Review Article

A Review on Major Bioactivities of Bacopamonnieri.

Gayatridevi Pushkar*[1], Bhupendra Pushkar[2], Rohini Sivabalan[1]

[1]Department of Zoology, Ramnarain Ruia College, Matunga, Mumbai. India
[2]Department of Biotechnology, University of Mumbai, Kalina campus, Santacruz (east),Mumbai, India.

Keywords: #########

Abstract

Bacopa monnieri (family: Scrophulariaceae) is a reputed drug of Ayurveda. It is used in traditional medicine to treat various nervous disorders and for promoting memory and intellect. This medicinal plant is locally known as Brahmi. It is known as a memory enhancer and many preparations of brahmi are now commercially available in the market. Herbal medicines are gaining importance hence B. monnieri has been studied extensively for its chemical constituents, constituents responsible for memory enhancing effect and also its various other useful effects. As now a days natural products are much preferred so the possible use of brahmi as a neuropsycotropic drug is also gaining importance. Some of its effects has been established in several in vivo and in vitro models. This article reviews the useful effects of this plant.

***Corresponding author:**
Gayatridevi Pushkar, Department of Zoology, Ramnarain Ruia College, Matunga, Mumbai-400 019, INDIA.
Email: pushkargayatri16@gmail.com.

Introduction

The interest in the use of herbal medicines are gaining importance all around the world. The World Health Organization (WHO) estimates that 80% of the world's population presently uses herbal medicine for some aspects of primary health care [1].Similarly the use of natural productfor neuropsycotropic drugs are alsogaining importance. In this context*Bacopamonnieri* can be useful herbal drug option for neuropsycotropic disorders.Since it is extensively used as a nerve tonic and thought to improve memory in ayurvedic medicines[2].Though Brahmi is now promoted as the 'brain booster' of the new millennium, Ayurvedic medicine has known this for centuries. It is highly valued in conditions affecting the nervous system and brain. This review summarizes our current knowledge of the major bioactivities of *Bacopamonnieri*.

Description of plant

Bacopamonnieri(BM) or Brahmi, a plant in the family Scrophulariaceae, has been used in the Ayurvedic system of medicine for centuries. It has been claimed as a nerve tonic and extensively used for treatment of various neurological and neuropsychiatric diseases[2].BM locally known as brahmi in India, has been used for centuries in the Ayurveda.

The herb has been mentioned in several ancient Ayurvedic treatises including the 'CharakaSamhita' 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][2]. Specific uses include the treatment of asthma, insanity and epilepsy[4][2]. The plant has been utilized extensively as a nootropic, digestive aid and to improve learning, memory and respiratory function[5],[6]. The herb is a small creeping herb with numerous branches, small oblong leaves and light purple or small and white flowers, with four or five petals . 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[7]. The entire plant is used medicinally[8].

Chemical composition

The pharmacological effects of *Bacopamonnieri* are attributed to the presence of a number of biologically active compounds, including alkaloids, saponins and sterols[9]. The compounds responsible for the memory enhancing effects of *Bacopamonnieri* are triterpenoidsaponins called "bacosides"[12]. The major chemical entity shown to be responsible for neuropharmacological 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[13].The isolation of D-mannitol and a saponin, hersaponin and potassium salts was also reported [2][11]. On acid hydrolysis, bacosides yield a mixture of aglycones, bacogenin A1, A2, A3, [14],[15],[16] which are artefacts, and two genuine sapogenins, jujubogenin andpseudojujubogenin and bacogenin, A4, identified as ebelin lactone pseudojujubogenin, were isolated[17].Successively, a minor saponinbacoside A1 and a new triperpenoidsaponin, bacoside A3, were isolated[2][17].Later, three new dammarane-type triterpenoidsaponins of biological interest, bacopasaponins A, B and C, isolated and identified as 3-O-α-L-arabinopyranosyl- 20-O-α-Larabinopyrasonyl-jujubogenin, 3-O-[α-Larabinofuranosyl-(1→2)- α-L-arabinopyranosyl] pseudojujubogenin and 3-O-β- D- glucopyranosyl (1→3)-{α-L-arabinofuranosyl-(1→2)}-α-L arabinopyrasonyl] pseudojujubogenin and also a new dammarane-type pseudojujubogenin glycoside, bacopasaponin D, 3-O-[α-L-arabinofuranosyl- (1→2)-β-D- glucopiranosyl] pseudojujubogenin were identified by spectroscopic and chemical transformation methods[9][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 with structures 3-O α-L- arabinofuranosyl-(1→2)-β-D-glucopyranosyljujubogenin, 3- O-β-D-glucopyranosyl- (1→3)-α-L- arabinopyranosyljujubogenin, 3-O-β-D-glucopyranosyl-(1→3)- α-Larabinofuranosyl pseudojujubogenin 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][28]. Moreover, an isolation of a new saponin, a juju-

bogenin, named bacopasaponin G, and a new glycoside, phenylethyl alcohol was also reported [22][28] . The drug is characteristically designated on the basis of its total bacosides content which are tetra cyclic triterpenoidsaponins. These steroidal saponins called Bacoside A &Bacoside B are considered Bacopa's most therapeutic constituents.The chemical structures of saponinsisolated from BM are shown In [Figure 1a], bacoside A levorotatory, and [Figure 1b], bacoside B dextrorotatory, [Figure 2]triterpinoidsaponin and bacogenin A4.

