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PS Geetha
Department of Differently Abled Studies, Community Science College and Research Institute, Tamil Nadu Agricultural University, Madurai, Tamil Nadu, India

S Kanchana
Department of Human Development and Family Studies, Community Science College and Research Institute, Tamil Nadu Agricultural University, Madurai, Tamil Nadu, India

E Pasupathi
Department of Differently Abled Studies, Community Science College and Research Institute, Tamil Nadu Agricultural University, Madurai, Tamil Nadu, India

M Murugan
Department of Agricultural Entomology, Centre of Plant Protection Studies, Tamil Nadu Agricultural University, Coimbatore, Tamil Nadu, India

C Rohini
Department of Food Science and Nutrition, Community Science College and Research Institute, Tamil Nadu Agricultural University, Madurai, Tamil Nadu, India

Corresponding Author:
PS Geetha
Department of Differently Abled Studies, Community Science College and Research Institute, Tamil Nadu Agricultural University, Madurai, Tamil Nadu, India

A review on putative mechanism of action of nootropic herb *Bacopa monnieri*

PS Geetha, S Kanchana, E Pasupathi, M Murugan and C Rohini

Abstract
Bacopa monnieri (BM) has been used by ayurvedic medical practitioners for centuries for a variety of purposes, including improving memory, reducing anxiety and treating epilepsy *Bacopa monnieri* (L) Penn. (Family: Scrophulariaceae) commonly known in both India and Bangladesh as 'Brahmi' is an ancient and renowned medicinal plant with legendary reputation as a memory vitalizer (Brimson *et al*., 2021) in the traditional system of medicine (Ayurveda). Brahmi is classified as medhya rasayana, a drug that is supposed to counteract the effect of mental stress and improved the intelligence and memory function. Brahmi have an effect on various neurodegenerative diseases as they modulate signaling pathways (Maity, 2019). Brahmi is found to be effective in the case of anxiety and neurosis. Numerous studies suggested that *B. monnieri's* bioactive components (i.e. bacosides) protect the brain against oxidative damage and age related cognitive deterioration with several mechanisms of action (Manap, 2019). It possesses anti-inflammatory, analgesic and anti-pyretic activity. It is also used to treat asthma, insanity epilepsy, enlargement of spleen, snakebite, rheumatism, leprosy, eczema, ring worm and as a diuretic and cardio tonic. Present review will amalgamate molecular neuroscience with behavioral research and also to examine the prominent effects of standardized extract of *Bacopa monnieri* on the action of the central nervous system.

Keywords: Ayurveda, brahmi, *Bacopa monnieri*, nootropic, neurotransmitters, putative mechanism

Introduction
Neurological disorders include a wide array of problems including neuronal deterioration, cognitive decline, depression, anxiety and have been considered as one of the greatest risks to human health (Pan, 2020) [4]. Nootropics are also known as smart drugs that are being developed for over three decades and are the predominantly used method for treating neurological disorders (Srivastava *et al*., 2019) [5]. It has been derived from two words, that is, "noos," pertaining "to mind" and "tropein," signifying "to monitor." In general, it means any given substance that influences the cognitive ability in a positive way (Colucci *et al*., 2012) [6]. They probably act by altering the levels of neurotransmitters, hormones and enzymes that are available to the brain, through improvement of brain's oxygen supply or stimulation of nerve growth. However, the detailed description of their efficacy seems to be incomplete as yet. This is because of the absence of a scale to quantitatively measure cognition and intelligence. Herbs acting as memory herbs enhance the level of neurotransmitters like acetylcholine and also increase blood flow directed towards the brain, thereby nurturing it with increased supply of oxygen and nutrients, which further refines brain function and memory (Amin and Sharma, 2015) [7].

