REVIEW ARTICLE

A review on *Bacopa monniera:* Current research and future prospects

Kashmira J. Gohil[1], Jagruti A. Patel
Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, [1]Maliba Pharmacy College, Bardoli, Surat, Gujarat, India

In recent times, the use of herbal products has increased tremendously in the western world as well as in developed countries. Lately, one of the outstandingly important medicinal plants, widely used therapeutically in the orient and becoming increasingly popular in the west is *Bacopa monniera*, a well-known nootropic. The present review summarizes our current knowledge of pharmacological actions, preclinical and clinical studies, major bioactives, reported mechanisms of actions, clinical efficacy, safety and the possibility of interactions of the herb with the conventional drugs. Simultaneously, research updates as well as avenues for further research are also mentioned concerning the plant.

Key words: *Bacopa monniera*, neurotonics, clinical studies, herb-drug interactions, preclinical studies

INTRODUCTION

Recently, the interest in the use of herbal products has grown dramatically in the western world as well as in developed countries.[1] It is now becoming exceedingly apparent that available psychotherapeutics does not properly meet therapeutic demands of a vast majority of patients with mental health problems, and that herbal remedies remain to be the ultimate therapeutic hope for many such patients in the western world and elsewhere.[2] The vast majorities of currently available psychoactive drugs as herbal remedies today seem to be a reflection of such a situation. In the folklore of Indian medicine, several herbs have been used traditionally as brain or nerve tonics. One of the most popular of these herbs is *Bacopa monniera* (BM), a well-known memory booster. This comprehensive review summarizes our current knowledge of the major bioactivities and clinical efficacy of BM, one of the currently popular central nervous system (CNS)-activating herbal plants.

Description of the Plant

BM, also referred to as, *Herpestis monniera*, water hyssop, locally known as brahmi or Jalanimba in India, has been used for centuries in the Ayurveda, a holistic system of medicine originating from India. The name brahmi is derived from the word 'Brahma', the mythical 'creator' in the Hindu pantheon. Because the brain is the centre for creative activity, any compound that improves the brain health is called brahmi, which also means 'bringing knowledge of the supreme reality' In India; BM is largely treasured as a revitalizing herb used by Ayurvedic medical practitioners for almost 3000 years. It is classified as a *medhyarasayana*, a drug used to improve memory and intellect (medhya). The herb has been mentioned in several ancient Ayurvedic treatises including the 'Charaka Samhita' since sixth century AD, in which it is recommended in formulations for the management of a range of mental conditions including anxiety, poor cognition and lack of concentration, as a diuretic and as an energizer for the nervous system and the heart.[3] Specific uses include the treatment of asthma, insanity and epilepsy.[4] The plant has been utilized extensively as a nootropic, digestive aid and to improve learning, memory and respiratory function.[5,6] The herb is from a family S*crophulariaceae* and is a small creeping herb with numerous branches, small oblong leaves and light purple or small and white flowers, with four or five petals [Figure 1. *B. monniera* herb]. It is found in wetlands throughout the Indian subcontinent in damp and marshy or sandy areas near streams in tropical regions. The genus Bacopa includes over 100 species of aquatic herbs distributed throughout the warmer regions of the world, apart from India, Nepal, Sri Lanka, China, Taiwan and Vietnam and is also found in Florida and other southern states of the USA.[7] The entire plant is used medicinally.[8]

Active Constituents

Compounds responsible for the pharmacological effects of BM include alkaloids, saponins and sterols. Detailed investigations first reported the isolation of the alkaloid 'brahmine' from BM.[9] Later, other alkaloids like nicotine and herpestine have

Address for correspondence: Prof. Kashmira J. Gohil, Department of Pharmacology, Maliba Pharmacy College, Gopalvidhyanagar, Bardoli- 394 350, Surat, Gujarat, India. E-mail: kjgohil@yahoo.com
Received: 15-02-2009; **Accepted:** 05-06-2009; DOI: 10.4103/0973-8258.62156

Figure 1: *Bacopa monniera* herb

also been reported.[10] Subsequently, the isolation of D-mannitol and a saponin, hersaponin and potassium salts was reported.[11] The major chemical entity shown to be responsible for neuropharmacological effects and the nootropic action or antiamnestic effect of BM is bacoside A, assigned as 3-(a-L-arabinopyranosyl)-O-b-D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene.[12] Bacoside A usually co-occurs with bacoside B; the latter differing only in optical rotation and probably an artefact produced during the process of isolating bacoside A.[13] On acid hydrolysis, bacosides yield a mixture of aglycones, bacogenin A1, A2, A3,[14-16] which are artefacts, and two genuine sapogenins, jujubogenin and pseudojujubogenin and bacogenin, A4, identified as ebelin lactone pseudojujubogenin, were isolated.[17] Successively, a minor saponin bacoside A1 and a new triperpenoid saponin, bacoside A3, were isolated.[17] Later, three new dammarane-type triterpenoid saponins of biological interest, bacopasaponins A, B and C, pseudojujubogenin were isolated and a new dammarane-type pseudojujubogenin glycoside, bacopasaponin D, were identified by spectroscopic and chemical transformation methods.[18] In view of the increasing interest in this herbal plant, yet two new pseudojujubogenin glycosides designated as bacopaside I and II were isolated from glycosidic fraction of the methanol.[19] Subsequently, three new saponins from BM, designated as bacopasides III, IV and V were isolated.[20] In addition, the isolation of three new phenylethnoid glycosides, viz. monnierasides I–III along with the known analogue plantainoside B was reported from the glycosidic fraction of BM.[21] Moreover, an isolation of a new saponin, a jujubogenin, named bacopasaponin G, and a new glycoside, phenylethyl alcohol was also reported[22] [Figure 2a and b]. The chemical structures of saponins[23] isolated from BM are shown In Figure 2a, bacoside A levorotatory, and Figure 2b, bacoside B dextrorotatory.

