



A REVIEW ON PHARMACOLOGICAL PROPERTIES OF BACOPA MONNIERI

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ABSTRACT

According to legend, Bacopa monnieri (BM) has been used in India for at least three thousand years to enhance memory. It was listed in the 800 BC vedic classic "Athar-Ved Samhila" (3:1) and in Ayurveda for its medical benefits, specifically its ability to boost memory. Several herbs have been traditionally utilised as brain or nerve tonics in Indian folk medicine. The most well-known of these neurotonics is BM, a renowned memory enhancer. Religious institutions have been using brahmi to help pupils improve their memory for memorising lengthy religious hymns. It is also used as an anti-stress, diuretic, nervine tonic, tranquillizer, sedative, enhancer of speech, use in mania, epilepsy, hysteria, esthenia, nervous breakdown, and imagination, memory enhancer, and cardio-tonic and imagination, diuretic and nervine tonic, antistress. It is a little, succulent, creeping herb. The family Scrophulariaceae plants, which grow close to the banks of freshwater streams and ponds, paddy fields, and other wet areas, produce leaf and flower bearing stems that are 10–30 cm long and emerge from creeping stems that establish roots at the nodes. Alkaloids, saponins, herpestine, brahmine, and herpes are the main phytoconstituents found.

INTRODUCTION

The term "Brahmi" refers to substances that enhance brain health. Brahma is the name of the Hindu pantheon's mythological creator, and the brain is the seat of all creative activity in the human body.

In Charak Samhita (1), where Brahmi is recommended as a treatment for mental disease (retardation) that results in insanity, the first explicit mention of Brahmi in relation to memory enhancement can be found.

According to Charak, the causes of the mental condition are a combination of anxiousness, a poor mind, and a lack of focus. The Susruta Samhita, a different genuine Ayurvedic text, describes Brahmi is effective in preventing memory and cognitive decline. It is categorised as a "Medhya Rasayan" medicine and has been used by Ayurvedic doctors in India for almost 3000 years to enhance memory and cognition. Traditional medicine has employed plants in a variety of formulations to treat a variety of diseases, and research suggests that some natural compounds in those formulations have nootropic action (2).

The active components of Brahmi known as bacosides are in charge of boosting memory and cognition as well as treating associated diseases and increasing the efficiency of nerve impulse transmission (3).

Herbal medicines are becoming more popular, which may be because they have less negative effects than more contemporary synthetic pharmaceuticals. To combat this issue, the pharmaceutical industry creates synthesis of medicinal plants and their extracts using an in vitro system (4)

Plant Description and Morphology

Bacopa monnieri, a member of the Scrophulariaceae family, is a small, creeping herb with numerous branches, small oblong leaves, and light purple flowers. In India and the tropics, it grows naturally in wet soil, shallow water, and marshes. It is also found in Nepal, Sri Lanka, China, Taiwan, Vietnam, Florida and Southern states of USA. It is widely distributed in warmer parts of Asia, Australia, America and India commonly known as Brahmi or Indian water hyssop has been investigated (5)

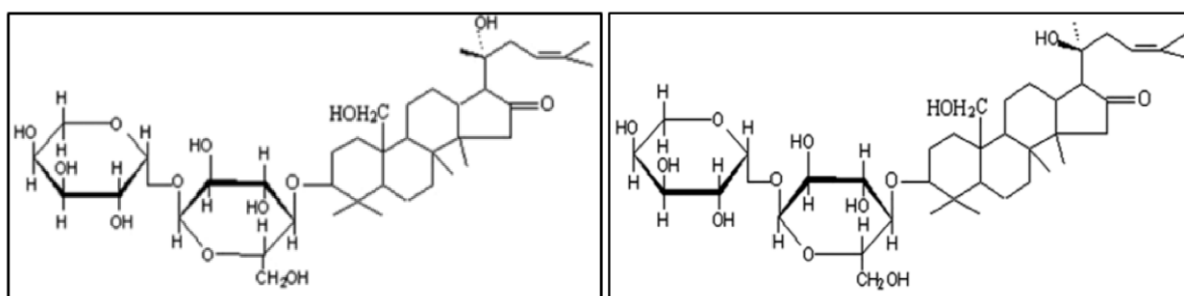
Bacopa monnieri, a member of the Scrophulariaceae family, Herb *bacopa monnieri* is not scented. This plant has oblong, succulent leaves that are 4-6 mm (0.16-0.24 in) thick. Oblanceolate leaves are oppositely placed on the stalk. The actinomorphic, white, tiny blooms have four to five petals. Even mildly brackish conditions can support its growth. Cuttings are a common method for achieving propagation. [6]



