms. Significant inhibitory effects have been reported against pathogenic bacteria such as: *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Phytochemical investigations have led to the identification of several eudesmane-type sesquiterpenes, including carissone, dehydrocarissone, and carindone, which may contribute to the observed antibacterial effects. Some of these isolated constituents have demonstrated minimum inhibitory concentration (MIC) values below 0.5 mg/mL against the tested bacterial strains. Microbroth dilution assays have been utilised to determine the antibacterial potency of both crude extracts and purified compounds, supporting the potential of *C. lanceolata* as a source of naturally occurring antibacterial agents [120].

Polyphenol-rich plant foods have attracted considerable attention because of their potential role in reducing the risk of lifestyle-associated disorders, particularly diabetes and cardiovascular diseases. In recent years, interest in lesser-known and underutilised fruits has increased because of their abundance of naturally occurring phenolic compounds and other health-promoting constituents. *Carissa spinarum* (CS), commonly referred to as currant bush or conkerberry, is an underexploited fruit species belonging to the family Apocynaceae and is naturally distributed across tropical and subtropical areas of Asia, Africa, and Australia. The plant has traditionally been valued for its medicinal importance and produces small, berry-like fruits characterised by an appealing flavour, distinctive texture, and considerable nutritional value. In addition to their nutritional attributes, the fruits contain a range of bioactive polyphenols, including anthocyanins, resveratrol, epicatechin, and syringic acid. The presence of these compounds enhances the potential of *C. spinarum* fruit as a valuable source of functional ingredients and nutraceuticals, with possible applications in the food and beverage industries [121].

Carissa spinarum (Conkerberry): Nutritional Profile, Phytochemistry, Traditional Uses, and Therapeutic Potential

Carissa spinarum, commonly known as conkerberry and belonging to the family Apocynaceae, is an evergreen shrub that generally reaches a height of approximately 2–3 m. The species has previously been identified as *Carissa edulis* and is known by regional names such as Heen Karamba. Its natural distribution extends across several tropical and subtropical regions, including Australia, India, Ethiopia, Malaysia. The plant produces seasonal, ovoid to globular fruits that occur in clusters, usually containing approximately 3–10 fruits. During development, the fruits change from green when immature to red and eventually reddish-purple at full maturity [122].

The nutritional composition of *C. spinarum* fruits varies according to geographical origin and growing conditions. Fruits examined in India have been reported to contain approximately 81% moisture, 19% carbohydrates, 2% protein, and 1.3% fat, whereas fruits from Ethiopia have shown comparatively lower moisture content of about 59–62%, together with higher carbohydrate and fat levels of approximately 26–28% and 5%, respectively. These variations indicate that environmental and geographical factors may influence the nutritional characteristics of the fruit [122].

Considerable antioxidant potential has been documented for *C. spinarum* fruits. Studies conducted on Indian fruit samples reported antioxidant capacities of approximately 1013 mg ascorbic acid equivalent antioxidant capacity (AEAC)/100 g dry weight using the DPPH assay and 2118 µM AEAC/g using the FRAP assay. Investigations involving African populations of the plant have also demonstrated substantial antioxidant activity, although the reported values differed among samples. Importantly, antioxidant capacity appears to decline as the fruit progresses toward maturity, indicating that the stage of harvesting may significantly influence the concentration and activity of antioxidant constituents. Extracts have demonstrated IC₅₀ values of approximately 4.69–4.88 mg/mL in DPPH assays and 35.67 mg/mL in FRAP-based assessments. In general, immature fruits have exhibited greater antioxidant capacity than mature fruits, suggesting a possible reduction in certain antioxidant constituents during ripening.