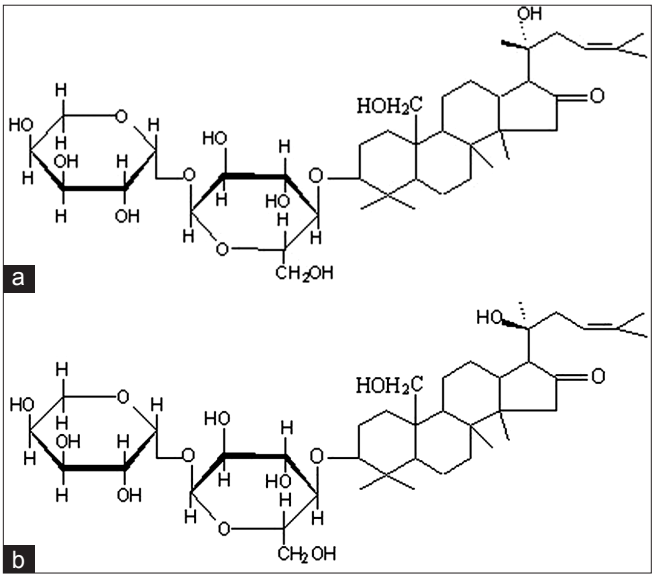

Figure 2: Chemical structures of some well-known saponins from *Bacopa monniera*.[11] (a) Bacoside A (levorotatory); (b) Bacoside B (dextrorotatory)

Mechanism of Action Based on Preclinical Studies

The BM extracts and isolated bacosides have been extensively investigated for their neuropharmacological effects. The triterpenoid saponins and their bacosides are said to be responsible for BM's ability to enhance nerve impulse transmission. It was suggested that bacosides induce membrane dephosphorylation, with a concomitant increase in protein and RNA turnover in specific brain areas.[24] The other proposal that was put forward was that BM enhances protein kinase activity in the hippocampus which may also contribute to its nootropic action and thus it would aids in repair of damaged neurons by enhancing kinase activity, neuronal synthesis and restoration of synaptic activity and ultimately nerve impulse transmission.[25]

Sedative and Tranquillizing Properties

Earlier studies reported a sedative effect of glycosides named hersaponins.[26] A subsequent study has found that the alcoholic extract, and to a lesser extent the aqueous extract of the whole plant exhibited tranquilizing effects on albino rats and dogs.[27] On the other hand, it has been found that the alcoholic extract of the plant and chlorpromazine improved the performance of rats in motor learning.[28] A previous study has reported that a single dose of the glycoside hersaponin is better than pentobarbitone in facilitating acquisition and retention of brightness discrimination reaction.[29]

Cognition

A team of other researcher reported that a standardized bacosides-rich extract of BM, reversed the cognitive deficits induced by intracerebroventricularly administered colchicines and injection of ibotenic acid into the nucleus *Basalis magnocellularis*.[30] In the same study, BM was

also shown to reverse the depletion of acetylcholine, the reduction in choline acetylase activity and a decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus. The cognition facilitating activity of the BM extract is attributed to the saponins, Bacoside A and Bacoside B, which are effective in much lower doses in various model studies, including tests for conditioned taste aversion and conditioned shock avoidance response.[31,32] BM's antioxidant properties and its ability to balance super oxide dismutase (SOD) and catalase levels were postulated to account for this effect.[33]

Antidepressant and Antianxiety Effects

Research using a rat model of clinical anxiety demonstrated that a BM extract containing 25% bacoside A exerted anxiolytic activity comparable to lorazepam, a common benzodiazepine anxiolytic drug, and it was attentively noted that the BM extract did not induce amnesia, side effects associated with lorazepam, but instead had a memory-enhancing effect.[34,35] The antidepressant potential of BM has been evaluated in an earlier study, wherein it showed a significant antidepressant activity in the most commonly used behaviour paradigms in animal models of depression, namely, forced swim test and learned helplessness tests.[36] In the study, the BM extract in the dose range of 20-40 mg/kg was given once daily for 5 days and it was found comparable to standard anti-depressant drug imipramine in anti-depressant activity in rodent animals. The same study has postulated the role of serotonin and GABA (gamma amino butyric acid) in the mechanism of action attributed for its antidepressant action along with its anxiolytic potential, based on the compelling evidence that the symptoms of anxiety and depression overlap each other.[37]

Anti-Epileptic Effects

Although BM has been indicated as a remedy for epilepsy in Ayurvedic medicine,[38] research in animals showed 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 and mentioned the possibility of its use as an adjuvant in treatment of epilepsy.[39] One Indian study examined the anticonvulsant properties of BM extracts in mice and rats. Researchers determined that intraperitoneal injections of high doses of BM extract (close to 50% of LD_{50}) given for 15 days demonstrated anticonvulsant activity. When administered acutely at lower doses (approaching 25% of LD_{50}), anticonvulsant activity was not observed.[40] It is postulated that the anti-convulsive effects could be mediated through GABA which is involved in neural impulse transmission, because substances which stimulate GABA are known to possess anticonvulsant, pain relieving and sedative activities.