Kingdom	Plantae
Division	Anthophyta
Class	Dicotyledoneae
Order	Scrophulariales
Family	Scrophulariaceae
Genus	Bacopa
Species	Monnieri

Structure of Major Chemical Entity

Bacoside A and B are the *Bacopa monnieri* isolate with neuroprotective activity. Bacoside A is one of many structural analogues found in the Ayurvedic nootropic herb *Bacopa monnieri* [6].



Bacoside A (levorotatory);

(b) Bacoside B (dextrorotatory)

Fig 2: Chemical structures of some well-known Saponins from *Bacopa monnieri* [6]

Chemical Composition of Brahmi

Brahmi (*Bacopa monnieri*) contains 88.4% moisture along with carbohydrates, fat, protein and minerals. The major chemical composition of the herb is given in table below.

Table 1: Chemical Composition of *Brahmi* ^[5]

Component	Amount (/100gm)
Moisture	88.4 gm
Protein	2.1 gm
Fat	0.6 gm
Carbohydrates	5.9 gm
Crude Fiber	1.05 gm
Ash	1.9 gm
Calcium	202.0 mg
Phosphorus	16.0 gm
Ascorbic Acid	63.0
Nicotinic acid	0.3
Iron	7.8 mg
Energy	38 cal

Mode Of Action Brahmi (*Bacopa monnieri*)

Extracts of Brahmi (*Bacopa monnieri*) have been extensively investigated for their neuropharmacological effects. There are some compounds such as Saponins and their bacosides present in Brahmi, which are responsible to enhance the nerve impulse transmission [7]. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission. In animals, *Bacopa* has a relaxant effect on pulmonary arteries, aorta, trachea, and ileal and bronchial tissue, possibly mediated by inhibition of calcium-ion influx into cell membranes [4]. There are numerous clinical trials and studies have been performed by various researchers to check the nootropic effects of *Bacopa monnieri*.

Functional/ Therapeutic Properties of Brahmi (*Bacopa monnieri*)
It is a well proven herb of many medicinal properties. All the parts of the plant can be used as medicine. In Ayurveda, Brahmi has been used to promote memory and intellect and also used for treatment of neurological disorders and also as a rejuvenator [5]. It has also an ability to improve cognitive function. Brahmi has many medicinal properties such as antispasmodic, anticholinesterase, neuroprotective, antioxidant, Alzheimer's disease, antidepressant, bronchodilatory, antiulcerogenic, anti-inflammatory, antibacterial, anticancer, cell stabilization, antileishmanial, etc.

Dosage

Therapeutic doses of *Bacopa* are not associated with any known side effects, and *Bacopa* has been used safely in Ayurvedic medicine for several hundred years [8]. Traditional daily doses of *Bacopa* are 5- 10 g of non-standardized powder, 8-16 mL of infusion, and 30 mL daily of syrup (*Brahmi*). Dosages of a 1:2 fluid extract are 5-12 mL per day for adults and 2.5-6 mL per day for children ages 6- 12 [9]. For *Bacopa* extracts standardized to 20-percent bacosides A and B the dosage is 200-400 mg daily in divided doses for adults, and for children, 100-200 mg daily in divided doses to achieve the medicinal/therapeutic properties of Brahmi.

Pharmacological Properties:

Anti Asthmatic Activity:

BM extract possessed relaxant properties in tracheal muscle rabbit and guinea-pigs with a partial contribution by (beta)-adrenoreceptor and prostaglandins (16). It also produced broncho dilation in anaesthetized rats (17) supported the traditional use of this plant in for various respiratory ailments (18). Bronchodilator property of extract may be reflected by antagonism of carbachol-induced effects on inspiratory and expiratory pressures. Extract exhibited a dual action on bronchoconstriction induced by carbachol. At low doses (25 and 37 mg/kg), predominantly inhibited inspiratory pressure, but at a high dose (50 mg/kg) inhibited only expiratory pressure. This property of the plant extract implies that more than one mechanism of action may be responsible for broncho-dilation. Some of the possible mechanisms include (beta)-adrenoreceptor activation, muscarinic receptor antagonism, prostaglandin release or interference with calcium mobilization. A more recent study by the same authors demonstrates the calcium antagonistic activity is present in ethanol extract of BM (19). In addition, it has been reported that BM methanolic extract exhibited a potent mast cell stabilizer, indicating the potential usefulness of BM leaves in allergic conditions (20).