Phytochemical and molecular mechanism of action
Unlike the potentially addictive and forceful action of widely used psychostimulants, chronic and moderate administration of *Bacopa monnieri* (BM) appears to nourish rather than deplete neurons, an action compatible with 1400 years of Ayurvedic study (Aguiar and Borowski, 2013) [8]. BM was initially described around the 6th century anno domini (AD) in texts such as the Charaka Samhita, Athar-Ved and Susrutu Samhita as a medhya rasayana class herb taken to sharpen intellect and attenuate mental deficits. The herb was allegedly used by ancient Vedic scholars to memorize lengthy sacred hymns and scriptures. BM is colloquially called Brahmi, named after the Hindu creator god Brahma, especially when combined with other alleged intellect sharpening herbs like *Centella asiatica* (Gotu Kola). BM is consistently found in the many Ayurvedic preparations prescribed for cognitive dysfunction. *B. monnieri* in a cocktail with other plant extracts were able to significantly reduce the effects of Alzheimer's

disease and depression which cannot be solely credited as the effect of *B. monnieri* (Brimson, 2021) [1]. Aguiar and Borowski (2013) [8] stated that behavioral research with neuromolecular mechanisms putatively involved with the low toxicity cognitive enhancing action of *Bacopa monnieri* (BM), a medicinal ayurvedic herb. BM is traditionally used for various ailments, but is best known as a neural tonic and memory enhancer. Numerous animal and in vitro studies have been conducted, with many observable adverse effects at standard dosages. BM demonstrates anti-oxidant, hepatoprotective and neuroprotective activity. This research demonstrates several mechanisms of action acetylcholinesterase inhibition, choline acetyltransferase activation, β-amyloid reduction, increased cerebral blood flow and monoamine potentiation. Several randomized, double-blind, placebo-controlled trials have substantiated BM's nootropic utility in humans. There is also evidence for potential attenuation of dementia, Parkinson's disease and epilepsy. BM appears to exhibit low toxicity in model organisms and humans; however, long-term studies of toxicity in humans have yet to be conducted.

The milieu of nootropic phytochemicals found within *Bacopa monnieri* (BM), primarily triperpenoid saponins called bacosides, exhibit minimal observable adverse effects at standard dosages.BM demonstrates anti-oxidant, hepatoprotective and neuroprotective activity (Kumar *et al*., 2016) [9]. *Bacopa* extract has been shown to possess dose dependent free radical scavenging capacity and protective effect on DNA cleavage (Masliah *et al*., 1993) [10, 48]. Its antioxidant property, which is about half potent to that of vitamin E on weight basis (Thal *et al*., 2008) [11] is thought to be responsible for its antistress, immunomodulatory, cognition facilitatory, anti-inflammatory and antiageing effect (Kahol *et al*., 2004; Kulkarni *et al*., 2012; Aguiar and Borowski, 2013; Singh and Dhawan, 1997; Gupta *et al*., 2014; Russo and Borrelli, 2005; Barrett and Strother, 1978 and Basu and Lamsal, 1947) [8, 12-14, 16-18, 54]. Its antilipid peroxidation property is credited to the memory enhancing action and it has been recommended for low dose long-term therapy rather than single high dose administration (Thal *et al*., 2008) [11]. Oxidative stress is one of the most important factors in aging and age-related illnesses (Jenny, 2012). Various free radicals playing an important part in oxidative damage are hydroxyl (OH'), hydrogen peroxide (H_2O_2), Peroxynitrite (ONO_2-) and superoxide free radical (O_2-') (Floyd and Hensley, 2002). Oxygen is absolutely important for survival but its excess results in the formation of reactive oxygen species (ROS) which can damage the brain (Parletta *et al*., 2013) [21]. Brain is particularly susceptible to free radical damage due to its high metabolic rate, unsaturated fatty acids in cell membranes, lower activity of antioxidant mechanisms like glutathione peroxidase (GPx) and catalase (CAT), and cytotoxic actions of glutamate (Bhattacharya *et al*., 2000) [22].