Antioxidant and Adaptogenic Properties

BM extract or bacosides have shown an antioxidant activity[41-46] and antistress.[47] A previous study suggests an involvement of the GABA-ergic system in the mediation of these central nervous system effects of BM.[48] Based on animal study results, bacosides were shown to have antioxidant activity in the hippocampus, frontal cortex and striatum.[49] Animal research has shown that the BM extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain.[50] It was suggested that the adaptogenic properties of the herb would be beneficial in the management of stress related conditions as BM showed the potential to be effective in stress in a study on rats.[51] In the study, BME was found not only to induce the constitute expression of heat-shock protein (HSP 70) but also induce the CYP 450 enzymes in all regions of brain. The level of Hsp70 was found to be increased in brain as a response to stress. On the other hand, the group that was pre-treated for 1 week with 20-40 mg/kg/daily, before giving stress, the Hsp70 was found to be in lower concentration. An increase in the activity of CYP 450-dependent enzymes 7-pentoxyresorufin-odealkkylase (PROD) and 7-ethoxyresorufin-o-deethylase (EROD) was observed in all the brain regions after exposure to stress alone and with both doses of BME although the magnitude of induction observed was less with a higher dose of the same. Thus, it was suggested that the BM primed the brain for stress by stockpiling these useful enzymes even before stressful conditions and that our susceptibility to stress could be lowered by using this medicinal herb. It was speculated that this induction may be an adaptive response to the stress which needs further investigation. The level of SOD was also increased in brain in the groups pre-treated with BME. The data indicated that BME has a potential to modulate the activities of HSP 70, CYP 450 and SOD and thereby possibly allowing the brain to be prepared to act under adverse condition like stress.

Researchers concluded that BM helps in coping with combined hypoxic, hypothermic and immobilization stress that could lead to onslaught of 'free radicals'.[52] The results of the above-mentioned study have indicated that this extract exhibits interesting antioxidant properties, expressed by its capacity to scavenge superoxide anion and hydroxyl radical, and to reduce H_2O_2-induced cytotoxicity and DNA damage in human fibroblast cells.[45,53,54] BM extract has shown neuroprotective effect against aluminium-induced oxidative stress in the hippocampus of rat brain.[55] Aqueous extract of BM reduced nicotine-induced lipid peroxidation (LPO) and conferred geno protection in Swiss mice in one study.[56] Yet another study suggested that BM extract reduces amyloid levels in PSAPP mice and can be used in the therapy of Alzheimer's disease.[57] One of the recent studies has shown the protective role of bacoside A against

chronic cigarette smoking-induced oxidative damage in rat brain.[58] This antioxidant activity of BM is able to explain, at least in part, the reported antistress, cognition-facilitating and antiageing effects produced by it in experimental animals and in clinical situations[59] and may justify further investigation of its other beneficial biological properties.

Gastrointestinal Effects

Some *in vitro*, animal and human studies have investigated the effects of BME on the gastrointestinal tract. *In vitro* studies have demonstrated direct spasmolytic activity on intestinal smooth muscle, via inhibition of calcium influx across cell membrane channels. This property suggests that BME may be of benefit in conditions characterized by intestinal spasm such as irritable bowel syndrome (IBS).[60,61] The results indicated the direct action of the extract on smooth muscles. Also, calcium chloride-induced responses observed in the rabbits' blood vessels and jejunum were reduced in the presence of the BME (10-700 mcg/mL), suggesting direct interference with the influx of calcium ions. However, since the extract did not affect contractions induced by noradrenalin or caffeine, the authors concluded that the extract had no appreciable effect on the mobilization of intracellular calcium. Based on the results of the experiment, it is postulated that the spasmolytic effect of BME on smooth muscles is predominantly due to the inhibition of calcium influx, applicable to both electrical impulse-mediated and receptor-mediated calcium channels in the cell membrane. Animal and *in vitro* studies suggested that BM may have a protective and curative effect on gastric ulcers, and studies were reported for its antiulcerogenic activity.[62-66] In rats, a BME standardized for bacoside A was evaluated for its prophylactic and healing effects in five models of gastric ulcers.[67] At a dose of 20 mg/kg for 10 days, BME 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 LPO in rat gastric mucosa. BM's antioxidant properties and its ability to balance SOD and catalase levels were postulated to account for this effect.[67] A recent *in vitro* study also demonstrated its specific anti-microbial activity against *Helicobacter pylori*, a bacterium associated with chronic gastric ulcers. When the extract was incubated with human colonic muscosal cells and *H. pylori*, it resulted in the accumulation of prostaglandin E and prostacycline, prostaglandins known to be protective for gastric mucosa.[68]