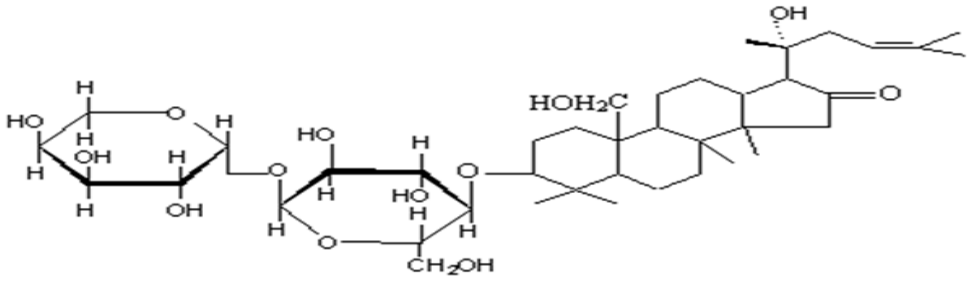

Fig 1a: BACOSIDE A (Levorotatory)

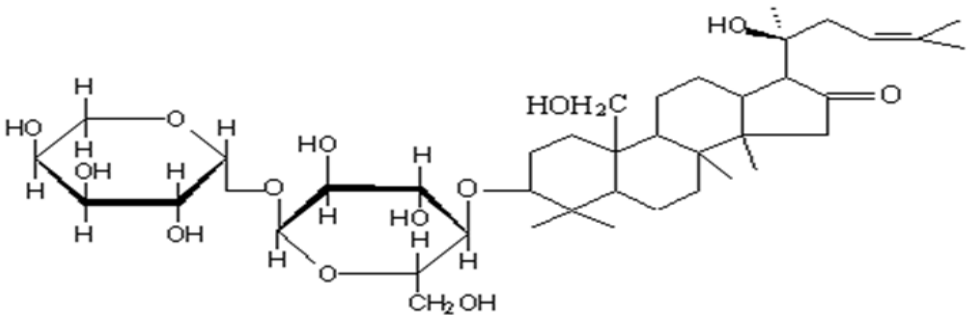

Fig 1b: BACOSIDE B (Dextrorotatory)

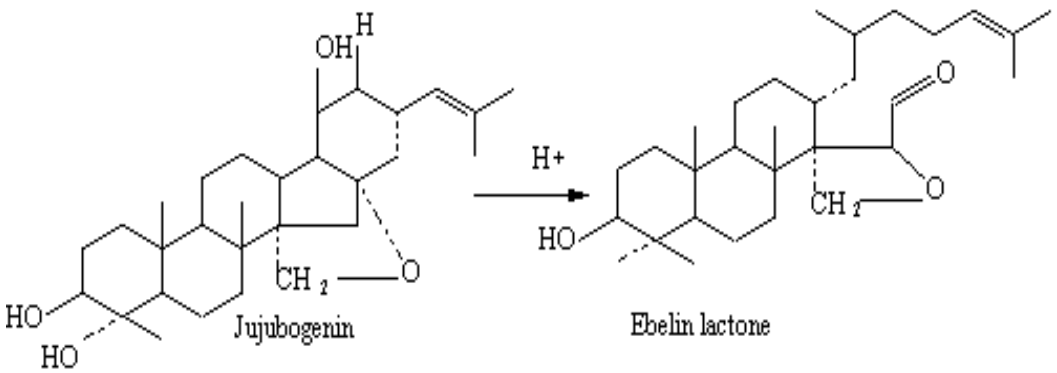

Fig 2: TRITERPENOID SAPONIN and BACOGENIN A4

The possible mode of action of brahmi on brain

The BM extracts and isolated bacosides have been extensively investigated for their neuropharmacological effects. The triterpenoidsaponins and their bacosides are said to be responsible for BM's ability to enhance nerve impulse transmission [28]. 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].It is clear that brahmi exhibit useful effects on brain and required further research so that its mode of action can be identified. However some of these useful effect which have been studiedare discussed below.