Anti cancer activity:

Pre treatment with BM significantly reduced the acute stress (AS)-induced increase in and creatine kinase (CK) (21) in cancerous patients. This was due to the presence of bacosides in BM, which have anticancer activity. The methanolic extract exhibited potent mast cell stabilizer (22) activity. *Bacopa monnieri* is a known hyperaccumulator of Cd, Cr, Pb, and Hg and is used as a phytoremedy (23).

Anticonvulsive

the ulcer index, adrenal gland weight, plasma glucose, aspartate aminotransferase (AST), *Bacopa* has been indicated as an remedy for epilepsy in Ayurvedic medicine, and animal research has shown anticonvulsant activity only at high doses over extended periods.

It has also been reported that crude water extract of BM controls epilepsy in experimental animals (24). The naturally exhibited sedative effect and significantly prolonged the hypnotic action of phenobarbitone. These substances, which stimulate GABA, are known to possess anticonvulsant, pain-relieving, and sedative effects (26). This suggests that the GABAergic system is involved in mediating the central nervous system (25). BM alone and in combination phenytoin (PHT) for its effect on P-Task, maximal electroshock seizures, and locomotor activity in mice (27). Both acquisition and retention of memory improved without affecting PHT anticonvulsive activity. Further investigations using BM alone or in combination with other antiepileptic drugs are warranted to determine the full potential of BM in epilepsy.

Antidepressant:

When administered at doses of 20 and 40 mg/kg orally for five days, the extract was found to have significant antidepressant activity in forced swim and learned helplessness models of depression and was comparable to that of imipramine (28).

Anti inflammatory:

Bacopa monnieri has the ability to inhibit inflammation through modulation of pro-inflammatory mediator release (29) and possesses significant anti-inflammatory activity that may be relevant to its effectiveness in the healing of various inflammatory conditions in traditional medicine (30). It also significantly inhibited 5-lipoxygenase (5-LOX), 15-LOX and cyclooxygenase-2 (COX-2) activities (31). This activity may be attributed to the presence of triterpenoids and bacosides.

Anti-analgesic activity:

Aqueous extract of *Bacopa monnieri* (AEBM) exhibits analgesic activity through multiple pain pathways (32) i.e. involvement of β 1 adrenergic, α 2 -adrenergic receptors and 5-HT receptors in analgesic activity. It was also

observed that when AEBM was administered in combination with naloxone, the latencies of the analgesic effects did not increase, indicating the involvement of opioid receptors in analgesic activity.

Antioxidant activity:

Alcoholic and hexane extracts of BM exhibit antioxidant properties (33) by inhibiting lipid peroxidation. A recent study explored the antioxidant effect of BM through other mechanisms, such as inhibition of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) activities (34). We also observed that the hydroalcoholic extract of whole BM plant exhibited an inhibitory effect on superoxide released from polymorphonuclear cells in a nitroblue assay (35). Sumathy et al. (2001) investigated the hepatoprotective activity of alcoholic BM extract in morphine-treated rats (36). This may be due to decreased brain mitochondrial enzyme activity in rats (37). Methanolic extract of BM is able to directly inhibit superoxide anion formation in an adose-dependent manner because it reduces the concentrations of nitric oxide (NO), generated (enzymatic and non-enzymatic) by activated astrocytes, and may be involved in a variety of neurodegenerative diseases, such as AD, ischemia, and epilepsy (38, 39).

Anti stress Activity:

The standardized extract of BM possesses adaptogenic activity. Pretreatment with a low dose of BM extract significantly reversed changes in ulcer index and plasma AST only, whereas pretreatment with higher doses significantly reversed changes in ulcer index, adrenal gland weight, CK, and AST (40).

Anti Spasmodic Activity:

BM extract has pasmolytic activity in smooth muscles due to inhibition of calcium influx via both voltage and receptor-operated calcium channels of the cell membrane (41). However, the absence of any modification of either noradrenaline- or caffeine-induced

in the presence of BM extract suggests that this natural compound has no detectable effect on the mobilization of intracellular calcium.