Saha *et al*. (2020) [23] reported that pharmacologically active compounds of *Bacopa* include saponins, steroids and alkaloids. Comprehensive studies first confirmed that *B. monnieri* isolated the alkaloid 'brahmine'. In the same year, other alkaloids such as herpestine and nicotine were also reported. D-mannitol and a saponin, hersaponin and potassium salts were subsequently isolated. Bacoside A, known as 3- (a-L-arabinopyranosyl)-O-b-D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene, is the major chemical entity shown to be responsible for neuro pharmacological effects and the nootropic activity or antiamnestic effect of *Bacopa*. Bacoside A typically co-occurs with Bacoside B; the latter only varies in optical rotation probably in an artefact produced during the bacoside A isolation process. The major chemical components isolated and characterized by different major spectral, chemical and two-dimensional nuclear magnetic resonance spectroscopy (2D NMR) studies carried out by various research groups from the herbal alcoholic extract are dammarane type of triterpenoid saponins with jujubogenin andpseudojujubogenin as aglycones. Bacosides yield a mixture of aglycones on an acid hydrolysis, bacogenin A1, A2, A3 (Kulshreshtha and Rastogi, 1973) [24]. Three new triterpenoid saponins of biological interest, bacopasaponins A, B and C, pseudojujubogenin were isolated and a new dammarane type pseudojujubogenin glycoside, bacopasaponin D, was identified using chemical transformation and spectroscopic methods. Two new pseudojujubogenin glycosides, known as bacopaside I and II, have been isolated from glycosidic fraction of the methanol (Singh and Dhawan, 1982) [97]. Thereafter, three new saponins, called Bacopasides III, IV, and V were isolated. Furthermore, three new phenylethnoid glycosides (monnierasides I to III) were identified from the glycosidic fraction of *B. monnieri* along with the known analogue plantainoside B.

Chaudri *et al*. (2017) observed that our body has many free radical scavenger mechanisms which are enzymatic or non-enzymatic. Enzymatic ones include superoxide dismutase (SOD), catalase (CAT), glutathione reductase that act as a first line of defense against Reactive Oxygen Species while non-enzymatic ones like vitamin A, C and E, selenium, coenzyme Q10 and glutathione (GSH) whose antioxidant actions protect neuronal tissue from free radical damage. Imbalance between protective antioxidant mechanisms and free radical species is the basis for free radical damage resulting in aging and cognitive decline (Sohal and Orr, 2012) [27]. Extract of *Bacopa monnieri* (EBm) was administered to the rats for 21 days. It showed increase inactivity of enzymes SOD, CAT and GPx in prefrontal cortex, hippocampus and striatum. In comparison, deprenyl, a known antioxidant demonstrated increase in activity of these enzymes in prefrontal cortex and striatum but not in hippocampus (Bhattacharya *et al*., 2000) [22]. In another in vitro study, human non-immortalized fibroblasts were tested for the DNA damage and free radical mediated cytotoxicity by H_2O_2, in which EBmwas found to be protective (Russo *et al*., 2003) [28].

Dhanasekaran *et al*. (2007) [29] stated that *Bacopa monniera* reduces beta-amyloid deposits in the brain of an Alzheimer's Disease (AD) animal model. The objective of the study was to establish the presence of endogenous substances in *Bacopa monniera* extract (BmE) 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. The extract contained polyphenols and sulfhydryl contents suggestive of endogenous antioxidant activity. The results demonstrated that BmE reduced divalent metals, dose-dependently scavenged reactive oxygen species, decreased the formation of lipid peroxides and inhibited lipoxygenase activity. These data combined with their previous studies that have shown that BmE treatment reduces beta-amyloid levels in the brain of an AD doubly transgenic mouse model of rapid amyloid deposition (PSAPPmice)

suggesting mechanisms of action relevant to the treatment of AD.