Antidepressant and Antianxiety Effects

Currently available treatment of depression is often associated with several undesirable side effects and it is effective only in a certain portion of the patients [27]. Hence the search for novel pharmacotherapy from medicinal plants for psychiatric illnesses has progressed significantly. From ancient timebrahmi have been used to treat psychiatric disorders and can be potential candidate for neuropsycotropic drug.According to one study, the BM extract in the dose range of 20-40 mg/kg was found comparable to standard anti-depressant drug imipramine in anti-depressant activity in rodent animals[29] 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[29].

The traditional use of BM as an anti-anxiety remedy in Ayurvedic medicine is supported by both animal and clinical research[28].One of the study with 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[30].In another study, effects of a standardized BM (300 mg/day) on cognitive performance, anxiety and depression in the elderly was evaluated[31]. The study provided further evidence that BM has a good potential for safely enhancing cognitive performance in the ageing. [31]

Anti-Epileptic Effects

The use of *Bacopamonnieri* for treatment of epilepsy has been studied ,since it exhibit various effects on brain. According to one of the study on the neuroprotective role of *B. monnieri* extract in alteration of glutamate receptor binding and gene expression of (N-methyl-D-aspartate) NMDA R1 in hippocampus of temporal lobe of epileptic rats along with pilocarpine-induced epilepsy, there was significant down regulation of NMDA R1 gene expression and glutamate receptor binding without any change in its affinity. *B. monnieri* treatment of epileptic rats significantly reversed the expression of NMDA R1 and glutamate receptor binding alterations to near-control levels. This study also showed a significant increase in the activity of glutamate dehydrogenase, which neared the control level after *B.monnieri* treatment [32]. This indicate the neuroprotective role of *B. monnieri* extract in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring in association with pilocarpine-induced epilepsy[32] One of the research 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[33].

One of the study examined the anticonvulsant properties of BM extracts in mice and rats[34].When administered acutely at lower doses anticonvulsant activity was not observed. But intraperitoneal injections of high doses of BM extract given for 15 days demonsterated anticonvulsant activity[34]. 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[34].The glutamate gene expression during epilepsy in adult and hypoxic insult to brain during the neonatal period and the therapeutic role of neuroprotective supplement were studied and also the role of metabotropic glutamate-8 receptor (mGluR8) gene expression in cerebellum during epilepsy and neuroprotective role of *Bacopamonnieri* extract in epilepsy were evaluated[35].During epilepsy a significant down-regulation of mGluR8 gene expression was observed which was up-regulated near control level after *B. monnieri* treatment. This showed that *B. monnieri* treatment to epileptic rats significantly brought the reversal of the down-regulated mgluR8 gene expression toward control level[35].

Antioxidant and Adaptogenic Properties

As stress is linked to many diseases, research on an effective antistress agent (adaptogen) from plants has gained importance. In one of the study the adaptogenic property of a standardized extract of *Bacopamonnieri* against acute stress (AS) and chronic stress (CS) models in rats was studied[36].The Pretreatment with *B. monnieri* at 40 mg/kg significantly reduced the AS-induced increase in the ulcer , adrenal gland weight, plasmaglucose,(aspar-

tate aminotransferase) AST, and(creatine kinase) CK. A dose of 80 mg/kg significantly reversed the AS-induced changes in adrenal gland weight, spleen weight, plasma glucose, alanine aminotransferase (ALT), and AST[36]. BM extract or bacosides have shown an antioxidant activity [37],[38],[39],[40],[41],[42] and antistress[43]. A previous study suggests an involvement of the GABA-ergic system in the mediation of these effects of BM[44].Based on animal study results, bacosides were shown to have antioxidant activity in the hippocampus, frontal cortex and striatum[45].One of the study has shown that the BM extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain[46].

In one of the study on rats BM showed the potential to be effective in stress and can be beneficial in the management of stress related conditions[47].BM was found to induce the constitute expression of heat-shock protein (HSP 70), and also induced the(cytochrome P450) CYP 450 enzymes in all regions of brain[47].The level of Hsp70 was found to be increased in brain as a response to stress. 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 BM although the magnitude of induction observed was less with a higher dose of the same[47].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[47]. It was sugessted that this induction may be an adaptive response to the stress which needs further investigation. The level of super oxide dismutase (SOD) was also increased when pre-treated with BM. This data indicates that BM 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[47].

One of the study concluded that BM helps in coping with combined hypoxic, hypothermic and immobilization stress that could lead to onslaught of 'free radicals'[48].The results also indicated that this extract exhibits interesting antioxidant properties, expressed by its capacity to scavenge superoxide anion and hydroxyl radical, and to reduce H 2 O 2 -induced cytotoxicity and DNA damage in human fibroblast cells[41],[49],[50]. BM extract has also shown neuroprotective effect against aluminium-induced oxidative stress in the hippocampus of rat brain[51].According to one study aqueous extract of BM reduced nicotine-induced lipid peroxidation (LPO) and conferred geno protection in Swiss mice[52].One of the recent study has shown the protective role of bacoside A against chronic cigarette smoking-induced oxidative damage in rat brain[54]. This antioxidant activity of BM is able to explain, at least in part, the reported antistress, cognition-facilitating and antiageing effects of BM[55]. and may justify further investigation of its other beneficial biological properties and the potential antistress agent.

