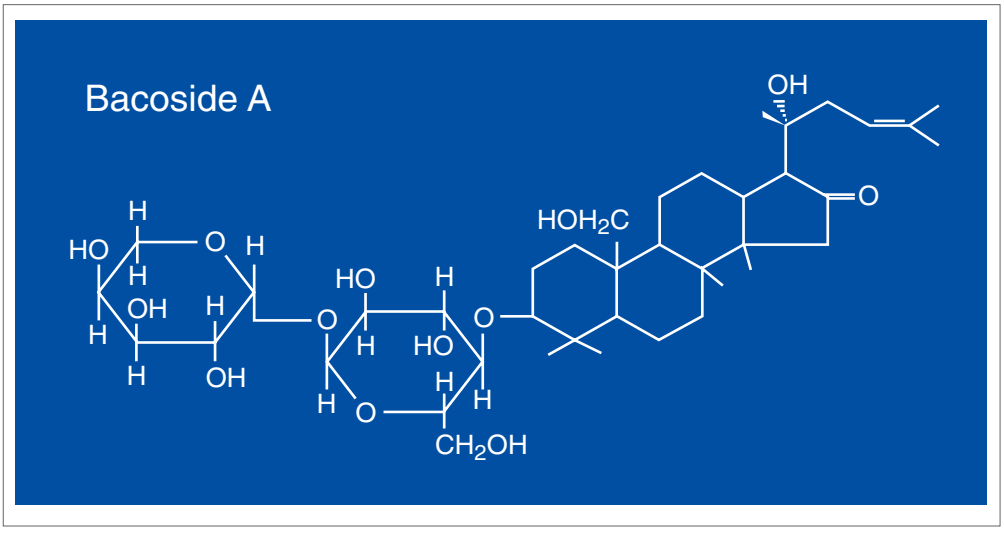
Bacopa monniera

Introduction

Bacopa monniera, also referred to as *Bacopa monnieri*, *Herpestis monniera*, water hyssop, and "Brahmi," has been used in the Ayurvedic system of medicine for centuries. Traditionally, it was used as a brain tonic to enhance memory development, learning, and concentration,[1] and to provide relief to patients with anxiety or epileptic disorders.[2] The plant has also been used in India and Pakistan as a cardiac tonic, digestive aid, and to improve respiratory function in cases of bronchoconstriction.[3] Recent research has focused primarily on Bacopa's cognitive-enhancing effects, specifically memory, learning, and concentration, and results support the traditional Ayurvedic claims. Research on anxiety, epilepsy, bronchitis and asthma, irritable bowel syndrome, and gastric ulcers also supports the Ayurvedic uses of Bacopa. Bacopa's antioxidant properties may offer protection from free radical damage in cardiovascular disease and certain types of cancer.



Description

Bacopa monniera, 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. The herb can be found at elevations from sea level to altitudes of 4,400 feet, and is easily cultivated if adequate water is available. Flowers and fruit appear in summer and the entire plant is used medicinally.[2,4]

Active Constituents and Pharmacokinetics

Compounds responsible for the pharmacological effects of Bacopa include alkaloids, saponins, and sterols. Many active constituents – the alkaloids Brahmine and herpestine, saponins d-mannitol and hersaponin, acid A, and monnierin – were isolated in India over 40 years ago. Other active constituents have since been identified, including betulic acid, stigmastarol, beta-sitosterol, as well as numerous bacosides and bacopasaponins. The constituents responsible for Bacopa's cognitive effects are bacosides A and B.[5-9]

Mechanisms of Action

Since Bacopa's primary therapeutic use is to enhance cognitive function, most research has focused on the mechanism behind these properties. The triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission.[10]

Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer's disease.[11] Based on animal study results, bacosides appear to have antioxidant activity in the hippocampus, frontal cortex, and striatum.[12] Animal research has shown Bacopa extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain.[13] *In vitro* research has shown Bacopa exerts a protective effect against DNA damage in astrocytes[14] and human fibroblasts.[15]

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.[16] Bacopa appears to stabilize mast cells *in vitro*,[17] and possesses anti-inflammatory activity via inhibition of prostaglandin synthesis and lysosomal membrane stabilization.[18] *In vitro* research suggests an anticancer effect for Bacopa extracts, possibly due to inhibition of DNA replication in cancer cell lines.[19]

