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Review Article

PHARMACOLOGICAL PROFILES OF *BACOPA MONNIERI: A Review*

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ABSTRACT

In recent times, the use of herbal products has increased tremendously in the western world as well as in developed countries. One of the important medicinal plants, widely used therapeutically in the orient and becoming increasingly popular in the west is *Bacopa monnieri*, a well-known nootropic herb. The plant being traditional Ayurvedic medicine used for centuries as a memory enhancing, anti-inflammatory, analgesic, antipyretic, sedative and antiepileptic agent. The present review summarizes current knowledge of pharmacological actions, major bioactive(s), reported mechanisms of actions 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.

Keywords: *Bacopa*, Brahmi, Memory and Nootropic.

INTRODUCTION

The Bacopa monniera (BM) is a creeping, glabrous, succulent herb, rooting at nodes whose habitat include wetlands and muddy shores. Stem 10-30 cm long, 1-2 mm thick, soft, glabrous; branches ascending. Leaves 0.6-2.5 cm long and 3-8 mm broad, sessile, obovate-oblong or spathulate, entire, nerves obscure and lower surface dotted, flowers blue or white with purple veins, axillary and solitary on long pedicles and capsule ovoid glabrous, upto 5 mm long. No distinct odour; taste slightly bitter[1, 2]. The plant is propagated through cuttings. It is known as *Brahmi, Nir-brahmi* in Sanskrit, *Brihmi-sak, Jalanimba* in Bangali, *Brahmi* in Hindi, *Nirubrahmi* in Kannada, *Nirbrahmi* in Malayalam, Marathi & Tamil, *Sambranichettu* in Telugu[3, 4]. *Bacopa monniera*, also known as *Bacopa monnieri*, *Herpestis monniera*, water hyssop, and "*Brahmi*," and used in the Ayurvedic system of medicine for centuries. Earlier, it used as a brain tonic to enhance memory development, learning, and concentration[5] and to provide relief to patients with anxiety or epileptic disorders[6]. The plant has also been used in India and Pakistan as a cardiao tonic, digestive aid and to improve respiratory function in cases of bronchoconstriction[7]. From recent research it was focused primarily on its cognitive-enhancing effects, specifically memory, learning and concentration. The plant possesses antioxidant properties, which finally provide protection from free radical damage in cardiovascular disease and certain types of cancer.

Chemical constituent: Compounds responsible for the pharmacological effects of BM include alkaloids, saponins and sterols; the detailed photochemical nature of the plant is given in Table 1. Brahmin an alkaloid was first reported as isolated compound[8] of the plant. Later, other alkaloids like nicotine and herpestine have also been reported. BM contains major constituents such as des-saponin glycosides-triterpenoid Saponins (Bacosides A & B) [9-10]. It also includes other minor constituents saponins, bacosides A_1 & A_3[11-12], hersaponin[13], Betulic acid, monnierin[14], alkaloids, Herpestin and Brahmine[15], flavonoids[16], luteolin-7-glucoside, glucoronyl-7-apigenin and gluucoronyl-7-luteonin, common phytosteroids[17].

Isolated Phytochemicals:
Four cucurbitacins, bacobitacin A-D as well as, a known cytotoxic, cucurbitacin E together with three known phenylethanoid glycosides, monnieraside I, III and plantioside B were isolated from the aerial part of BM[18]. A detailed phytochemical investigation of Bacopa monniera resulted in the isolation of two new dammarane glycosides along with eight known compounds. They have been identified as glycosides of the 20-deoxy derivatives of jujubogenin and pseudojujubogenin[19]. A new sterol glycoside, bacosterol-3-O-beta-D-glucopyranoside along with bacopasaponin-C, bacopaside-I, bacopaside-II, bacosterol, bacosine and luteolin-7-O-beta-glucopyranoside has been isolated[20]. Three new saponins designated as bacopasides III, IV and V have been isolated from BM[21]. Two new saponins, 3-O-[6-O-sulfonyl-beta-d-glucopyranosyl-(1-->3)]-alpha-l-arabinopyranosyl pseudojujubogenin and 3-O-[alpha-l-arabinofuranosyl-(1-->2)]-alpha-l-arabinopyranosyl jujubogenin , a new matsutaka alcohol derivative, (3R)-1-octan-3-yl-(6-O-sulfonyl)-beta-d-glucopyranoside, a new phenylethanoid glycoside, 3,4-dihydroxyphenylethyl alcohol (2-O-feruloyl)-beta-d-glucopyranoside , and a new glycoside, phenylethyl alcohol [5-O-p-hydroxybenzoyl-beta-d-apiofuranosyl-(1-->2)]-beta-d-glucopyranoside , were isolated from BM[22].