Miscellaneous Studies

In vitro research has shown a protective effect of BM against DNA damage in astrocytes[69] and human fibroblasts.[70] *In vitro* research has suggested that an anticancer effect of BM extracts is possibly due to inhibition of DNA replication in cancer cell lines.[71] A study in mice demonstrated high doses (200 mg/kg) of BME increased the thyroid hormone, T4, by 41% when given orally. T3 was not stimulated, suggesting that 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 indicated that BM extract did have a stimulatory effect on thyroid function, the doses were very high and it was assumed that the typical 200-400 mg daily dose in humans may not have the same effect.[72] BM was also reported to possess anti-inflammatory activity via inhibition of prostaglandin synthesis and lysosomal membrane stabilization.[63,73] *In vitro* research using rabbit aorta and pulmonary artery has demonstrated that BME 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.[61] Animal studies have demonstrated that BME have a relaxant effect on chemically-induced bronchoconstriction, probably via inhibition of calcium influx into cell membranes. An earlier *in vitro* study demonstrated the broncho-vasodilatory activity of BM on rabbit and guinea pig trachea, pulmonary artery and aorta.[60] A subsequent rat study with BME confirmed the earlier results in which methanol sub-fractions of BME were given to anesthetized rats prior to induction of bronchoconstriction with carbachol, an acetylcholine analogue. Nearly all of the BME subfractions inhibited carbachol-induced bronchoconstriction, hypotension and bradycardia in this animal model.[74] An *in vitro* study also demonstrated that a methanol extract of BM possessed potent mast cell stabilizing activity comparable to disodium cromoglycate, a commonly used allergy medication.[75] These studies indicated the potential usefulness of BM extracts in bronchoconstrictive and allergic conditions and warrant human studies.

Clinical Studies: Cognition

Numerous clinical studies have been carried out to date to establish the efficacy of BM in memory and attention disorders and to study its acute and chronic effects clinically on cognitive function. A study was conducted to measure the effect of BME on human memory.[76] Seventy-six adults aged between 40 and 65 years volunteered for the double-blind randomized, placebo control study. The results showed a significant effect of BME on the test for the retention of new information. In the follow-up tests, it was found that the rate of learning was unaffected, suggesting that BM decreases the rate of forgetting of newly acquired information. In adults, only chronic administration was shown to enhance cognitive effects. In a double-blind, placebo-controlled trial of 38 healthy volunteers (ages 18-60), subjects were given a single dose of 300 mg BME (standardized to 55% combined bacosides A and B) or placebo.[77] Subjects were tested 2 h after drug administration, coinciding with maximum pharmacodynamic effect. Acute administration of this

dose of BME resulted in no significant changes in cognitive function when compared to baseline values. On the other hand, significant cognitive-enhancing benefits have been demonstrated with more chronic administration of BME, as demonstrated in a double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and same dose of BME (300 mg daily) containing 55% combined bacosides.[78] 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 5 weeks. These results were attributed to BM's antioxidant properties and/or its effect on the cholinergic system.[78] BM's ability to modulate or enhance cognitive function has also been studied in children.[79] In another double-blind, randomized, placebo controlled trial of 36 children with diagnosed attention deficit/hyperactivity disorder was conducted over a 16-week period.[80] Nineteen children received an extract of BM, standardized to contain 20% bacosides at a dosage of 50 mg twice daily for 12 weeks, and 17 subjects were given a placebo. Active drug treatment was followed by 4 weeks of placebo and the children were evaluated on numerous cognitive function tests at baseline, 4, 8, 12 and 16 weeks. A significant benefit was observed in BM-treated subjects at 12 weeks as evidenced by improvement on sentence repetition, logical memory and paired associated learning tasks. Evaluation showed that these improvements were maintained at 16 weeks after 4 weeks placebo administration.[80] In one double-blind, placebo-controlled randomized study, the efficacy of standardized BME (SBME) in subjects with age-associated memory impairment (AAMI) without any evidence of dementia or psychiatric disorder was evaluated. The subjects received either 125 mg of SBME or placebo twice a day for a period of 12 weeks followed by a placebo period of another 4 weeks (total duration of the trial 16 weeks). SBME produced significant improvement in mental control, logical memory and paired associated learning during the 12-week drug therapy. SBME was found to be efficacious in subjects with age-associated memory impairment.[81]

Anxiety and Depression

The traditional use of BM as an anti-anxiety remedy in Ayurvedic medicine is supported by both animal and clinical research. A 1-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.[82] In one latest study, effects of a standardized BME (300 mg/day) on cognitive performance, anxiety and depression in the elderly were evaluated in a randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of 6 weeks and a treatment period of 12 weeks.[83] BM participants had enhanced Auditory Verbal Learning Test (AVLT), delayed word recall memory scores relative to placebo, decreased Center for Epidemiologic Studies Depression scale (CESD10) depression scores, combined state plus trait anxiety scores and heart rate over time compared to that of the placebo group. This study provided further evidence that BM has a good potential for safely enhancing cognitive performance in the ageing.[83]

Gastrointestinal Disorders

A double-blind, randomized, placebo-controlled trial of 169 patients with IBS compared the effects of an Ayurvedic preparation containing BM and *Aegle marmelos* to standard therapy (clidinium bromide, chlordiazepoxide and psyllium).[84] Subjects were divided into five subgroups based on type of IBS, and randomly assigned to standard drug treatment, botanical treatment or placebo for 6 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 diarrhoea. This result was attributed to the *Aegle marmelos*, a commonly known antidiarrhoeal in India, although the two botanicals were not given separately, so individual effects could not be confirmed.