Clinical Indications

Cognitive Effects

Adults

Bacopa monniera has been studied clinically for its acute and chronic effects on cognitive function. In adults, it appears only chronic administration is associated with cognitive-enhancing effects. In a double-blind, placebo-controlled trial of 38 healthy volunteers (ages 18-60), subjects were given a single dose of 300 mg *Bacopa monniera* extract (standardized to 55-percent combined bacosides A and B) or placebo. Subjects were tested two hours after drug administration, coinciding with maximum pharmacodynamic effect. Acute administration of this dose of Bacopa extract resulted in no significant changes in cognitive function when compared to baseline values. Parameters assessed included attention, working and short-term memory, verbal learning, decision making, memory consolidation, executive processes, planning and problem solving, speed of information processing, and motor responsiveness.[20]

On the other hand, significant cognitive-enhancing benefits have been demonstrated with more chronic administration of Bacopa extracts. Australian researchers conducted a double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and same dose of Bacopa extract (300 mg daily) containing 55-percent combined bacosides. Forty-six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12-week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks. These results may be attributed to Bacopa's antioxidant properties and/or its effect on the cholinergic system.[21]

Children

Bacopa's ability to modulate or enhance cognitive function has also been studied in children. Forty children from rural India (ages 6-8) were divided into treatment and placebo groups of 20 children each. Children in the treatment group received one teaspoon Bacopa syrup (350 mg Bacopa powder/teaspoonful) three times daily for three months. The placebo group received Syrup Simplex (details not available). A series of tests measuring visuomotor and perceptual abilities and memory span were administered at baseline and at the end of treatment. Significant improvements were noted in strengthened exploratory drive (as measured by maze learning), improved perceptual images of patterns, and increased perceptual organization and reasoning ability (as measured by reaction time). This study, however, was not double-blinded.[22]

A double-blind, randomized, placebo-controlled trial of 36 children with diagnosed attention deficit/hyperactivity disorder was conducted over a 16-week period. Nineteen children received an extract of Bacopa (standardized to contain 20-percent bacosides) at a dosage of 50 mg twice daily for 12 weeks, and 17 subjects were given a placebo. The mean age of the children in the two groups was 8.3 years and 9.3 years, respectively. Active drug treatment was followed by four weeks of placebo and the children were evaluated on numerous cognitive function tests at baseline, four, eight, 12, and 16 weeks. A significant benefit was observed in Bacopa-treated subjects at 12 weeks as evidenced by improvement on sentence repetition, logical memory, and paired associate learning tasks. Evaluation showed these improvements were maintained at 16 weeks (after four weeks placebo administration).[23]

Anxiety and Depression

Bacopa's traditional use as an anti-anxiety remedy in Ayurvedic medicine is supported by both animal and clinical research. Research using a rat model of clinical anxiety demonstrated a Bacopa extract of 25-percent bacoside A exerted anxiolytic activity comparable to Lorazepam, a common benzodiazapene anxiolytic drug. Importantly, the Bacopa extract did not induce amnesia, side effects associated with Lorazepam, but instead had a memory-enhancing effect.[24]

A one-month, limited clinical trial of 35 patients with diagnosed anxiety neurosis demonstrated that administration of Brahmi syrup (30 mL daily in two divided doses, equivalent to 12 g dry crude extract of Bacopa) resulted in a significant decrease in anxiety symptoms, level of anxiety, level of disability, and mental fatigue, and an increase in immediate memory span. Other changes noted were increased body weight, decreased respiration rate, and decreased systolic blood pressure.[25]

Epilepsy

Although Bacopa has been indicated as a remedy for epilepsy in Ayurvedic medicine, research in animals shows anticonvulsant activity only at high doses over extended periods of time. Early research in India demonstrated that hersaponin (an active constituent) exhibited protection against seizures in mice.[26] A more recent Indian study also examined the anticonvulsant properties of Bacopa extracts in mice and rats. Researchers determined that intraperitoneal injections of high doses of Bacopa extract (close to 50 percent of LD50) given for 15 days demonstrated anticonvulsant activity. When administered acutely at lower doses (approaching 25 percent of LD50), anticonvulsant activity was not observed.[27]