Three new phenylethanoid glycosides, viz. monnierasides I-III along with the known analogue plantainoside B were isolated from the glycosidic fraction of BM[23]. Two saponins, designated as bacopaside I and II, have been isolated from BM[24]. Two new dammarane-type jujubogenin bisdesmosides, bacopasaponins E and F of biological interest have been isolated from the reputed Indian medicinal plant BM[25]. Three new dammarane-type triterpenoid saponins, bacopasaponins A, B and C, of biological interest have been isolated from the reputed Indian medicinal plant BM[26]. A new triterpenoid saponin, bacoside A3, a constituent of bacosides the saponin mixture of Bacopa monniera, was isolated[27].

Ethno Botanical Uses: Alcoholic extract increases the learning performance of rats and the activity is attributed to a saponin mixture consisting of bacosides A, B and other saponins[28, 29]. Other pharmacological effects of the extracts include sedative[30], antiepileptic[31], cardio tonic, and vasoconstrictor and anti-inflammatory[32] activities. The whole plant is reported for its uses as Nerve tonic, Asthma, epilepsy, insanity, hoarseness, diuretic, boils, and toothache and as a blood purifier. While stem and leaves are reported for their beneficial role in snake bite and the decoction of the leaves is useful in the treatment for cough and rheumatism. The juice along with ginger juice and sugar is used for children's stomach disorders[33].

Alkaloids Brahmin was isolated from the plant & found its therapeutic action resembles strychnine but less toxic. It contains 3 bases B_1 oxalate, B_2 oxalate, B_3 chloroplatinate and a sterol also it contains alkaloid herpestine[34]. Contemporary formulas often combine *Bacopa monniera* with other herbs and nutritional supplements known to promote mental functioning, such as Ginkgo biloba, ginseng, and phosphatidylserine. Such formulas may also be applicable as protection against the onset of Alzheimer's disease and other conditions of mental deterioration associated with aging. Traditional Ayurvedic medicine uses *Bacopa monniera* to enhance memory and alleviate anxiety neurosis. The plant is used to increase the speed of learning and to increase sharpness and the perception by the sense organs. In India, traditional uses of the *Brahmi* include dermatosis, anemia and diabetes. Brahmi is also known to promote fertility and prevent miscarriage. In India, *Brahmi* tea is given to babies to encourage optimal mental development.

PHARMACOLOGICAL ACTIONS

Nervous system: It has shown by the recent study that, the mode of action of neuroprotective effects of Brahmi appeared to be the results of its antioxidant to suppress neuronal oxidative stress and the acetyl cholinesterase inhibitory activities.

Therefore, treating patients with Brahmi extract may be an alternative direction for ameliorating neurodegenerative disorders[35]. In one more study it has shown that the neuroprotective role of BM extract in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring in

association with Pilocarpine-induced epilepsy[36]. The results showed that BM treatment for epileptic rats significantly brought the reversal of the down-regulated metabotropic glutamate receptor (mgluR8) gene expression toward control level. In neonatal rats, hypoxia induced expressional and functional changes in the N-methyl D-asparatate receptor of neuronal cells which is corrected by supplementation of glucose alone or glucose followed by oxygen during the resuscitation to prevent the glutamate related neuronal damage[37]. It was found that the presence of endogenous substances in the Bacopa monniera extract that will impact components of the oxidative stress cascade such as the reduction of divalent metals, scavenging of reactive oxygen species, alterations of lipoxygenase activity and hydrogen peroxide-induced lipid peroxidation. From the study it was shown that its extract treatment reduces beta-amyloid levels in the brain of an Alzheimer's disease[38].