Side Effects and Toxicity

BM has a record of several hundred years of safe therapeutic use in Ayurvedic medicine. A double-blind, placebo-controlled clinical trial of healthy male volunteers investigated the safety of pharmacological doses of isolated bacosides over a 4-week period. Concentrated bacosides given in single (20-30 mg) and multiple (100-200 mg) daily doses were well tolerated and without adverse effects.[25] The LD_{50} of aqueous and alcoholic extracts of BM in rats were 1000 mg and 15 g/kg by the intraperitoneal route, respectively.[39] The aqueous extract given orally at a dose of 5 g/kg did not show any toxicity. The LD_{50} of the alcoholic extract was 17 g/kg given orally. Both extracts did not produce any gross behavioural changes at these levels.[85]

Dosage

The daily doses of BM generally recommended in traditional practice are 5-10 g of non-standardized powder, 8-16 mL of infusion and 30 mL daily of syrup. For BM extracts standardized to 20%, 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.[85]

Herb-Drug Interactions

In vitro and animal studies have demonstrated that the

BME might potentiate the effect when taken with some synthetic drugs or it might have a protective effect against certain drugs and their negative side effects. BM has been noted in animal models to decrease the toxicity of morphine and phenytoin. Administration of BME with morphine significantly decreased LPO and increased levels of antioxidant enzymes and glutathione in rat hepatic tissue, when compared to morphine alone. These results suggested a protective effect for BM on the hepatic antioxidant status in morphine-treated rats.[86] In mice, BM administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory.[87] The mice received phenytoin (25 mg/kg orally for 14 days). BM (40 mg/kg for 7 days) given along with phenytoin in the second week of the 2-week regimen significantly reversed PHT-induced impairment of cognitive function as determined from the PA results. Both acquisition and retention of memory were improved without affecting the anti-convulsant activity of PHT. These effects were independent of motor stimulation. These results suggested a potential corrective effect of BME in phenytoin-induced cognitive deficit.[88] The herb has also been shown, albeit inconsistently, to have a slight sedative effect, so caution is advised in combination with other known sedatives. Both cold aqueous infusion and 95% alcoholic extract of BM potentiated the sleep induced by phenobarbital[39,89] An *in vitro* study using guinea pig ileum isolates examined the effect of BME on drug-induced morphine withdrawal. Addition of 1000 μg/mL BME to the tissue isolates prior to injection of morphine was shown to significantly reduced the naloxone-induced withdrawal effects,[90] an effect that may be attributed to the anticholinergic and calcium antagonistic activity reported by other researchers. The same researchers reported a similar effect for brain mitochondrial enzyme activity of morphine-treated rats.[43] Also, since it appeared to stimulate T4 thyroid hormone activity in animals at high doses.[72] An animal study found that the effects of chlorpromazine, a drug similar to (perphenazine, prochlorperazine, thioridazine), were enhanced when a BME was given along with it.[28,40] Until more is known, people taking medications from these family of drugs mentioned above are advised to exercise caution while taking BM simultaneously.

CURRENT FINDINGS AND FUTURE PROSPECTS: CONCLUSION

In a recent study, the neuroprotective role of BME was investigated in hippocampus of temporal lobe of epileptic rats.[91] The study concluded that BME treatment potentiate the therapeutic effect by reversing the alterations in glutamate receptor binding and NMDA R1 gene expression that occur during epilepsy, resulting in reduced glutamate-mediated excitotoxity in the over-stimulated hippocampal neurons. Apropos to a crucial role that glutamate and its receptors play in consolidation of memory, the current study hypothesized the role of glutamatergic synapses as a potential target for bacoside action.[92] Hence, the effect of chronic bacoside supplementation on the glutamatergic transmission was studied by investigating the expression of NR1 subunit of NMDA receptor and activity of glutamate dehydrogenase that catalyzes glutamate synthesis. In the study, the standardized BME administration was seen to enhance learning ability in rats along with augmentation in memory retrieval and prevention of dendritic atrophy following hypoxic exposure. In addition, it was shown to decrease oxidative stress, plasma corticosterone levels and neuronal degeneration. Bacoside administration also increased cytochrome c oxidase activity along with a concomitant increase in ATP levels, and it was suggested that the administration of bacosides could be a useful therapeutic strategy in ameliorating hypobaric hypoxia-induced cognitive dysfunctions and other related neurological disorders.

In light of many reports showing important activities of BME, the wide variety of neuropharmacological actions of BM opens up interesting avenues for further research and offers new perspectives in the treatment of these diseases. Larger clinical trials and further research are required to ascertain the findings mentioned in this review. While the activity of BM both as an anxiolytic and anti-depressant needs further evaluation, its potential as an anti-epileptic treatment and as a treatment to correct side effects of anti-epileptic drugs is another area to be studied in future. Also, the antioxidant capacity of BM may explain, at least in part, the reported antistress, immunomodulatory, cognition-facilitating, anti-inflammatory and antiageing effects produced by it in experimental animals as well as in clinical situations and may justify further investigation of its other beneficial properties. Moreover, these experimental evidences suggest that because of its antioxidant activity, it may be useful in the treatment of human pathologies in which free radical production plays a key role. Also, the antifertality potential of BM was recently disclosed in male mice, wherein it was shown to cause reversible suppression of spermatogenesis and fertility, without producing apparent toxic effects.[93] BM has also shown to have thrombolytic activity in one recent *in vitro* study.[94] In addition to all pharmacological studies mentioned above, herb-drug and herb-herb interactions of BM need to be studied. The diverse studies indicated that interactions between herbal medicines and synthetic drugs exist and can have serious consequences.[95,96] Therefore, it is necessary to consider the possibility of BM-drug interactions.