The phenolic composition of *C. spinarum* also changes considerably during fruit maturation. Ripe fruits possess substantial total phenolic content (TPC), reported within the range of approximately 273–1880 mg gallic acid equivalents (GAE)/100 g fresh weight, while total flavonoid content (TFC) has been reported to reach approximately 454 mg quercetin equivalents (QE)/100 g. Phytochemical investigations have identified numerous phenolic constituents, including: protocatechuic acid, gentisic acid, chlorogenic acid, vanillic acid, epicatechin, syringic acid, p-coumaric acid, sinapinic acid, myricetin, quercetin, luteolin, cinnamic acid, apigenin, and resveratrol. Interestingly, quercetin, luteolin, apigenin, and resveratrol have been detected predominantly in ripe rather than unripe fruits. Among the identified compounds, syringic acid and resveratrol have been reported as particularly prominent constituents, with approximate concentrations of 21 and 8.2 mg/100 g, respectively [122].

Anthocyanins represent another important group of bioactive compounds present in the fruit. Fresh *C. spinarum* fruits have been reported to contain approximately 50 mg cyanidin-3-glucoside equivalents (C3GE)/L. However, drying can substantially decrease anthocyanin levels, probably because these pigments are sensitive to processing and storage conditions. Similar reductions have been observed in TPC and TFC following drying, emphasising the importance of suitable processing and preservation strategies for maintaining the biological value of the fruit [122].

The presence of resveratrol is particularly noteworthy because this polyphenol is widely recognised for its biological and pharmaceutical importance. Although grapes are commonly regarded as an important dietary source of resveratrol, *C. spinarum* fruit also contains appreciable quantities of this compound. Resveratrol has been investigated for its potential anti-aging and

anticancer properties and has also been associated with biological effects relevant to obesity, diabetes, hypertension, cardiovascular disorders, and renal diseases. In addition, its antiplatelet activity has been documented in experimental studies. Nevertheless, the presence of these compounds in *C. spinarum* should not by itself be interpreted as evidence of clinical efficacy [122].

The fruit has considerable potential for food and nutraceutical applications. Fully ripe fruits are traditionally or commercially utilised in products such as jams, jellies, juices, ice cream, puddings, and cakes, whereas immature fruits have been used in preparations including chutneys, candies, and pickles. Some reports have raised concerns regarding the consumption of unripe fruits because of possible toxic effects; however, the available evidence remains limited, and further systematic toxicological studies are needed to establish the safety of fruits at different stages of maturity. Because the fresh fruit is seasonal and has a relatively short shelf life, researchers have also explored value-added products such as fruit wine. Such studies have reported acceptable sensory characteristics together with measurable antioxidant, phenolic, and flavonoid content. Similarly, a functional beverage containing 40% *C. spinarum* fruit extract has been developed, although prolonged storage may result in degradation of sensitive constituents such as anthocyanins, vitamin C, and flavonoids [122].

Both ripe and unripe fruits have a history of use in traditional medicine for managing various minor ailments. Ripe fruits have traditionally been associated with the management of diarrhoea, loss of appetite, excessive thirst, hematemesis, and intermittent fever. Immature fruits have been used traditionally for conditions such as: fever, oral ulcers, sore throat, and certain skin disorders, including scabies. However, the specific compounds responsible for these traditional therapeutic effects have not yet been conclusively established, highlighting the need for further phytochemical and pharmacological investigations [122].

Recent studies have also suggested promising therapeutic properties of *C. spinarum*. Investigated its potential antidiabetic activity and identified constituents capable of inhibiting α -glucosidase, an enzyme involved in carbohydrate digestion. Such inhibition may contribute to the plant's potential for controlling postprandial glucose availability. In addition, extracts or constituents of the fruit have demonstrated anticancer, antimalarial, and antimicrobial activities in experimental investigations. Antimicrobial effects have been reported against several bacterial species, including: *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus faecalis*, and *Salmonella typhimurium*. **From a comprehensive perspective**, the nutritional richness, polyphenolic composition, antioxidant capacity, traditional applications, and preliminary pharmacological evidence indicate that *C. spinarum* represents a promising underutilised fruit for further investigation in food, nutraceutical, and pharmaceutical research [122].