Receptor mechanism:

Cerebellar dysfunction is a recognized complication of temporal lobe epilepsy and it is associated with seizure generation, motor deficits and memory impairment. So data suggested that the neuroprotective role of BM through the up regulation of 5-HT (2C) receptor in epileptic rats and this have clinical significance in the management of epilepsy[39]. The results showed that BM plays an important role in the alteration of glutamate receptor binding and gene expression of NMDA R1 in hippocampus of temporal lobe epileptic rats. In association with pilocarpine-induced epilepsy, there was significant down regulation of NMDA R1 gene expression and glutamate receptor binding without any change in its affinity. NMDA receptor antagonists and nitric oxide synthase inhibitors induce amnesia in animals. From the data it is revealed that L-NNA (N-Nitro-L-arginine) and MK-801 produced anterograde and retrograde amnesia and BM significantly attenuated the L-NNA-induced anterograde amnesia, partially reversing L-NNA-induced retrograde amnesia. On the other hand it was found that BM neither attenuated the MK-801-induced anterograde amnesia nor improved retrograde amnesia caused by it[40].

Mechanism of action:

Zhou *et.al* were isolated three new saponins, bacopasides IX-XI, together with their known analogues bacopaside I, bacopaside II, bacopasaponsin C and bacopasaponsin D from the whole plant of BM. It was proved that administration of bacosides could be a useful therapeutic strategy in ameliorating hypobaric hypoxia induced cognitive dysfunctions and other related neurological disorders[41]. Benzodiazepines are known to produce amnesia by the involvement of GABAergic system and by the interference of long term potentiation. Behavioral results showed that Bacopa monniera significantly reversed the diazepam induced amnesia in Morris water maze task[42]. Benzodiazepines are known to produce amnesia by involvement of the GABAergic system. BM significant as it progressively reduced escape latency time when mice treated with diazepam were subjected to acquisition trials. The antiamnesic effects of Bacopa suggested likely a GABA pathway possibly affecting long-term potentiation[43]. From their findings it was suggested that pretreatments with aqueous extracts of BM markedly attenuated ischemia-reperfusion induced cerebral injury in terms of decreased infarct size, increase in short-term memory, motor incoordination and lateral push response[44]. Three new triterpene glycosides, bacopasides VI-VIII, together with three known analogues, bacopaside I, bacopaside II and bacopasaponsin C, were isolated from the whole plant of Bacopa monnieri. Compounds 4, 5 and 6 were shown antidepressant activity when tested on forced swimming and tail suspension in mice, respectively, these results support its neuropharmacological effects[45]. From the study it was indicated that the adaptogenic activity of BM might be due to the normalization of stress induced alteration in plasma corticosterone and the levels of monoamines like NA, 5-HT and DA in the cortex and hippocampus regions of the brain, which are more vulnerable to stressful conditions analogous to the effects of PQ[46, 47]. BM is a perennial herb, and is used as a nerve tonic. From the findings it was strongly implicated that Bacopa monniera has potential to protect the brain from oxidative damage resulting from aluminum toxicity[48]. It was suggested that Bacoppa Monniera Extract lowers A-beta 1-40 and 1-42 levels in the cortex by as much as 60%, and reverses Y-maze performance and open field hyperlocomotion behavioral changes present in PSAPP mice. Hence it has potential application in Alzheimer's disease therapy[49]. Observations showed that Bacopa's neuroprotective effects were comparable to those of l-deprenyl at both biochemical and microscopic levels[50]. Administration of Bacoside A prevented expression of hsp70 and neuronal apoptosis during cigarette smoking[51]. On the basis of the results it was concluded that bacosides facilitates anterograde memory and attenuate anterograde experimental amnesia induced by scopolamine and sodium nitrite possibly by improving the acetylcholine level and hypoxic conditions, respectively. Beside this bacosides also reversed BN52021 induced retrograde amnesia, probably due to increase in platelet activating factor