Anxiolytic effect:

Higher doses of the BM extract produced significantly greater anxiolytic effects than LBP (42). However, BM has a distinct advantage over lorazepam (LBP) because it does not induce amnesia and has memory-promoting action in animals and humans (43, 44). These results were also observed by Shanker and Singh, who reported that the BM extract possessed an anxiolytic effect (45).

Cardiovascular activity: The ethanolic extract of BM shows cardiac depressive activity on left ventricular contractility, heart rate, and coronary flow in isolated rabbit hearts (46). It also demonstrated a protective effect of BM on the pulmonary artery and aorta (47).

Gastroprotective activity:

The anti-ulcer and ulcer-healing activities of the *Bacopa monnieri* extract may be due to its effects on various mucosal offensive and defensive factors (48). It also has a beneficial role in intestinal spasms such as irritable bowel syndrome (49). This may be due to its spasmolytic activity on intestinal smooth muscle via inhibition of calcium influx across cell membrane channels. Fresh BM juice (BMJ) and BM extracts have been reported to have significant antiulcerogenic activity (50, 51, 52). Ulcer protective effect of BMJ may be due to its effect on mucosal defensive factors such as enhanced mucin secretion, mucosal glycoprotein and decreased cell shedding, rather than on offensive factors such as acid and pepsin.

Hepatoprotective activity:

It was found that pre treatment with BM extract was found to have a significant protective effect against morphine-induced liver and kidney dysfunction in terms of serum glutamateoxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, lactate dehydrogenase, and gamma-glutamyl transferase activities, and urea, creatinine, and uric acid levels, respectively (53). Pre-treatment with bacoside A also prevents the elevation of lipid peroxidation (Lipid Peroxidase) and the activity of serum marker enzymes and maintains the antioxidant system, thus protecting rats from diethylnitrosamine-induced hepatic toxicity (54).

Use of Brahmi

As a Memory Enhancer

Medicinally, the entire plant has been used in different formulations to treat various disorders, particularly those involving poor memory, intellect, and anxiety since the prehistoric times. Bacosides, which are the dynamic elements of Brahmi, are responsible for improving the efficiency of signal transmission along nerve fibers, which in turn fortifies memory and cognition [9]. Accounting for the multifactorial nature of these illnesses, present-day prescription-based psychoactive medications have met with constrained achievement. In this manner, there is a growing interest in novel items that could focus on numerous pathways and enhance mental capacities either freely or in combination with regular medications. *Centella asiatica* appears to be exceptionally valuable in enhancing learning and memory. It is also utilized as a brain tonic to promote brain growth and cerebrum development. Research confirms that *Centella asiatica* has neuroprotective properties and nootropic movement with helpful ramifications for patients with memory misfortune. These findings indicate that *Centella asiatica* can repair damaged neurons [10] and stimulate neuronal dendritic growth during neurodegeneration [11].

Medicinal Benefits

In one of the studies, the findings indicated that daily administration of *Centella asiatica* for two months reduced stress, attenuated anxiety, negated depression, and enhanced adjustment and attention in patients. Therefore, *Centella asiatica* has the potential to regulate the hypothalamo-pituitary-adrenocortical axis (HPA axis), especially during stress-related disorders, strengthening the opinion that *Centella asiatica* may be a safer alternative to benzodiazepines for the treatment of stress-related clinical disorders [12]. Another study concluded that the regular use of Brahmi could be helpful as a supplement in the treatment of neurological disorders caused by free radical damage. Free radicals, or highly reactive oxygen species, are formed by exogenous chemicals or endogenous metabolic processes in the human body. These are capable of oxidizing biomolecules such as nucleic acids, proteins, lipids, and DNA, and can initiate different degenerative diseases such as urological disorders, cancer, emphysema, cirrhosis, atherosclerosis, and arthritis. Brahmi is rich in antioxidants, which are compounds that terminate the attack of free radicals, thus reducing the risk of these disorders [13].

Brahmi dosage along with standard therapies is likely to improve cognition and social skills in Children [14].

Centella asiatica aids in antiepileptic activity by reducing motor activity [15], restoring the level of growth-stimulating hormone [16], and enhancing neuronal dendrites in stress and memory disorders [17]. It has been used as a memory enhancing, strength promoting,

immune booster, anti-anxiety, anti-epilepsy, and anti-stress substance since ancient times [18,19].