Limpeanchob *et al*. (2008) [30] demonstrated that Brahmi extract protected neurons from beta-amyloid-induced cell death, but not glutamate-induced excitotoxicity. This neuroprotection was possibly due to its ability to suppress cellular acetylcholinesterase activity but not the inhibition of glutamate-mediated toxicity. In addition, culture medium containing Brahmi extract appeared to promote cell survival compared to neuronal cells growing in regular culture medium. Further study showed that Brahmi treated neurons expressed lower level of reactive oxygen species suggesting that Brahmi restrained intracellular oxidative stress which in turn prolonged the lifespan of the culture neurons. Brahmi extract also exhibited both reducing and lipid peroxidation inhibitory activities. From this study, the mode of action of neuroprotective effects of Brahmi appeared to be the results of its antioxidant to suppress neuronal oxidative stress and the acetylcholinesterase inhibitory activities. Therefore, treating patients with Brahmi extract may be an alternative direction for ameliorating neurodegenerative disorders associated with the overwhelming oxidative stress as well as Alzheimer's disease.

Bacoside-A in particular has been reported to alleviate the amnesic effects (Das *et al*., 2002; Russo and Borrelli, 2005) [16, 31]. BM also restores epilepsy-associated cognitive deficits. In pilocarpine-induced epilepsy rat model, there was a significant down-regulation in N-methyl D-aspartate receptors (NMDA) expression and glutamate receptor function, whereas BM significantly reversed these alterations and increase the activity of glutamate dehydrogenase to near control levels. BM also demonstrates stress-decreasing activity in acute and chronic stress situations (Bhattacharya *et al*., 2000; Rai *et al*., 2003) [22].

Brain Derived Neurotrophic Factor (BDNF) is a member belonging to the family neurotrophin is an important marker of neuronal plasticity and has a critical role in the transcription of gene Arc which is connected with neuronal plasticity and memory. Low levels of BDNF predispose a person to Alzheimer's Disease (Zheng *et al*., 2009) [33]. Glial Fibrillary Acidic Protein (GFAP) is an important marker of glial plasticity which regulates morphology of astrocytes, interactions between neuroglia and memory forming mechanisms (Drozdov and Chorna, 2003) [34]. Expression of GFAP is also substantially decreased in amnesic conditions (Konar *et al*., 2011) [35] they found out that administration of EBm alone resulted in increased expression of BDNF by 1.3 times and Arc expression by 2 times however expression of GFAP was not increased upon treatment. In scopolamine-treated mice, pre and post-administration of EBm resulted in enhancement of plasticity markers in cerebrum the effect being more marked in expression of BDNF and Arc expression than that of GFAP. Thus EBm has a significant role in the improvement of brain plasticity by a variety of mechanisms.

Anbarasi *et al*. (2006) [36] assessed the neuroprotective role of bacoside A against Oxidative Stress (OS) in the brains of rats exposed to cigarette smoke by measuring concentrations of enzymatic and non-enzymatic anti-oxidants as well as trace elements. The researchers administered 10 mg/kg aqueous bacoside A gavage daily and found that BM significantly increased brain levels of glutathione, Vitamin C, Vitamin E, and Vitamin A in rats exposed to cigarette smoke (perhaps an anti-oxidant conservation effect). Bacoside A administration increased the activities of superoxide dismutase (SOD), catalase (CAT), GPx (Glutathione peroxidase-1) and GSR. As a result, the levels of glutathione (primary endogenous anti-oxidant conjugate) in the brain were significantly increased as well. The researchers found that cigarette smoke depletes Zinc and Selenium levels in the brain, which is especially problematic because zinc is a SOD co-factor and selenium is a GPx co-factor. Administration of bacoside A also restored Zinc and Selenium levels.

Saini *et al*. (2012) [37] found that BM (50 mg/kg per day oral) supplementation reversed memory impairment in colchicine-treated (15 μg in 5 μL artificial cerebrospinal fluid, intra cerebroventricularly infused) rat model of Alzheimer disease. Colchicine is a microtubule-distrupting agent that induces cognitive decline via OS and neural death in the subventricular zone, dentate gyrus and basal forebrain (Goldschmidt and Steward, 1982). BM significantly diminished colchicine-induced lipid peroxidation and protein carbonyl levels and restored activity of several anti-oxidant enzymes. In the elevated plus maze, colchicine increased transfer latency by 64%, whereas BM co-administration significantly reduced latency by 62%. Colchicine increased lipid peroxidation by 45% in the cortex and 33% in the hippocampus. Protein carbonyl levels were increased by 61% in the cortex and 63% in the hippocampus. Glutathione levels were reduced by 47% in the cortex and 45% in the hippocampus of colchicine-treated rats. All damage was restored to control levels by BM.