Bronchitis and Asthma

Animal studies have demonstrated Bacopa extracts have a relaxant effect on chemically-induced bronchoconstriction, probably via inhibition of calcium influx into cell membranes. An earlier *in vitro* study by Dar and Channa demonstrated the broncho-vasodilatory activity of *B. monniera* on rabbit and guinea pig trachea, pulmonary artery, and aorta.[28] A subsequent rat study with Bacopa extracts confirmed the earlier results. Methanol subfractions of Bacopa extracts were given to anesthetized rats prior to induction of bronchoconstriction with carbachol, an acetylcholine analogue. Nearly all of the Bacopa extract subfractions inhibited carbachol-induced

bronchoconstriction, hypotension, and bradycardia in this animal model.[16] An *in vitro* study also demonstrated a methanol extract of Bacopa possessed potent mast cell stabilizing activity comparable to disodium cromoglycate, a commonly used allergy medication.[17] These studies indicate the potential usefulness of Bacopa extracts in bronchoconstrictive and allergic conditions, and warrant human studies.

Gastrointestinal Disorders

In vitro, animal, and human studies have investigated the effects of Bacopa extracts on the gastrointestinal tract. *In vitro* studies[28,29] have demonstrated direct spasmolytic activity on intestinal smooth muscle, via inhibition of calcium influx across cell membrane channels. This property suggests Bacopa extracts may be of benefit in conditions characterized by intestinal spasm such as irritable bowel syndrome (IBS).

A double-blind, randomized, placebo-controlled trial of 169 patients with IBS compared the effects of an Ayurvedic preparation containing *Bacopa monniera* and *Aegle marmelos* to standard therapy (clidinium bromide, chlordiazepoxide, and psyllium). Subjects were divided into five subgroups based on type of IBS, and randomly assigned to standard drug treatment, botanical treatment, or placebo for six weeks. Treatment was administered orally as 5 g drug, botanical, or placebo three times daily. Data analysis revealed standard drug therapy to be superior to the Ayurvedic preparation, except in patients with IBS characterized by diarrhea. This result was attributed to the *Aegle marmelos*, a commonly known antidiarrheal in India, although the two botanicals were not given separately, so individual effects cannot be confirmed. Ayurvedic therapy was superior to placebo in all parameters examined, but no benefit could be linked specifically to the Bacopa portion of the Ayurvedic preparation.[30]

Animal and *in vitro* studies suggest Bacopa may have a protective and curative effect for gastric ulcers. In rats a Bacopa extract standardized for bacoside A was evaluated for its prophylactic and healing effects in five models of gastric ulcers. At a dose of 20 mg/kg for 10 days, Bacopa extract significantly healed penetrating ulcers induced by acetic acid, significantly strengthened the mucosal barrier, and decreased mucosal exfoliation. The extract also alleviated stress-induced ulcers as observed by significant reduction in lipid peroxidation in rat gastric mucosa. Bacopa's antioxidant properties and its ability to balance SOD and catalase levels may account for this effect.[31] A recent *in vitro* study also demonstrated Bacopa extract's specific anti-microbial activity against *Helicobacter pylori*, a bacteria associated with chronic gastric ulcers. When the extract was incubated with human colonic muscosal cells and *H. pylori* it resulted in accumulation of prostaglandin E and prostacycline, prostaglandins known to be protective for gastric mucosa.[32]

Cardiovascular Effects

Use of Bacopa as a "cardiotonic" is frequently mentioned in Ayurvedic medicine texts, but no clinical studies have been conducted. *In vitro* research using rabbit aorta and pulmonary artery has demonstrated Bacopa extract exerts a vasodilatory effect on calcium chloride-induced contraction in both tissues. It is believed to exert this effect via interference with calcium channel flux in tissue cells.[29]

Hypothyroidism

A study in mice demonstrated high doses (200 mg/kg) of Bacopa extract increased the thyroid hormone, T4, by 41 percent when given orally. T3 was not stimulated, suggesting the extract may directly stimulate synthesis and/or release of T4 at the glandular level, while not affecting conversion of T4 to T3. While this study indicates Bacopa extract does have a stimulatory effect on thyroid function, the doses were very high and the typical 200-400 mg daily dose in humans may not have the same effect.[33]

Protection from Drug Toxicity

In vitro and animal studies have demonstrated Bacopa extracts may have a protective effect against certain drugs and their negative side effects. An *in vitro* study using guinea pig ileum isolates examined the effect of Bacopa extract on drug-induced morphine withdrawal. Addition of 1,000 µg/mL Bacopa extract to the tissue isolates prior to injection of morphine significantly reduced the naloxone-induced withdrawal effects,[34] an effect that may be attributed to the anticholinergic and calcium antagonistic activity reported by other researchers.[29]