Molecular Pharmacology of Brahmi

Brahmi basically contains triterpene acids [25], volatile and fatty acid that contains glycerides of palmitic, stearic, linoleic, and linonic acids [26], alkaloids [27], Glycosides [28] and flavonoids which is isolated from the leaves of the Brahmi plants. The plant also contains amino acids, magnesium, sodium and potassium which have healing properties.

Pharmacological Studies of Brahmi

In field of Ayurveda medicine brahmi is most useful medicinal plant and several research studies in this field suggested different biological activities. Some biological activities are as following.

Gastric ulcer healing

In case of gastric ulcer it prevents development of cold induced gastric ulcer which is formulated due to stress. It helps in enhancement of GABA level in the brain and generates protective action against the stress induced ulcer due to its adaptogenic property. It also strengthens the mucosal barrier and reduces the damaging effects of free radicals [29].

Wound healing

It helps in wound healing by producing triterpenoid fraction extracted from *Centella asiatica* which helps to increase the percentage of collagen in cell layer fibronectin and promotes wound healing [30]. Asiatic Acid is the extract of brahmi leaves increases the peptidic hydroxyproline and helps in remodeling of collagen synthesis in wounds.

Memory enhancing

Brahmi plants have significant results on learning and memory enhancer. It helps to decrease the level of norepinephrine and dopamine in the brain that results in increased cognitive ability [31]. Aquatic extract of brahmi decreased the pentylenetetrazole kindled seizure and shows improvement in the learning.

Comparison to Pharmaceutical Cognitive Enhancers

The mechanisms of action on the brain of herbal medicines such as *Bacopa monnieri* are often different than pharmaceutical enhancers. Herbal medicines often require chronic administration and therefore significant time to exert their influence compared to acute effects of pharmaceutical cognitive enhancers such as amphetamines or modafinil. Despite their different mechanisms of action and treatment time to cognitive improvement, a recent attempt has been made to compare the effect size or magnitude of effect of different cognitive enhancers. Neale et al (17) compared the effect sizes of herbal medicines such as EBm and Ginseng with pharmaceuticals such as Modafinil and concluded that although the time course for cognitive improvement were different the magnitude of cognitive improvement were similar.

Studies Currently Underway

Improving Cognition in the Elderly

One study (20), specifically designed to address the issue of cognitive aging, was the Australian Research Council Longevity Intervention Study (ARCLI, ANZCTR12611000487910). The mechanisms by which *Bacopa monnieri* acts on cells appear to be promising for ameliorating cognitive decline.

Research on cognitive aspects of aging (typically in 60 to 90 year-olds) has identified consistent deficits in reasoning and decision making, spatial abilities, perceptual-motor and cognitive speed, and most robustly memory. Longitudinal studies on aged populations have illuminated the time course of cognitive deterioration. Using 5 to 10 year re-test intervals significant decrements across cognitive capacities become evident. A recent review of longitudinal ageing studies concludes that crystallized intelligence (e.g., factual knowledge) remains intact until late ageing whereas measures of speed, information processing and aspects of memory (e.g., working memory) are more sensitive to decline from age (21).

These psychological and cognitive changes mirror brain changes over the same

period. As we get older, changes in ventricular enlargement, reduction in gross brain volume, reductions in frontal and temporo-parietal brain volume, higher levels of cortical atrophy, and increased white matter hyperintensities can be observed (22). These changes in brain morphology are often paired with increases in neuropathological events, such as an increase in β -amyloid ($A\beta$) protein deposition, formation of neurofibrillary tangles, and increased neuroinflammatory reactions (23-28). Later changes are also seen in neurodegenerative disorders, such as Alzheimer's dementia (AD) and other neurodegenerative disorders associated with increased age. These brain processes are not exclusive to neurodegenerative disorders such as AD, and in fact occur in a large proportion of cognitively intact individuals as they age.