Alzheimer's disease

Since it has been claimed that *B. monnieri* is efficacious in the treatment of memory loss, it can bepotentialiy beneficial in the treatment of Alzheimer's[26]. According to one study involving short- and long-term treatment with *B. monnieri* extract showed reduction in brain Aβ (amyloid beta) levels in the cortex and reversed the behavioural deficits in mice[53]. The effect of subchronic (14 days) administration of a standardized extract of *Bacopamonnieri* (bacoside A content 82%) was evaluated on two animal models of Alzheimer's disease induced by intracerebroventricular administration of colchicines and by lesioning of the nucleus basalismagnocellularis (nbm) with ibotenicacid[69]. Subchronic administration of *Bacopamonnieri* at a dose of 10mg/kg significantly reduced the magnitude of memory deficits induced by both compounds as observed on days 7 and 14, while the effects were evident with the lower dose only on day 14 [69]. 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[69]. The study indicates the potential of *B. monnieri* as a therapeutic agent for treatment of alzheimer's disease further research in this area.

Gastrointestinal Effects

Even while Brahmi is widely used to improve intellectual functions, a study was done on the prophylactic and curative effects of standardized extract of Brahmi in various gastric ulcer models[56]. And the study also included evaluation of standardized Brahmi extract on other contributing factors towards ulcerogenesis. And it was found that the effect was due to augmentation of the defensive mucosal factors like increase in mucin secretion, life span of mucosal cells and gastric antioxidant effect rather than on the offensive acid-pepsin secretion[56]. 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[57],[58],[59],[60],[61]. A recent in vitro study also demonstrated its specific an-

ti-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[62]. Further study is required to find the exact mechanism of this effect and to correlate its use in gastric related diseases.

Sedative and Tranquillizing Properties

Bacopamonnieri as a sedative and tranquillizing properties was also studied[28]. According to one study sedative effect was due to glycosides named hersaponins [63]. And subsequent studies 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[64]. It has also been found that the alcoholic extract of the plant and chlorpromazine improved the performance of rats in motor learning[65]. Another study has reported that a single dose of the glycoside hersaponin is better than pentobarbitone in facilitating acquisition[66].

Cognition

Cognition is the mental processing that includes the attention of working memory, comprehending and producing language, calculating, reasoning, problem solving, and decision making. It is the process by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used. In general cognition refers to an information processing view of an individual[67]. *B. monnieri* demonstrated enhanced attention and cognitive processing capability together with enhanced working memory[68]. According to one studystandardized bacosides-rich extract of BM, reversed the cognitive deficits induced by intracerebroventricularly administered colchicines and injection of ibotenic acid into the nucleus Basalismagnocellularis [69]. Also BM was 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[69]. 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[70],[71].

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[28].One of the study was done on Seventy-six adult volunteers aged between 40 and 65 years. The results showed a significant effect of BM on the test for the retention of new information. In the follow-up tests, it was found that the BM decreases the rate of forgetting of newly acquired information. In adults, only chronic administration was shown to enhance cognitive effects[73]. In another study on 38 healthy volunteers (ages 18-60), subjects were given a single dose of 300 mgBM[73][74]. These results were attributed to BM's antioxidant properties and/or its effect on the cholinergic system[75] [76].

In one of the study conducted on 36 children diagnosed with attention deficit/hyperactivity[77].A significant benefit was observed in BM-treated subjects as evidenced by improvement on sentence repetition, logical memory and paired associated learning tasks[77]. The efficacy of standardized BM in subjects with age-associated memory impairment (AAMI) without any evidence of dementia or psychiatric disorder was evaluated in one of the study. BM produced significant improvement in mental control, logical memory and paired associated learning during the 12-week drug therapy.BM was found to be efficacious in subjects with age-associated memory impairment[78].

Side Effects and Toxicity

BM has a record of several hundred years of safe therapeutic use in Ayurvedic medicine. In one of the study the aqueous extract given orally at a dose of 5 g/kg and the alcoholic extract given orally at a dose of 17 g/kg and both extracts did not produce any gross behavioural changes at these levels[28]. According to one study concentrated bacosides given in single (20-30 mg) and multiple (100-200 mg) daily doses were well tolerated and without adverse effects[79].