REFERENCES

1. Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J Clin Oncol 2004;22:2489-503.
2. Husain GM, Mishra D, Singh PN, Rao ChV, Kumar V. Ethnopharmacological review of native traditional medicinal plants for brain disorders. Pharmacog Rev 2007;1:20-8.
3. Mukheijee DG, Dey CD. Clinical trial on Brahmi. Int J Exp Med Sci 1966;10:5-11.
4. Chopra RN. Indigenous Drugs of India. 2nd ed. Calcutta, India: U.N. Dhur and Sons; 1958. p. 341.
5. Nadkarni KM. The Indian Materia Medica. Columbia, MO: South Asia Books; 1988. p. 624-25.
6. Kirtikar KR, Basu BD. Indian Medicinal Plants, part II. Allahabad: Indian Press; 1918. p. 930-1.
7. Russo A, Borrelli F. *Bacopa monniera*, a reputed nootropic plant: an overview. Phytomed 2005;12:305-17.
8. Satyavati GV, Raina MK, Sharma M. Medicinal Plants of India. Vol 1. New Delhi: Ind Council Med Res; 1976. p. 112-8.
9. Bose KC, Bose NK. Observations on the actions and uses of *Herpestis monniera*. J Ind Med Assoc 1931;1:60.
10. Chopra RN, Nayar L, Chopra IC. Glossary of Indian Medicinal Plants, vol. 32. Council of Scientific and Industrial Research, New Delhi: 1956.
11. Shastri MS, Dhalla NS, Malhotra CL. Chemical investigation of *Herpestis monniera Linn* (Brahmi). Ind J Pharmacol 1959;21:303-4.
12. Chatterji N, Rastogi RP, Dhar ML. Chemical examination of *Bacopa monniera* Wettst: part II -isolation of chemical constituents. Ind J Chem 1965;3:24-9.
13. Rastogi RP. Compendium of Indian Medicinal Plants. Vol 1. New Delhi: CSIR; 1990. p. 118-22.
14. Kulshreshtha DK, Rastogi P, Bacogenin A1: a novel dammerane triterpene sapogenin from *Bacopa monniera*. Phytochem 1973;12:887-92.
15. Kulshreshtha DK, Rastogi RP. Bacogenin A2: a new sapogenin from bacosides. Phytochem 1973;13:1205-6.
16. Chandel RS, Kulshreshtha DK, Rastogi RP. Bacogenin A3: a new sapogenin from *Bacopa monniera*. Phytochem 1977;16:141-3.
17. Rastogi S, Pal R, Kulshreshtha DK. Bacoside A3-a triterpenoid saponin from *Bacopa monniera*. Phytochem 1994;36:133-7.
18. Garay S, Mahato SB, Ohtani K, Yamasaki K. Dammarane-type triterpenoid saponins from *Bacopa monniera*. Phytochem 1996;42:815-20.
19. Chakravarty AK, Sarkar T, Masuda K, Shiojima K, Nakane T, Kawahara N. Bacopa side I and II: two pseudojujubogenin glycosides from *Bacopa monniera*. Phytochem 2001;58:553-6.
20. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara, N. Bacopasides III-V: three new triterpenoid glycosides from *Bacopa monniera*. Chem Pharm Bull 2003;51:215-7.
21. Chakravarty AK, Sarkar T, Nakane T, Kawahara N, Masuda K. New phenylethanoid glycosides from *Bacopa monniera*. Chem Pharm Bull 2002;50:1616-8.
22. 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;65:1759-63.
23. Deepak M. The need for establishing identities of `bacoside A and B? The putative major bioactive saponins of Indian medicinal plant. Phytomed 2003;11:264-8.
24. Singh HK, Rastogi RP, Srimal RC, Dhawan BN. Effect of bacosides A and B on avoidance responses in rats. Phytother Res 1988;2:70-5.
25. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monniera Linn*. (Brahmi). Ind J Pharmacol 1997;29:S359-S65.
26. Malhotra CK, Das PK. Pharmacological studies of *Herpestis monniera Linn* (Brahmi). Ind J Med Res 1959;47:294-305.
27. Aithal HN, Sirsi M. Pharmacological investigation on *Herpestis monniera*. Ind J Pharmacy 1961;23:2-5.
28. Prakash JC, Sirsi M. Comparative study of the effects of brahmi (*Bacopa monniera*) and chlorpromazine on learning in rats. J Sci Indust Res 1962;21:93-6.
29. Sinha MM. Some empirical behavioural data indicative of concomitant biochemical reactions. Proceeds Ind. Sci. Congress Part II, Bangalore: 1971. p. 1-26.
30. Bhattacharya SK, Kumar A, Ghosal S. Effect *of Bacopa monniera* on animal models of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. In: DV Siva Sankar, editors. Molecular Aspects of Asian Medicines. New York: PJD Publications; 1999. p. 27-58.
31. Singh HK, Dhawan BN. Effect of *Bacopa monnieri Linn.* (Brahmi) extract on avoidance responses in rat. J Ethnopharmacol 1982;5:205-8.
32. Singh HK, Rastogi RP, Srimal RC, Dhawan BN. Effect of bacosides A and B on avoidance responses in rats. Phytother Res 1988;2:70-5.
33. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of *Bacopa monniera* in gastric ulcer models. Phytomed 2001;8:423-30.
34. Bhattacharya SK, Ghosal S. Anxiolytic activity of a standardized extract of *Bacopa monniera*: an experimental study. Phytomed 1998;5:77-82.
35. Shankar G, Singh HK. Anxiolytic profile of standardized brahmi extract. Ind J Pharmacol 2000;32:152.
36. Sairam K, Dorababu M, Goel RK, Bhattacharya SK. Antidepressant activity of standardized extract of *Bacopa monniera* in experimental models of depression in rats. Phytomed 2002;9:207-11.
37. Shader RI, Greenblatt DJ. Pharmacotherapy of acute anxiety. In: Bloom FE, Kupfer DJ. editors. Psycopharmacology: Fourth generation of progress. New York: Raven Press; 1995. p. 1341-8.
38. Shanmugasundaram ER Akbar GK, Shanmugasundaram B, Rahmighritham KR. An Ayurvedic herbal formula for the control of epilepsy. J Ethnopharmacol 1991;33:269-76.
39. Martis G, Rao A, Karanth KS. Neuropharmacological activity of *Herpestis monniera.* Fitoterapia 1992;63:399-404.
40. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from *Herpestis monniera, Linn*. (Brahmi). Ind J Med Res 1967;55:473-82.
41. Singh S, Eapen S, D'Souza SF. Cadmium accumulation and its influence on lipid peroxidation and antioxidative system in an aquatic plant, *Bacopa monnieri L.* Chemosphere 2006;62:233-46.
42. Bafna PA, Balaraman R. Antioxidant activity of DHC-1, an herbal formulation, in experimentally-induced cardiac and renal damage. Phytother Res 2005;19:216-21.
43. Sumathy T, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of *Bacopa monniera* on morphine-induced brain mitochondrial enzyme activity in rats. Fitoterapia 2002;73:381-5.
44. Pawar R, Gopalakrishnan C, Bhutani KK. Dammarane triterpene saponin from *Bacopa monniera* as the superoxide inhibitor in polymorphonuclear cells. Planta Med 2001;67:752-4.
45. Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP. *Bacopa monniera* Linn. as an antioxidant: mechanism of action. Ind J Exp Biol 1996;34:523-6.
46. Kapoor KR, Srivastava SS, Kakkar P. *Bacopa monnieri* modulates antioxidant responses in brain and kidney of diabetic rats. Environ Toxicol Pharmacol 2008. [In Press].
47. Bhakuni DS, Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN. Screening of Indian plants for biological activity: Part II. Ind J Exp Biol 1969;7:250-62.
48. Singh HK, Shanker G, Patnaik GK. Neuropharmacological