synthesis by enhancing cerebral glutamate level[52]. Administration of Bacoside A inhibited lipid peroxidation, improved the activities of ATPases and maintained the ionic equilibrium. The results of the study indicated that Bacoside A protects the brain from cigarette smoking induced membrane damage[53]. This data supports the traditional use of BM and indicated that it has a therapeutic potential in treatment or prevention of neurological diseases[54]. One more study suggests that the BM extract may be useful in reducing the withdrawal symptoms induced by morphine[55]. BM restores enzymes at normal level before the administration of morphine[56]. The extract when given, was found to have significant antidepressant activity in the forced swim and learned helplessness models of depression[57].

Muscle relaxant and digestive system: Ethanolic extract of whole plant of BM has shown cardiac depressive activity on left ventricular contractility, heart rate and coronary flow in isolated rabbit heart and it were found that, the activity in all parameters appears similar like quinidine[58]. Animal studies have demonstrated that the Bacopa extract has a relaxant effect on chemically-induced bronchoconstriction and the effect probably via inhibition of calcium influx into cell membranes. Earlier to this Dar and Channa have demonstrated the broncho-vasodilatory activity of B. monnieri on the rabbit and guinea pig trachea by *in-vitro.* They also demonstrated the effect of BM on pulmonary artery and aorta[59].

The anti-ulcer and ulcer-healing activities of the Bacoppa Monniera Extract may be due to its effects on various mucosal offensive and defensive factors[60]. *In vitro* studies have demonstrated direct spasmolytic activity on intestinal smooth muscle, *via* inhibition of calcium influx across cell membrane channels. This property of BM may be has a beneficial role in conditions characterized by intestinal spasm such as irritable bowel syndrome. The results indicated the direct action of the extract on smooth muscles[61]. Bacopa Monniera Extract showed anti-Helicobacter pylori activity in vitro and increased in vitro of prostanoids (PGE and PGI2) in human colonic mucosal incubates[62].

Antioxidant & Hepatoprotective activity: BM possesses protective effect against morphine-induced liver and kidney toxicity in rats. It was found that pretreatment with BME has shown to possess a significant protective effect against morphine-induced liver and kidney functions in terms of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, lactate dehydrogenases and gamma-glutamyl transferase activities and urea, creatinine and uric acid level respectively[63]. One more study reveals that pretreatment of bacoside A prevents the elevation of LPO (Lipid Peroxidase) and activity of serum marker enzymes and maintains the antioxidant system and thus protects the rats from Diethylnitrosamine-induced hepatotoxicity[64]. Even alcohol extract of BM exerted a hepatoprotective effect against morphine induced liver toxicity[65].

Sedative and tranquilizing properties: Hersaponins, glycosides isolated from BM are reported for sedative effect[66]. A subsequent study 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[67]. 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[68].

Other Uses: The anticancer activity of BM was carried out by Elangovan *et.al*. They found that BM induces dose and time-dependent loss of cell viability with maximum cytotoxicity at 48 h at a concentration of 550 mg/ml. The study concluded that, BM induces cell death by apoptosis in S-180 cells[69]. Brahmi treatment causes reversible suppression of spermatogenesis and fertility, without producing apparent toxic effects[70]. BM contains pseudojujubogenin glycosides as pharmacologically active compounds. The glycosides in the sample competed in binding to the limited amount of antibodies in the detection reagent with the immobilised bacopaside I-HSA conjugates and, hence, positive samples showed no colour in the capture spot zone[71]. BM prevents formation of malondialdehyde and lipofuscin pigments which are the indicators of aging[72]. BM extract slightly suppressed splenocyte proliferation and decreased T-lymphocyte proliferation with concanavalin A. Bacoside A gave the highest splenocyte proliferation and strongly increased T-lymphocyte proliferation with concanavalin A. It is possible to attribute the effect of the BM extract on the splenocyte proliferation to the presence of bacoside A with other combined components[73].