In a comprehensive study, Rastogi *et al*. (2012) [39] investigated the neuroprotective mechanisms of purified bacosides (comprised of bacopaside I [5.37%], bacoside A3 [5.59%], bacopaside II [6.9%], bacopasaponin C isomer [7.08%] and bacopasaponin C [4.18%]) at dosages 50, 100, 200, 400, and 800 mg/kg per day orally for 3 months) on the aging biomarker lipofuscin), oxidative stress, acetylcholine (ACh), monoamine levels as well as behavioral deficits in the aged rat brain. BM restored ACh and AChE concentrations to those seen in young rats. The authors supported the hypothesis (Ahirwar *et al*., 2012; Das *et al*., 2002; Gray and Brimijoin, 2003) [31, 40, 41] that the primary ACh-boosting mechanism of BM is not AChE inhibition but choline acetyltransferase activation (synthesis of ACh) and that up-regulated AChE expression is a response to heightened ACh tone. The authors assayed the integrity of CA3 hippocampal neurons, finding that BM "profoundly" protected against age-related structural alterations. SOD and catalase (CAT) activity were not significantly improved, but GPx deficits in middle-aged rats were abolished. The increase in age-dependent protein carbonyl formation was not significantly attenuated by BM. Strong correlations between age-related biomarkers (lipid hydroperoxides and lipofuscin) and behavioral deficits were identified. Lipofuscin and 5-hydroxytryptamine (5-HT) levels were inversely correlated. Transfer latency and ambulation time in the passive avoidance test were inversely correlated with lipid hydroperoxide levels. Monoamine potentiation (5-HT and DA) was a remarkable finding, with concentrations in aged rats significantly restored to levels seen in the young. The behavioral effect was modeled using the tail-suspension depression test, showing an antidepressant effect in accordance with past research. This study demonstrated the efficacy of BM in preventing lipofuscin accumulation and enhancing acetylcholine synthesis, monoamine modulation, and inhibition of lipid peroxidation (Sairam *et al*., 2002) [42].

According to Liu *et al*., (2012) [43] bacopaside I exhibits neuroprotective, anti-oxidant and cerebral ATP-increasing effects post-cerebral ischemia in rats (3, 10 and 30 mg/kg orally for 6 days). The singular bacopaside significantly reduced neurological deficits and infarct volume while significantly increasing brain ATP content, energy charge, total adenine nucleotides, nitric oxide, Na + K + ATPase and Ca2 + Mg2 + ATPase activity. Bacopaside I treatment also improved anti-oxidant enzyme activities includingSOD, CAT, GPx and markedly inhibited the increase in malondialdehyde (a free radical marker) content of the brain.

A research by Piyabhan and Wetchateng (2012) [44] investigated the neuroprotective function of BM (40 mg/kg per day orally for 14 days, n = 72) on novel object recognition in a phencyclidine-induced rat model of schizophrenia, finding highly significant protection and improved performance. The same authors conducted another study on vesicular glutamate transporter 1 (VGLUT1), of which schizophrenics have a deficit in the prefrontal cortex, striatum, and hippocampus. A phencyclidine rat model was used. The researchers found significant improvement in all three brain-regions in the BM group.