Phytochemical Diversity of Carissa Species

Phytochemical investigations of the genus *Carissa* have revealed a wide diversity of secondary metabolites distributed across different plant species and tissues. The reported constituents include: triterpenoids, sesquiterpenes, monoterpenes, flavonoids, phenolic acids, lignans, sterols, coumarins, fatty acids, vitamins, and other specialised metabolites. Among the triterpenoid constituents, **lupeol, ursolic acid, oleanolic acid, α -amyrin, β -amyrin, betulinic acid, carissic acid, carissol, and arjunolic acid** have been identified from roots, leaves, fruits, stems, and aerial parts of species such as: *C. carandas*, *C. opaca*, *C. congesta*, *C. macrocarpa*, and *C. spinarum*. Several sesquiterpenoid compounds, including: **(+)-carissone, dehydrocarissone, carindone, carissanols, β -eudesmol, germacrenone, cryptomeridiol, and zicrone**, have also been reported, particularly from roots and stems. The essential-oil fractions of *Carissa* species contain various volatile constituents such as: **pinene, myrcene, limonene, sabinene, camphene, α -terpineol, p-cymene, linalool, geraniol, nerolidol, farnesol, citronellal, and piperitone**, with several of these compounds identified from flowers and roots [123].

Flavonoids and other phenolic constituents represent another important phytochemical group within the genus. Compounds such as: **rutin, epicatechin, epicatechin gallate, quercetin, kaempferol, naringin, piceatannol, resveratrol, syringic acid, vanillic acid, p-coumaric acid, caffeic acid, ellagic acid, chlorogenic acid, and scopoletin** have been detected in different *Carissa* species and plant parts. Lignans, including: **secoisolariciresinol, carrisanol, carinol, lariciresinol, pinoresinol, nortrachelogenin, olivil, and hydroxypinoresinol**, have primarily been reported from roots, stems, and aerial tissues. The genus also contains phytosterols such as: **β -sitosterol, campesterol, stigmasterol, cholesterol derivatives, and their glycosides**. In addition, fatty acids including: **hexadecanoic, octadecanoic, eicosanoic, oleic, and linoleic acids** have been identified, particularly in seeds and roots. Other constituents, including: **ascorbic acid, vitamin E, pinitol, vanillin, isofraxidin, and various aliphatic hydrocarbons**, further contribute to the chemical complexity of these plants. The occurrence of such structurally diverse compounds across different *Carissa* species provides a biochemical basis for the numerous biological activities reported for the genus and highlights its potential as a source of pharmacologically and nutritionally valuable natural products [123].

Conclusion:

In conclusion, the extensive body of research on *Bacopa monnieri* (Brahmi) emphasises its multifaceted therapeutic potential, particularly in the realms of cognitive enhancement, neuroprotection, and anti-inflammatory effects. **Figure 6**. The herb demonstrates promising outcomes in various models, including those related to memory deficits, neurotoxicity, and cognitive dysfunction. **Figure 4**. Potential chemical substances found in *Bacopa monnieri* include: Bacoside A3, Bacopaside II, Bacopaside X, Bacopasaponin C, and others. Organised in **Table 20**. Its actions on GABAergic neurons, calcium-binding proteins, and modulation of glutamate-related pathways suggest a complex yet beneficial impact on cognitive function, especially in conditions like schizophrenia.

Moreover, the herb's interaction with cytochrome **P450** enzymes raises concerns about potential herb-drug interactions, especially with medications metabolised by **CYP1A2, CYP3A4, CYP2C9, and CYP2C19**. **Table 16, Table 17, Table 18, and Table 19**. This highlights the importance of cautious co-administration and individualised considerations, particularly in the context of gastrointestinal concentrations, liver metabolism, and genetic polymorphisms.

The anti-tumour potential of specific compounds, such as bacopaside II, in colon cancer cells adds another layer to *Bacopa monnieri*'s pharmacological profile, hinting at its diverse applications in various health conditions; apart from its cognitive enhancement effect and other neurological responses and benefits.