A second study examined the effects of an alcohol extract of Bacopa on morphine-induced hepatotoxicity in rats, as measured by lipid peroxide accumulation and antioxidant enzyme levels. Administration of Bacopa extract with morphine significantly decreased lipid peroxidation and increased levels of antioxidant enzymes and glutathione in rat hepatic tissue, when compared to morphine alone. These results suggest a protective effect for Bacopa on the hepatic antioxidant status in morphine-treated rats.[35] Some of the same researchers reported a similar effect for brain mitochondrial enzyme activity of morphine-treated rats.[36]

It has also been reported that antiepileptic drugs, such as phenytoin, can result in cognitive impairment.[37] In mice, Bacopa administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory. These results suggest a potential corrective effect of Bacopa extracts in phenytoin-induced cognitive deficit.[38]

Cancer

In vitro research demonstrated Bacopa saponin fractions have cytotoxic activity for sarcoma-180 cells. It is thought this might be due to Bacopa's inhibition of DNA replication in the cancerous cell line.[19] Research in humans may be indicated.

Drug/Botanical Interactions

Bacopa has been noted in animal models to decrease the toxicity of morphine[35] and phenytoin.[38] It has also been shown, albeit inconsistently, to have a slight sedative effect, so caution is advised in combination with other known sedatives. Also, since it appears to stimulate T4 activity in animals at high doses, it is theorized it may potentiate the activity of thyroid-stimulating drugs or inhibit the effect of thyroid-suppressant drugs.

Side Effects and Toxicity

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. A double-blind, placebo-controlled clinical trial of healthy male volunteers investigated the safety of pharmacological doses of isolated bacosides over a four-week period. Concentrated bacosides given in single (20-30 mg) and multiple (100-200 mg) daily doses were well tolerated and without adverse effects.[10] The LD50 of Bacopa extracts administered orally to rats was 5 g/kg for aqueous extracts and 17 g/kg of the alcohol extract. Neither extract resulted in gross behavioral changes at these concentrations.[27]

Dosage

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. 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.

References

1. Mukherjee DG, Dey CD. Clinical trial on Brahmi. I. *J Exper Med Sci* 1966;10:5-11.
2. Chopra RN. *Indigenous Drugs of India*. 2nd ed. Calcutta, India: U.N. Dhur and Sons; 1958:341.
3. Nadkarni KM. *The Indian Materia Medica*. Columbia, MO: South Asia Books; 1988:624-625.

4. Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs: Monographs for the Western Herbal Practitioner*. Warwick, Queensland: Phytotherapy Press; 1996.
5. Kapoor LD. *CRC Handbook of Ayurvedic Medicinal Plants*. Boca Raton, FL: CRC Press Inc; 1990;61.
6. Chakravarty AK, Garai S, Masuda K, et al. Bacopasides III-V: three new triterpenoid glycosides from *Bacopa monniera*. *Chem Pharm Bull (Tokyo)* 2003;51:215-217.
7. Hou CC, Lin SJ, Cheng JT, Hsu FL. Bacopaside III, bacopasaponin G, and bacopasides A, B, and C from *Bacopa monniera*. *J Nat Prod* 2002;65:1759-1763.
8. Mahato SB, Garai S, Chakravarty AK. Bacopasaponins E and F: two jujubogenin bisdesmosides from *Bacopa monniera*. *Phytochemistry* 2000;53:711-714.
9. Chakravarty AK, Sarkar T, Masuda K, et al. Bacopaside I and II: two pseudojujubogenin glycosides from *Bacopa monniera*. *Phytochemistry* 2001;58:553-556.
10. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monniera* Linn. (Brahmi). *Indian J Pharmacol* 1997;29:S359-S365.
11. Enz A, Amstutz R, Boddeke H, et al. Brain selective inhibition of acetylcholinesterase: a novel approach to therapy for Alzheimer's disease. *Prog Brain Res* 1993;98:431-438.
12. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monniera* in rat frontal cortex, striatum, and hippocampus. *Phytother Res* 2000;14:174-179.
13. Chowdhuri DK, Parmar D, Kakkar P, et al. Antistress effects of bacosides of *Bacopa monnieri*: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. *Phytother Res* 2002;16:639-645.
14. Russo A, Borrelli F, Campisi A, et al. Nitric oxide-related toxicity in cultured astrocytes: effect of *Bacopa monniera*. *Life Sci* 2003;73:1517-1526.
15. Russo A, Izzo A, Borrelli F, et al. Free radical scavenging capacity and protective effect of *Bacopa monniera* L. on DNA damage. *Phytotherapy Res* 2003;17:870-875.
16. Channa S, Dar A, Yaqoob M, et al. Broncho-vasodilatory activity of fractions and pure constituents isolated from *Bacopa monniera*. *J Ethnopharmacol* 2003;86:27-35.
17. Samiulla DS, Prashanth D, Amit A. Mast cell stabilizing activity of *Bacopa monnieri*. *Fitoterapia* 2001;72:284-285.
18. Jain P, Khanna NK, Trehan TN, et al. Antiinflammatory effects of an Ayurvedic preparation, Brahmi Rasayan, in rodents. *Indian J Exp Biol* 1994;32:633-636.
19. Elangovan V, Govindasamy S, Ramamoorthy N, Balasubramaanian K. *In vitro* studies on the anticancer activity of *Bacopa monnieri*. *Fitoterapia* 1995;66:211-215.
20. Nathan PJ, Clarke J, Lloyd J, et al. The acute effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy normal subjects. *Hum Psychopharmacol* 2001;16:345-351.
21. Stough C, Lloyd J, Clarke J, et al. The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects. *Psychopharmacology* 2001;156:481-484.
22. Sharma R, Chaturvedi C, Tewari PV. Efficacy of *Bacopa monnieri* in revitalizing intellectual functions in children. *J Res Edu Indian Med* 1987;Jan-June:1-12.
23. Negi KS, Singh YD, Kushwaha KP, et al. Clinical evaluation of memory enhancing properties of Memory Plus in children with attention deficit hyperactivity disorder. *Ind J Psychiatry* 2000;42:Supplement. [Abstract]
24. Bhattacharya SK, Ghosal S. Anxiolytic activity of a standardized extract of *Bacopa monniera* in an experimental study. *Phytomedicine* 1998;5:77-82.
25. Singh RH, Singh L. Studies on the anti-anxiety effect of the Medyha Rasayana drug, Brahmi (*Bacopa monniera* Wettst.) – Part 1. *J Res Ayur Siddha* 1980;1:133-148.
26. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from *Herpestis monniera*, Linn. (Brahmi). *Ind J Med Res* 1967;55:473-482.
27. Martis G, Rao A. Neuropharmacological activity of *Herpestis monniera*. *Fitoterapia* 1992;63:399-404.
28. Dar A, Channa S. Relaxant effect of ethanol extract of *Bacopa monniera* on trachea, pulmonary artery and aorta from rabbit and guinea-pig. *Phytother Res* 1997;11:323-325.
29. Dar A, Channa S. Calcium antagonistic activity of *Bacopa monniera* on vascular and intestinal smooth muscles of rabbit and guinea-pig. *J Ethnopharmacol* 1999;66:167-174.
30. Yadav SK, Jain AK, Tripathi SN, Gupta JP. Irritable bowel syndrome: therapeutic evaluation of indigenous drugs. *Indian J Med Res* 1989;90:496-503.

31. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of *Bacopa monniera* in gastric ulcer models. *Phytomedicine* 2001;8:423-430.
32. Goel RK, Sairam K, Babu MD, et al. *In vitro* evaluation of *Bacopa monniera* on anti-*Helicobacter pylori* activity and accumulation of prostaglandins. *Phytomedicine* 2003;10:523-527.
33. Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. *J Ethnopharmacol* 2002;81:281-285.
34. Sumathi T, Nayeem M, Balakrishna K, et al. Alcoholic extract of *Bacopa monniera* reduces the *in vitro* effects of morphine withdrawal in guinea-pig ileum. *J Ethnopharmacol* 2002;82:75-81.
35. Sumathy T, Subramanian S, Govindasamy S, et al. Protective role of *Bacopa monniera* on morphine-induced hepatotoxicity in rats. *Phytotherapy Res* 2002;15:643-645.
36. Sumathy T, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of *Bacopa monniera* on morphine-induced brain mitochondrial enzyme activity in rats. *Fitoterapia* 2002;73:381-385.
37. Smith DB. Cognitive effects of anti-epileptic drugs. *Adv Neurol* 1991;55:197-212.
38. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by *Bacopa monniera*, a reputed Indian nootropic plant. *J Ethnopharmacol* 2000;71:383-390.