For example, in one study, the proportion of people without dementia with $A\beta$ deposits ranged from 3% in the 36-40 age group to 75% in the ≥ 85 age group (23). Increasing age also appears to be associated with numerous microscopic insults related to oxidative stress (24). Free radicals formed in the brain cause significant cellular damage and mediate processes that result in large-scale neural cell death. The generation of free radicals also leads to the generation of pro-inflammatory molecules and a state of low-level chronic inflammation, leading to further cellular damage, neurodegeneration, and apoptosis (25)

Dementia

Given the animal work indicating changes due to CDRI 08 to inflammatory and beta amyloid levels reviewed above we hypothesised that 6 month administration of 320 mg of CDRI 08 improves cognitive functioning in patients with Alzheimer's Dementia. This study is currently underway.

Cognition, Hyperactivity and Inattention in the Young

Recently, we commenced a multi-centre trial in which 6-14 year old boys with high levels of hyperactivity or inattention were administered placebo or EBm (CDRI 08) for 14 weeks. Hyperactivity and Inattention were the primary outcome variables, but other measures, including brain electrical activity, were also measured. The incidence of cognitive deficits, including inattention, is high in the Western world, and parents and practitioners are currently seeking alternative treatments to amphetamine-based medications in children. Given the cognitive enhancing potential shown for KeenMind in previous studies on healthy participants, it was hypothesized that chronic administration of KeenMind may assist children with attention problems. This study is currently underway.

Effect of Bacopa monnieri on Cognitive functions in Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder of uncertain cause and pathogenesis. It mostly affects the elderly. In mild cases it results in forgetfulness and as the disease progresses it affects both short and long term memory. It is the commonest cause of dementia in elderly, responsible for approximately 60-80 percent of cases 1-4. It has significant effect on quality of life. Currently available treatments can modulate the disease course and ameliorate some symptoms but no proven effective therapeutic cure for Alzheimer has been identified to date.

Bacopa monnieri (synonyms – Bacopa monniera, Herpestis monniera), family Scrophulariaceae 5, 6, also known as 'Brahmi', is an indigenous plant, found throughout India, Nepal, Sri Lanka, China, Taiwan, Vietnam and Florida, Hawaii and some other southern states of USA. It has been referred in Ayurveda since centuries as a 'Medhya Rasayan' 6.

Bacopa is a small tropical, creeping, succulent, marshy herb with short, petiolated, oblong leaves, rooting at nodes. Stem is 10-30 cm long, 1-2 mm thick, with soft, glabrous ascending branches. Leaves are 0.6-2.5 cm long and 3-8 mm broad. Flowers are blue or white with purple veins, axillary and solitary on long pedicels. Capsule is ovoid, glabrous, up to 5 mm long. It has no distinct odor but taste is slightly bitter 5. It has been used as a brain tonic for improvement of memory and concentration 7 and for the treatment of mental illness and epilepsy 6.

Bacopa's main chemical constituents include alkaloids brahmine, herpestine and nicotine, saponin monierin, hersaponin 8, bacoside A18, A2 9, A3 10 and B 11 and four saponin bacogenin A1 to A4 12. It is known to be safe and well tolerated in humans^{13, 14}. In a phase I study, bacoside A and B were found to be well tolerated in both single dose (20-300 mg) and multiple doses (100-200 mg) for 4 weeks by healthy human subjects¹³. Many clinical studies of Bacopa's actions on various systems have been published. Bacopa methanol extract has dose dependent free radical scavenging capacity and protective effect on DNA cleavage¹⁴. Its antioxidant property is postulated to be responsible for its antistress, immunomodulatory, cognition facilitatory, anti-inflammatory and anti-aging effects. Its anti lipid peroxidation property has been credited with memory enhancing and sedative actions. It is recommended for its efficacy in low doses for long term therapy rather than a single high dose¹⁵. Bacopa has been used to maintain youthful vitality and longevity. Ayurveda describes it as cold, bitter, astringent, digestive, carminative, laxative, diuretic, anti-inflammatory, depurative, bronchodilator, anticonvulsant and tonic for heart and nerves^{5, 6}. Its anxiolytic action is comparable to benzodiazepine in animal models of clinical anxiety¹⁶. No significant motor deficits were seen with its anxiolytic doses. Bacopa has been shown to reduce beta-amyloid deposits in the brain of animal models of Alzheimer's disease¹⁷. It has significant memory-promoting effect¹¹. It improves acquisition, retention and retrieval of learned tasks^{18, 19}. Brahmi Rasayan, an Ayurvedic preparation having Bacopa as the major ingredient, had anti-inflammatory actions in large oral doses in animal models of inflammation²⁰.

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Research Through Innovation