Other useful effect

Although BM is usually more known for its effect on brain and memory, it exhibit various other effects also. According to one study BM has shown protective effect against DNA damage in astrocytes [81] and human fibroblasts[82]. In another study anti-cancer effect of BMwas studied. And suggested that the anticancer effect of BM extracts is possibly due to inhibition of DNA replication in cancer cell lines[83]. Effect of brahmi on thyroid hormones was also studied. And it was found that high doses (200 mg/kg) of BM 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. This study indicated that BM extract did have a stimulatory effect on thyroid function, but on very high doses[84].

BM was also reported to possess anti-inflammatory activity via inhibition of prostaglandin synthesis and lysosomal membrane stabilization[85],[86]. In vitro study using rabbit aorta and pulmonary artery has demonstrated that BM 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[87]. Animal studies have demonstrated that BM have a relaxant effect on chemically-induced bronchoconstriction, probably via inhibition of calcium influx into cell membranes[28]. A subsequent study on rats in which methanol sub-fractions of BM were given to anesthetized rats prior to induction of bronchoconstriction with carbachol, an acetylcholine analogue. Nearly all of the BMsub-fractions inhibited carbachol-induced bronchoconstriction, hypotension and bradycardia in this animal model[88].

An invitro study also demonstrated that a methanol extract of BM possessed potent mast cell stabilizing activity comparable to disodium cromoglycate, a commonly used allergy medication[90]. These studies indicated the potential usefulness of BM extracts in bronchoconstrictive and allergic conditions[28]. In vitro and animal studies have demonstrated that the BM 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[28]. BM has been noted in animal models to decrease the toxicity of morphine and phenytoin (PHT). Administration of BM with morphine significantly decreased lipid peroxidation (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[91].

In mice, BM administration with phenytoin (PHT) significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory[92]. Both acquisition and retention of memory were improved without affecting the anti-convulsant activity of PHT. These results suggested a potential corrective effect of BM in phenytoin-induced cognitive deficit[93]. An animal study found that the effects of chlorpromazine, a drug similar to (perphenazine, prochlorperazine, thioridazine), were enhanced when a BM was given along with it[94],[95]. More study is required in this area.

Conclusion

*Bacopamonnieri*has been used in traditional Ayurvedic medicine for various indications including memory decline, inflammation, pain, pyrexia, epilepsy and as a sedative [7]. Accumulative lines of evidence have demonstrated that *Bacopamonnieri*has the wide variety of neuropharmacological actions. Further research are required to ascertain the findings mentioned in this review. 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. The antioxidant activity of brahmi may be useful in the treatment of human pathologies in which free radical production plays a key role which requires further study. Futher studies are required to establish the effect of *Bacopamonnieri* on thyroid hormones, astrocytes cells, bronco-constriction and also the possible mechanism by which it exibit this effects. Which opens up interesting avenues for further research and offers new perspectives in the treatment of these diseases. Hence *Bacopamonnieri* has a promising future prospect.

Abbrevations:

BM :*Bacopamonnieria*.
GABA : gamma amino butyric acid.
NMDA:N-methyl-D-aspartate .
mGluR8 :metabotropic glutamate-8 receptor.
AST : aspartate aminotransferase.
AS : acute stress.
CS : chronic stress.
CK :creatine kinase.
ALT : alanine aminotransferase.
HSP : heat-shock protein.
CYP450 :cytochrome P450.

PROD :pentoxyresorufin-odealkkylase .
EROD :ethoxyresorufin-o-deethylase.
SOD : super oxide dismutase.
LPO :lipid peroxidation.
Aβ : amyloid beta.
AAMI :age-associated memory impairment.
PHT : phenytoin.

Acknowledgements
None.

Funding
None.

Competing Interests
None declared.