and anti-stress effects of bacosides: a memory enhancer. Ind J Pharmacol 1996;28:47.
49. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monniera* in rat frontal cortex, striatum, and hippocampus. Phytother Res 2000;14:174-9.
50. Govindarajan R, Vijayakumar M, Pushpangadan P. Antioxidant approach to disease management and the role of 'Rasayana' herbs. Ayur J Ethnopharmacol 2005;99:165-78.
51. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effects of bacosides of *Bacopa monnieri*: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res 2002;16:639-45.
52. Rohini, G, Sabitha, KE., Devi, CS. *Bacopa monniera Linn*. extract modulates antioxidant and marker enzyme status in fibrosarcoma bearing rats. Ind J Exp Biol 2004;42:776-80.
53. Seiss H. Strategies of antioxidant defence. Eur J Biochem 1993;215:213-9.
54. Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh H. Adaptogenic effect of *Bacopa monniera* (Brahmi). Pharmacol Biochem Behav 2003;75:823-30.
55. Jyoti A, Sharma D. Neuroprotective role of *Bacopa monniera* extract against aluminium-induced oxidative stress in the hippocampus of rat brain. Neurotoxicol 2006;27:451-7.
56. Vijayan VA, Helen A. Protective activity of *Bacopa monniera Linn*. On nicotine-induced toxicity in mice. Phytother Res 2007;21:378-81.
57. Holcomb LA, Dhanasekaran M, Hitt AR, Young KA, Riggs M, Manyam BV. *Bacopa monniera* extract reduces amyloid levels in PSAPP mice. J Alzheimers Dis 2006;9:243-51.
58. Anbarasi K, Vani G, Balakrishna K, Devi CS. Effect of bacoside A on brain antioxidant status in cigarette smoke exposed rats. Life Sci 2006;78:1378-84.
59. Aloe A, Alleve E, Fiore M. Stress and nerve growth factor findings in animal models and humans. Pharmacol Biochem Behav 2002;73:159-66.
60. 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;11:323-5.
61. Dar A, Channa S. Calcium antagonistic activity of *Bacopa monniera* on vascular and intestinal smooth muscles of rabbit and guinea-pig. J Ethnopharmacol 1999;66:167-74.
62. Dorababu M, Prabha,T, Priyambada S, Agrawal VK, Aryya NC, Goel RK. Effect of *Bacopa monniera* and *Azadirachta indica* on gastric ulceration and healing in experimental NIDDM rats. Ind J Exp Biol 2004;42:389-97.
63. Jain P, Khanna NK, Trehan T, Pendse VK, Godhwani JL. Anti-inflammatory effects of an Ayurvedic preparation, Brahmi Rasayan, in rodents. Ind J Exp Biol 1994;32:633-6.
64. Rao CH, Sairam K, Goel RK. Experimental evaluation of *Bacopa monniera* on rat gastric ulceration and secretion. Ind J Physiol Pharmacol 2000;44:435-41.
65. Dharmani P, Palit G. Exploring Indian medicinal plants for antiulcer activity. Ind J Pharmacol 2006;38:95-9.
66. Goel RK, Sairam K. Anti ulcer drugs from indigenous sources with emphasis on *Musa sapientum*, tamrabhasma, *Asparagus racemosus* and *zinzibar officinale*. Ind J Pharmacol 2002;34:100-10.
67. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of *Bacopa monniera* in gastric ulcer models. Phytomed 2001;8:423-30.
68. Goel RK, Sairam K, Babu MD, Tavares IA, Raman A. *In vitro* evaluation of *Bacopa monniera* on anti- *Helicobacter pylori* activity and accumulation of prostaglandins. Phytomed 2003;10:523-7.
69. Russo A, Borrelli F, Campisi A, Acquaviva R, Raciti G, Vanella A. Nitric oxide-related toxicity in cultured astrocytes: Effect of *Bacopa monniera*. Life Sci 2003;73:1517-26.
70. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of *Bacopa monniera L.* on DNA damage. Phytother Res 2003;17:870-5.
71. Elangovan V, Govindasamy S, Ramamoorthy N, Balasubramaanian K. *In vitro* studies on the anticancer activity of *Bacopa monnieri*. Fitoterapia 1995;66:211-5.
72. 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;81:281-5.
73. Channa S, Dar A, Anjum S, Yaqoob M, Rahman A. Anti-inflammatory activity of *Bacopa monniera* in rodents. J Ethnopharmacol 2006;104:286-9.
74. Channa S, Dar A, Yaqoob M, Anjum S, Sultani Z, Rahman A. Bronchovasodilatory activity of fractions and pure constituents isolated from *Bacopa monniera*. J Ethnopharmacol 2003;86:27-35.
75. Samiulla DS, Prashanth D, Amit A. Mast cell stabilizing activity of *Bacopa monnieri*. Fitoterapia 2001;72:284-5.
76. Roodenrys A, Booth D, Bulzomi A, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (*Bacopa monnieri*) on human memory. Neuropsychopharmacol 2002;27:279-81.
77. Nathan PJ, Clarke J, Lloyd J, Hutchison CW, Downey L, Stough C. The acute effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy normal subjects. Hum Psychopharmacol 2001;16:345-51.
78. Stough C, Lloyd J, Clarke J, Downey LA, Hutchison CW, Rodgers T, *et al*. The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects. Psychopharmacol 2001;156:481-4.
79. Sharma R, Chaturvedi C, Tewari PV. Efficacy of *Bacopa monnieri* in revitalizing intellectual functions in children. J Res Edu Ind Med 1987;1:1-12.
80. Negi KS, Singh YD, Kushwaha KP, Rastogi CK, Rathi AK, Srivastava JS, *et al*. Clinical evaluation of memory enhancing properties of Memory Plus in children with attention deficit hyperactivity disorder. Ind J Psychiatry 2000;42:Supplement.
81. Raghav S, Singh RS, Dalal H, Srivastava PK, Asthana JS. Randomized controlled trial of standardized *Bacopa monniera* extract in age-associated memory impairment. Ind J Psychiatry 2006;48:238-42.
82. 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;1:133-48.
83. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized *Bacopa monnieri* extract on cognitive Performance, anxiety, and depression in the Elderly: A randomized, double-Blind, placebo-controlled trial. J Alt Comp Med 2008;14:707-13.
84. Yadav SK, Jain AK, Tripathi SN, Gupta JP. Irritable bowel syndrome: therapeutic evaluation of indigenous drugs. Ind J Med Res 1989;90:496-503.
85. No author listed. *Bacopa Monniera*. Monograph. Alt Med Rev 2004;9:79-85.
86. Sumathy T, Subramanian S, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of *Bacopa monniera* on morphine induced hepatotoxicity in rats. Phytother Res 2001;15:643-5.
87. Smith DB. Cognitive effects of anti-epileptic drugs. Adv Neurol 1991;55:197-212.
88. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by *Bacopa monniera*, a reputed Indian nootropic plant. J Ethnopharmacol 2000;71:383-90.
89. Brinker F. Updates and additions for herb contradictions and drug interactions. 3rd ed. 2008. [last accessed on 2008 Dec 30].
90. Sumathi T, Nayeem M, Balakrishna K, Veluchamy G, Devaraj SN. Alcoholic extract of *Bacopa monniera* reduces the *in vitro* effects

