

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

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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 *Scrophulariaceae* 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

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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 anti-amnesic effect of BM is bacoside A, assigned as 3-(α -L-arabinopyranosyl)-O- β -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 triperpenoid 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.

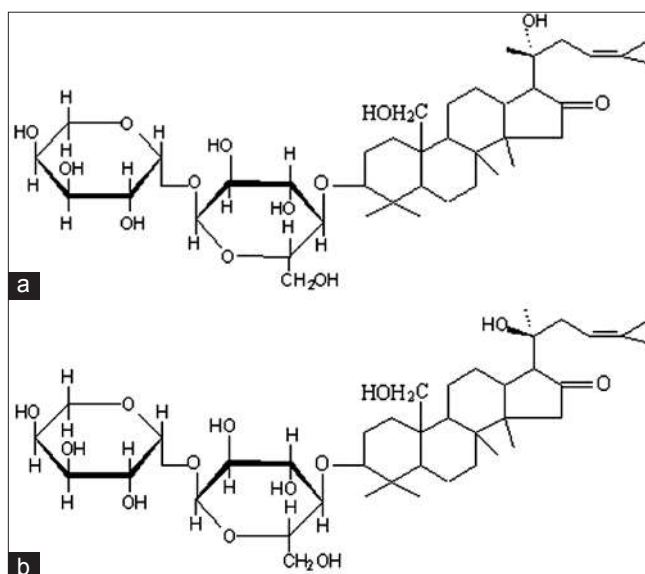


Figure 2: Chemical structures of some well-known saponins from *Bacopa monniera*.^[11] (a) Bacoside A (levorotatory); (b) Bacoside B (dextrorotatory)

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 aid 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 tranquillizing 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 superoxide 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 antidepressant 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 bacosaponin (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 LD₅₀) given for 15 days demonstrated anticonvulsant activity. When administered acutely at lower doses (approaching 25% of LD₅₀), 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 constitutive 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-pentoxoresorufin-odealkylase (PROD) and 7-ethoxoresorufin-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 H₂O₂-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 LD₅₀ 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 LD₅₀ 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 excitotoxicity 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 antifertility 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.

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