References

1. W.H.O., Traditional Medicine, Fact Sheet, World Health Organization, Geneva, Switzerland, no. 134, 2003.
2. Kashmira J Gohil, Jagruti A Patel "A review on Bacopamonniera: Current research and future prospects" Maliba Pharmacy College, Bardoli, Surat, Gujarat, India, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, India.
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. Bacopamonniera, 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. Srinivasa Rao Bammidi, Sharan Suresh Volluri, Seema Chaitanya Chippada, Sumanjali Avanigadda, Meena Vangalapati. "A Review on Pharmacological Studies of Bacopamonniera" Journal of Chemical, Biological and Physical Sciences.
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 Herpestismonniera Linn (Brahmi). Ind J Pharmacol 1959;21:303-4.
12. Chatterji N, Rastogi RP, Dhar ML. Chemical examination of BacopamonnieraWettst: 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 dammeranetriterpenesapogenin from Bacopamonniera. 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 Bacopamonniera. Phytochem 1977;16:141-3.
17. Rastogi S, Pal R, Kulshreshtha DK. Bacoside A3-a triterpenoidsaponin from Bacopamonniera. Phytochem 1994;36:133-7.
18. Garay S, Mahato SB, Ohtani K, Yamasaki K. Dammarane-type triterpenoidsaponins from Bacopamonniera. 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 Bacopamonniera. Phytochem 2001;58:553-6.
20. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara, N. Bacopasides III-V: three new triterpenoid glycosides from Bacopamonniera. Chem Pharm Bull 2003;51:215-7.
21. Chakravarty AK, Sarkar T, Nakane T, Kawahara N, Masuda K. New phenylethanoid glycosides from Bacopamonniera.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 Bacopamonniera. 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 Ayurvedicnoo tropic Bacopamonniera Linn. (Brahmi).Ind J Pharmacol 1997;29:S359-S65.
26. Srinivasa Rao Bammidi, Sharan Suresh Volluri, Seema Chaitanya Chippada, Sumanjali Avanigadda, Meena Vangalapati "A Review on Pharmacological Studies of Bacopamonniera" Journal of Chemical, Biological and Physical Sciences.
27. Nestler Eric J, Michel Barrot, Ralph J DiLeone Amelia J. Eisch, Stephen J. Gold, Lisa M. Monteggia. Neurobiology of Depression. Neuron.2002; 34: 13–25.
28. Kashmira J Gohil, Jagruti A Patel "A review on Bacopamonniera: Current research and future prospects" Maliba Pharmacy College, Bardoli, Surat, Gujarat, India, Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, India.
29. 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.
30. Singh RH, Singh L. Studies on the anti-anxiety effect of the MedyhaRasayana drug, Brahmi (Bacopamonniera-Wettst.) - Part 1. J Res Ayur Siddha 1980;1:133¬-48.
31. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopamonnieri 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.
32. 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 Bacopamonnieri extract. Epilepsy and Behav 2008;12:54-60.
33. Martis G, Rao A, Karanth KS. Neuropharmacological activity of Herpestismonniera.Fitoterapia 1992;63:399-404.
34. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from Herpestismonniera, Linn.(Brahmi).Ind J Med Res 1967;55:473-82.
35. Paulose CS, Chathu F, Khan SR, Krishnakumar A. Neuroprotective role of Bacopamonnieri extract in epilepsy and effect of glucose supplementation during hypoxia: glutamate receptor gene expression.Molecular Neurobiology and Cell Biology Unit, Centre for Neuroscience, Department of Biotechnology, Cochin University of Science and Technology.
36. Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh HK. Adaptogenic effect of Bacopamonniera (Brahmi). Pharmacology, Biochemistry, and Behavior 2003, 75(4):823-830
37. Singh S, Eapen S, D'Souza SF. Cadmium accumulation and its influence on lipid peroxidation and antioxidative system in an aquatic plant, Bacopamonnieri L. Chemosphere 2006;62:233-46. 38.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.
38. Sumathy T, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of Bacopamonniera on morphine-induced brain mitochondrial enzyme activity in rats. Fitoterapia 2002;73:381-5. 40.Pawar R, Gopalakrishnan C, Bhutani KK. Dammaranetriterpenesaponin from Bacopamonniera as the superoxide inhibitor in polymorphonuclear cells.Planta Med 2001;67:752-4.
39. Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP. Bacopamonniera Linn.as an antioxidant: mechanism of action. Ind J ExpBiol 1996;34:523-6.
40. Kapoor KR, Srivastava SS, Kakkar P. Bacopamonnieri modulates antioxidant responses in brain and kidney of diabetic rats. Environ ToxicolPharmacol 2008 (article in press).
41. Bhakuni DS, Dhar ML, Dhar MM, Dhawan BN, Mehrotra BN. Screening of Indian plants for biological activity: Part II. Ind J ExpBiol 1969;7:250-62.
42. Singh HK, Shanker G, Patnaik GK. Neuropharmacological and anti-stress effects of bacosides: a memory enhancer. Ind J Pharmacol 1996;28:47.
43. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of Bacopamonniera in rat frontal cortex, striatum, and hippocampus. Phytother Res 2000;14:174-9.
44. Govindarajan R, Vijayakumar M, Pushpangadan P. Antioxidant approach to disease management and the role of 'Rasayana' herbs. Ayur J Ethnopharmacol 2005;99:165-78.
45. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effects of bacosides of Bacopamonnieri: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res 2002;16:639-45.
46. Rohini, G, Sabitha, KE., Devi, CS. Bacopamonniera Linn. extract modulates antioxidant and marker enzyme status in fibrosarcoma bearing rats. Ind J ExpBiol 2004;42:776-80.
47. Seiss H. Strategies of antioxidant defence. Eur J Biochem 1993;215:213-9.

48. Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh H. Adaptogenic effect of Bacopamonniera (Brahmi). PharmacolBiochemBehav 2003;75:823-30.
49. Jyoti A, Sharma D. Neuroprotective role of Bacopamonniera extract against aluminium-induced oxidative stress in the hippocampus of rat brain. Neurotoxicol 2006;27:451-7.
50. Vijayan VA, Helen A. Protective activity of Bacopamonniera Linn. On nicotine-induced toxicity in mice.Phytother Res 2007;21:378-81.
51. Holcomb LA, Dhanasekaran M, Hitt AR, Young KA, Riggs M, Manyam BV. Bacopamonniera extract reduces amyloid levels in PSAPP mice. J Alzheimers Dis 2006;9:243-51.
52. 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.
53. Aloe A, Alleve E, Fiore M. Stress and nerve growth factor findings in animal models and humans. PharmacolBiochemBehav 2002;73:159-66.
54. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of Bacopamonniera in gastric ulcer models.Phytomed 2001;8:423-30.
55. Dorababu M, Prabha,T, Priyambada S, Agrawal VK, Aryya NC, Goel RK. Effect of Bacopamonniera and Azadirachtaindica on gastric ulceration and healing in experimental NIDDM rats.Ind J ExpBiol 2004;42:389-97.
56. Jain P, Khanna NK, Trehan T, Pendse VK, Godhwani JL. Anti-inflammatory effects of an Ayurvedic preparation, BrahmiRasayan, in rodents.Ind J ExpBiol 1994;32:633-6.
57. Rao CH, Sairam K, Goel RK. Experimental evaluation of Bacopamonniera on rat gastric ulceration and secretion.Ind J PhysiolPharmacol 2000;44:435-41.
58. Dharmani P, Palit G. Exploring Indian medicinal plants for antiulcer activity. Ind J Pharmacol 2006;38:95-9.
59. Goel RK, Sairam K. Anti ulcer drugs from indigenous sources with emphasis on Musa sapientum, tamrabhasma, Asparagus racemosus and zinzibarofficinale. Ind J Pharmacol 2002;34:100-10.
60. Goel RK, Sairam K, Babu MD, Tavares IA, Raman A. In vitro evaluation of Bacopamonniera on anti- Helicobacter pylori activity and accumulation of prostaglandins.Phytomed 2003;10:523-7.
61. Malhotra CK, Das PK. Pharmacological studies of Herpestismonniera Linn (Brahmi). Ind J Med Res 1959;47:294-305.
62. Aithal HN, Sirsi M. Pharmacological investigation on Herpestismonniera. Ind J Pharmacy 1961;23:2-5.
63. Prakash JC, Sirsi M. Comparative study of the effects of brahmi (Bacopamonniera) and chlorpromazine on learning in rats. J SciIndust Res 1962;21:93-6.
64. Sinha MM. Some empirical behavioural data indicative of concomitant biochemical reactions. Proceeds Ind. Sci. Congress Part II, Bangalore: 1971. p. 1-26.
65. Sternberg, R. J., & Sternberg, K. (2009). Cognitive psychology (6th Ed.). Belmont, CA: Wadsworth, Cengage Learning.
66. Tatimah Peth-Nui, Jintanaporn Wattanathorn, Supaporn Muchimapura, Terdthai Tong-Un, Nawanant Piyavhatkul, Poonsri Rangseekajee, KornkanokIngkaninan, and Sakchai Vittaya-areekul "Effects of 12-Week Bacopamonnieri Consumption on Attention, Cognitive Processing, Working Memory, and Functions of Both Cholinergic and Monoaminergic Systems in Healthy Elderly Volunteers"
67. Bhattacharya SK, Kumar A, Ghosal S. Effect of Bacopamonniera 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.
68. Singh HK, Dhawan BN. Effect of Bacopamonnieri Linn. (Brahmi) extract on avoidance responses in rat. J Ethnopharmacol 1982;5:205-8.
69. 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.
70. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of Bacopamonniera in gastric ulcer models.Phytomed 2001;8:423-30.
71. Roodenrys A, Booth D, Bulzomi A, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (Bacopamonnieri) on human memory. Neuropsychopharmacol 2002;27:279-81.
72. Nathan PJ, Clarke J, Lloyd J, Hutchison CW, Downey L, Stough C. The acute effects of an extract of Bacopamonniera (Brahmi) on cognitive function in healthy normal subjects. Hum sychopharmacol 2001;16:345-51.
73. Stough C, Lloyd J, Clarke J, Downey LA, Hutchison CW, Rodgers T, et al. The chronic effects of an extract of Bacopamonniera (Brahmi) on cognitive function in healthy human subjects. Psychopharmacol 2001;156:481-4.
74. Sharma R, Chaturvedi C, Tewari PV. Efficacy of Bacopamonnieri in revitalizing intellectual functions in children. J Res EduInd Med 1987;1:1-12.
75. 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.