of morphine withdrawal in guinea pig ileum. J Ethnopharmacol 2002;82:75-81.
91. Khan R, Krishnakumar A, Paulose CS. Decreased glutamate receptor binding and NMDA R1 gene expression in hippocampus of pilocarpine-induced epileptic rats: Neuroprotective role of *Bacopa monnieri* extract. Epilepsy and Behav 2008;12:54-60.
92. Hota SK, Barhwal K, Baitharu I, Prasad D, Singh S, Ilavazhagan G. *Bacopa monniera* leaf extract ameliorates hypobaric hypoxia induced spatial memory impairment. Neurobiology of Disease 2009;34:23-39.
93. Singh A, Singh SK. Evaluation of antifertality potential of brahmi in male mouse. Contraception 2009;79:71-9.
94. Prasad S, Kashyap RS, Deopujari JY, Purohit HJ, Taori GM, Daginawala HF. Effect of *Fagonia Arabica* (Dhamasa) on *in vitro* thrombolysis. BMC Compl Alt Med 2007;7:36.
95. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: A systematic review. Drugs 2001;61:2163-75.
96. GohilKJ, Patel JA. Herb-drug interactions: A review and study based on assessment of clinical case reports in literature. Ind J Pharmacol 2007;39:129-39.

Source of Support: Nil, **Conflict of Interest:** None declared.