While the herb demonstrates neuroprotective effects and cognitive benefits in both animal models and human trials, further long-term studies are needed to establish its safety profile conclusively. The observed positive impacts on spatial working memory,

neuroregeneration, and synaptic plasticity make *Bacopa monnieri* a compelling candidate for cognitive health and neurological disorders.

On the whole, the performed study emphasised the need for continued exploration of *Bacopa monnieri*'s actions at molecular, cellular, and clinical levels. This will not only contribute to a deeper understanding of its mechanisms but also guide its potential integration into therapeutic strategies for cognitive disorders, neurodegenerative conditions, and inflammatory disorders.

Thus,

- I. **Multifaceted therapeutic potential:** *Bacopa monnieri* (Brahmi) demonstrated broad pharmacological potential, particularly in **cognitive enhancement, neuroprotection, and anti-inflammatory activity**.
- II. **Cognitive-enhancing effects:** The herb showed promising effects in experimental models involving **memory deficits, cognitive dysfunction, and neurotoxicity**, supporting its potential application in cognitive disorders.
- III. **Neuroprotective activity:** *Bacopa monnieri* exhibited protective effects against neuronal damage and was associated with **neuroregeneration and improved synaptic plasticity**, indicating potential benefits in neurological and neurodegenerative conditions.
- IV. **Potential mechanism of cognitive action:** Modulation of **GABAergic neurons, calcium-binding proteins, and glutamate-related pathways** suggests that *Bacopa monnieri* may influence multiple neurological pathways involved in cognition and neuronal function.
- V. **Important bioactive constituents:** Several phytoconstituents, including **Bacoside A3, Bacopaside II, Bacopaside X, and Bacopasaponin C**, were identified as important chemical constituents that may contribute to the herb's pharmacological activities.
- VI. **Potential relevance to schizophrenia:** The observed modulation of neurotransmitter-related pathways indicates a possible therapeutic role of *Bacopa monnieri* in conditions involving cognitive impairment, including **schizophrenia**, although further investigation is required.
- VII. **Herb–drug interaction potential:** The interaction of *Bacopa monnieri* with **cytochrome P450 enzymes**, particularly **CYP1A2, CYP3A4, CYP2C9, and CYP2C19**, highlights the possibility of clinically relevant herb–drug interactions.
- VIII. **Need for individualised consideration:** Differences in **gastrointestinal exposure, hepatic metabolism, and genetic polymorphisms** may influence the response to *Bacopa monnieri*, supporting the need for careful consideration during concomitant drug administration.
- IX. **Anti-tumour potential:** Compounds such as **bacopaside II** demonstrated potential anti-tumour activity in colon cancer cell models, suggesting that the therapeutic applications of *Bacopa monnieri* may extend beyond neurological disorders.
- X. **Evidence from preclinical and clinical studies:** Both **animal studies and human trials** provide encouraging evidence regarding the cognitive and neuroprotective benefits of *Bacopa monnieri*.
- XI. **Need for long-term safety evaluation:** Despite promising therapeutic outcomes, **long-term clinical studies** are required to establish its safety, tolerability, efficacy, and potential interactions conclusively.
- XII. **Future therapeutic significance:** Continued investigation at the **molecular, cellular, pharmacokinetic, and clinical levels** may facilitate the development of *Bacopa monnieri* as a supportive therapeutic strategy for **cognitive disorders, neurodegenerative diseases, and inflammatory conditions**.

List of abbreviations:

- i. **AQP1** - Aquaporin-1,
- ii. **BM** - *Bacopa monnieri*,
- iii. **CNS** - Central Nervous System,
- iv. **CYP** - Cytochrome P450,
- v. **OBX** - Olfactory Bulbectomised,
- vi. **TMT** - Trial Making Test,
- vii. **VFT** - Verbal Fluency Test.