The plant possesses antiinflamamtory activity on carrageenan-induced rat paw edema and it has shown 82% edema inhibition when compared to indomethacin. BM also significantly inhibited 5-lipoxygenase (5-LOX), 15-LOX and cyclooxygenase-2 (COX-2) activities[74]. BM protected human lymphocytes against various clastogens. It also exhibited high antioxidant activity which might be responsible for the observed protective effects against the clastogens since the used clastogens are known to induce their clastogenic effects via the

production of oxidative radicals[75]. Nicotine an active component of cigarette smoke causes devastating effects in important biomolecules of the cell through generation of free radicals leading to genomic instability. BM is a reputed drug for its DNA protective effects and it was suggested that the plant extract exerts protective effects by modulating the extent of lipid peroxidation and enhancing the antioxidant status[76]. It was inferred that BM possesses significant anti-inflammatory activity that may well be relevant to its effectiveness in the healing of various inflammatory conditions in traditional medicine[77].

The anti-inflammatory activity of BM is due to the triterpenoid and bacoside present in the plant. The ability of the fractions containing triterpenoids and bacosides inhibited the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6. This was tested using lipopolysaccharide activated peripheral blood mononuclear cells and peritoneal exudate cells *in vitro*. So Bacopa monniera has the ability to inhibit inflammation through modulation of pro-inflammatory mediator release[78]. Chronic cigarette smoke exposure enhances oxidative stress and bacoside A protect the brain from the oxidative damage through its antioxidant potential[79]. Bacoside A administration improved the antioxidant status and maintained the levels of trace elements. BM extract promotes the antioxidant status, reduces the rate of lipid peroxidation and the markers of tumor progression in the fibrosarcoma bearing rats[80]. BM exerted a significant protective effect on H_2O_2-induced cytoxicity and DNA damage in human non-immortalized fibroblasts; it is due to its antioxidant activity. The plant may be useful in the treatment of human pathologies in which free radical production plays a key role[81]. Pretreatment with BM significantly reduced the AS-induced increase in the ulcer index, adrenal gland weight, plasma glucose, AST, and CK[82]. Bacoside A an active phytochemical present in BM has anticancer activity. This was shown anticancer effect by successive extracting ethanolic extract of BM[83]. Methanolic fraction exhibited potent activity comparable to disodium cromoglycate, a known mast cell stabilizer[84]. The antioxidant potential of BM has slightly protected the autooxidation and $FeSO_4$ induced oxidation of reduced glutathione[85]. Bacopa monnieri is a known hyper accumulator of cadmium, chromium, lead and mercury and as such can be used for phytoremediation[86]. Diethyl ether and ethyl acetate extracts of Bacopa monnieri have slight anti fungal activity but have a broad spectrum of antibacterial activity[87]. A study in mice demonstrated high doses (200 mg/kg) of Bacopa extract increased the thyroid hormone-T4 as well as have a stimulatory effect on thyroid function[88].

CURRENT FINDINGS AND FUTURE PROSPECTS

Recently, the interest in the use of herbal products has grown dramatically in the western world as well as in developed countries[89]. It has now become exceedingly apparent that available psychotherapeutic does not properly meet the 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[90]. The vast majorities of currently available psychoactive drugs as herbal remedies today seems to be a reflection of such a situation. In the folklore of Indian medicine, several herbs have been used traditionally as the brain or nerve tonics. One of the most popular of these herbs is *Bacopa monniera* (BM), a well-known memory booster BM has also shown to have thrombolytic activity in one recent *in vitro* study[91]. 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[92, 93]. Therefore, it is necessary to consider the possibility of BM-drug interactions. The anti fertility 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[94].

Table 1: Chemical constituents of *Bacopa monnieri*

Part	Major Chemicals	The activity responsible	Minor Constituent	Activity Responsible
Whole Plant	Brahmine, Herpestine	Nootropic Activity	Saponine, Bacoside A&B, Other saponines	Sedative, Antiepileptic, Cardiotonic, Vasoconstrictor, Anti-Inflammatory.
Leaves	D-Mannitol	Diuretic, Aperient	-	-

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