76. Raghav S, Singh RS, Dalal H, Srivastava PK, Asthana JS. Randomized controlled trial of standardized Bacopamonniera extract in age-associated memory impairment.Ind J Psychiatry 2006;48:238-42.
77. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedicnootropic Bacopamonniera Linn. (Brahmi).Ind J Pharmacol 1997;29:S359-S65.
78. Martis G, Rao A, Karanth KS. Neuropharmacological activity of Herpestismonniera. Fitoterapia 1992;63:399-404.
79. Russo A, Borrelli F, Campisi A, Acquaviva R, Raciti G, Vanella A. Nitric oxide-related toxicity in cultured astrocytes: Effect of Bacopamonniera. Life Sci 2003;73:1517-26.
80. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of Bacopamonniera L. on DNA damage. Phytother Res 2003;17:870-5.
81. Elangovan V, Govindasamy S, Ramamoorthy N, Balasubramaanian K. In vitro studies on the anticancer activity of Bacopamonnieri.Fitoterapia 1995;66:211-5.
82. 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
83. Channa S, Dar A, Anjum S, Yaqoob M, Rahman A. Anti-inflammatory activity of Bacopamonniera in rodents. J Ethnopharmacol 2006;104:286-9.
84. Jain P, Khanna NK, Trehan T, Pendse VK, Godhwani JL. Anti-inflammatory effects of an Ayurvedic preparation, BrahmiRasayan, in rodents.Ind J ExpBiol 1994;32:633-6.
85. Dar A, Channa S. Calcium antagonistic activity of Bacopamonniera on vascular and intestinal smooth muscles of rabbit and guinea-pig. J Ethnopharmacol 1999;66:167-74.
86. Channa S, Dar A, Anjum S, Yaqoob M, Rahman A. Anti-inflammatory activity of Bacopamonniera in rodents. J Ethnopharmacol 2006;104:286-9.
87. Channa S, Dar A, Yaqoob M, Anjum S, Sultani Z, Rahman A. Bronchovasodilatory activity of fractions and pure constituents isolated from Bacopamonniera. J Ethnopharmacol 2003;86:27-35.
88. Samiulla DS, Prashanth D, Amit A. Mast cell stabilizing activity of Bacopamonnieri. Fitoterapia 2001;72:284-5.
89. Sumathy T, Subramanian S, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of Bacopamonniera on morphine induced hepatotoxicity in rats. Phytother Res 2001;15:643-5.
90. Smith DB. Cognitive effects of anti-epileptic drugs.AdvNeurol 1991;55:197-212.
91. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by Bacopamonniera, a reputed Indian nootropic plant. J Ethnopharmacol 2000;71:383-90.
92. Prakash JC, Sirsi M. Comparative study of the effects of brahmi (Bacopamonniera) and chlorpromazine on learning in rats. J SciIndust Res 1962;21:93-6.
93. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from Herpestismonniera, Linn.(Brahmi).Ind J Med Res 1967;55:473-82.
94. N.Sheikh, A. Ahmad, K. B. Siripurapu, V.K. Kuchibhotla, S. Singh, G. Palit, J Ethnopharmcol,2007,111:671
95. Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J ClinOncol 2004;22:2489-503.
96. Russo A, Borrelli F, Bacopamonniera, a reputed nootropicplant, Anoverview, Phytomedicine, 12(4):305-317, 2005.
97. A. Anand, M. K. Saraf, S. Prabhakar, and K. L. Khanduja, "Bacopamonniera attenuates scopolamine-induced impairment of spatial memory in mice," Evidence-based Complementary and Alternative Medicine, vol. 2011, Article ID 236186, 10 pages, 2011.
98. N.Uabundit, J.Wattanathorn, S.Mucimapura, and K.Ingkaninan, "Cognitive enhancement and neuroprotective effects of Bacopamonnieri in Alzheimer's disease model," Journal of Ethnopharmacology, vol. 127, no. 1, pp. 26–31, 2010.
99. H. Joshi and M. Parle, "Brahmirasayana improves learning and memory in mice," Evidence-based Complementary and Alternative Medicine, vol. 3, no. 1, pp. 79–85, 2006.
100. S. Raghav, H. Singh, P. K. Dalal, J. S. Srivastava, and O. P. Asthana, "Randomized controlled trial of standardized Bacopamonniera extract in age-associated memory impairment," Indian Journal of Psychiatry, 2006:48,238–242.
101. M. P. Pase, J. Kean, J. Sarris, C. Neale, A. B. Scholey, and C. Stough, "The cognitive-enhancing effects of Bacopamonnieri: a systematic review of randomized, controlled human clinical trials," The Journal of Alternative and Complementary Medicine, vol. 18, no. 7, pp. 647–652, 2012.
102. G. Martis, A. Rao, and K. S. Karanth, "Neuropharmacological activity of Herpestismonniera," Fitoterapia, vol. 63, no. 5, pp. 399–404, 1992.