Key terms and definitions/terminology and definitions

- i. ***Bacopa monnieri* (BM):** A medicinal herb known for its cognitive-enhancing properties and traditional use in Ayurvedic medicine.
- ii. **Olfactory Bulbectomised (OBX) mice:** Mice subjected to **olfactory bulbectomy**, a surgical procedure that leads to impaired memory and cognitive deficits.
- iii. **Neuroprotective:** Having the ability to protect the nervous system, often from damage or degeneration.
- iv. **Muscarinic Receptor Antagonist:** A substance that blocks the action of muscarinic receptors, which are involved in acetylcholine signaling.
- v. **Synaptic plasticity:** The ability of synapses (connections between neurons) to strengthen or weaken over time, crucial for learning and memory.
- vi. **Brain-Derived Neurotrophic Factor (BDNF):** A protein that supports the survival and growth of neurons in the brain.
- vii. **Bacopaside I:** An active component of *Bacopa monnieri* that promotes the proliferation of neural progenitor cells.
- viii. **Saponins (Bacopasides IX-XI):** Bioactive compounds isolated from *Bacopa monnieri* with demonstrated nootropic effects.
- ix. **Triterpene Glycosides (Bacopasides VI-VIII):** Compounds from *Bacopa monnieri* with antidepressant effects.
- x. **Colon Cancer Cells (HT-29, SW480, SW620, HCT116):** Different types of cells used in the study exploring the anti-tumour potential of bacopaside II.
- xi. **Ayurvedic medicine:** Traditional medicine system originating from India, which uses *Bacopa monnieri* for various therapeutic purposes.
- xii. **Brahmi:** Another name for *Bacopa monnieri* used in traditional medicine.
- xiii. **GABAergic neurons:** Neurons that release gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.
- xiv. **Cytochrome P450 (CYP) enzymes:** A family of enzymes involved in the metabolism of drugs and endogenous substances.

xv. **CYP2C19, CYP2C9, CYP1A2, CYP3A4, CYP2D6:** Specific isoforms of Cytochrome P450 enzymes with distinct roles in drug metabolism.

xvi. **VGLUT1, VGLUT2, VGLUT3:** Vesicular glutamate transporters involved in packaging and releasing glutamate, a neurotransmitter.

xvii. **NMDAR1:** N-methyl-D-aspartate receptor subtype 1, involved in synaptic plasticity and cognition.

Supplementary Material:

Supplementary data are not available.

Author Contribution:

The author Dr. Saurabh Dilip Bhandare and Dr. Sarika Shivaji Malode conceived the study idea, and the supporting authors, co-authors designed and conducted the experiments, collected and analysed the data, interpreted the results, and wrote the manuscript. The author contributed equally to all aspects of the study and approved the final version of the manuscript for submission. Both Dr. Saurabh Dilip Bhandare and Dr. Sarika Shivaji Malode performed independent review of the work and reported conflicts and findings, which corrected in accordance to the interest of the main authors before the final merit was discussed, evaluated and submitted for publication.

Conflict of Interest:

The author declares no potential conflicts of interest that could adversely impact the publication, either through personal or professional connections. There is no involvement of third parties, whether technically or legally, hired to represent the author in communication related to the article. The author has not designated any third parties to communicate on their behalf in the present or foreseeable future. The work is independent of any companies or legal entities, and there is no association that could lead to the withdrawal of the publication without prior communication from the author. No permission has been granted to any third party purportedly involved. Any future changes will not have an impact on this publication. "No conflicts will be entertained in the future by the authors."

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Availability of material: Data material shall available on convincing request made to main author, Prof. Dr. Saurabh Dilip Bhandare only (saurabh_bhandare@yahoo.com, +91 8600087354). No, any other authors shall be in direct responsible for future communication on this work.

Data availability:

All the data haven been cited form the research articles or science articles of only quality findings and have been acknowledge wherever applicable in the reference section of the manuscript.

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