In a meta-analysis, Neale *et al*., (2012) [45] compared the nootropic effects of BM to *Panax ginseng* and modafinil (an eugeroic-wakefulness drug). Chronic BM produced the most consistent and largest effect sizes of the three natural nootropics. BM showed small to medium effect sizes for attention and information processing tasks. Larger effect sizes were evident for auditory verbal learning tasks, sizes ranging from d = 0.23 for delayed word pair memory to d = 0.95 for delayed word recall (on the Auditory Verbal Learning Test) and d = 1.01 for protection from proactive interference during delayed memory. These findings evidence the potency of BM, particularly in measures of verbal recall. Remarkably, contemporary findings appear to support the alleged use of BM in Vedic antiquity by scholars memorizing lengthy hymns.

Kumar *et al*. (2015) [46] investigated the effect of EBm on cold stress induced neuro degeneration in hippocampus of rats. Histologically, rat brains were divided into 4 groups: Group 1 consisted of rats which were kept in ideal laboratory conditions, Group 2 rats were given EBm in the dose 40 mg/kg, Group 3 rats were forced to swim in the cold water (temperature: 18 ± 2°C) for 1 month which generated cold water swim stress in their body and Group 4 were given cold water swim stress for 1 month which was followed by treatment by EBm for about 1 month in the dose of 40 mg/kg. Histophotometric study of hippocampus was done in which diameter of cells, total number of cells in the square and packing density of cells were taken into consideration. Group 3 cells showed decreased diameter of cells, number of cells per square and packing density of cells which was indicative of stress-induced damage while Group 4 cells showed increased cell diameter, number of cells per square and cell packing density. Group 4 rats showed the above parameters comparable to that of Group 1 rats. This study demonstrated that EBm has got important therapeutic effect in abolishing stress induced hippocampal damage.

Antiepileptic drug phenytoin causes cognitive impairment on regular use in many patients. Using this principle, Neurocognitive effect of Nootropic Drug Brahmi (*Bacopa monnieri*) in AD phenytoin was given to experimental rats in a dose of 25 mg/kg for 7 days resulting in significant cognitive impairment in the rats. Administration of EBm caused significant reversal of phenytoin-induced memory impairment (Vohora, 2000) [47].

Deposition of Aβ protein in the brain parenchyma causing neuronal degeneration is the most important mechanism of pathogenesis in Alzheimer's Disease (Masliah, 1993) [10, 48]. A study done by Mathew and Subramanian (2012) [49] on anti-amyloidogenic potentials of various herbs revealed that methanolic EBm decreased the formation of amyloid fibrils almost entirely and segregated the pre-formed amyloid fibrils up to a considerable extent.

Goswami *et al*. (2011) [50] investigated the effect over 6 months of a daily dose of 600 mg *B. monnieri* in 39 patients formally diagnosed with Alzheimer's disease. Te study found mild statistically significant increase in performance in various aspects of the MMSE tests and concludes that *B. monnieri* is beneficial in Alzheimer's disease patients. However, since this study is neither placebo-controlled or randomized and does not compare to a positive control such as donepezil, it is not possible to assess the true value of *B. monnieri* in Alzheimer's disease patient.

Early prenatal or post natal exposure to environmental insults such as valproic acid (VPA), thalidomide and ethanol could induce behavioral alterations similar to autistic symptoms. The purpose of the present study was to evaluate the effect of *B. monniera* on VPA induced autism. On 12.5 day of gestation the female pregnant rats were divided into control and VPA treated groups. They were administered saline/VPA (600 mg/kg, i.p.) respectively and allowed to raise their own litters. Group I male pups of saline treated mothers. On postnatal day (PND) 21 VPA induced autistic male pups were divided into two groups (n = 6); Group II received saline and Group III received *B. monniera* (300 mg/kg/p.o.) from PND 21-35. Behavioral tests (nociception, locomotor activity, exploratory activity, anxiety and social behavior) were performed in both adolescence (PND 30-40) and adulthood (PND 90-110) period. At the end of behavioral testing animals were sacrificed, brain was isolated for biochemical estimations (Serotonin, Glutathione, Catalase and Nitric oxide) and histopathological examination. Induction of autism significantly affected normal behavior, increased oxidative stress and serotonin level, altered histoarchitecture of cerebellum (decreased number of purkinje cells, neuronal degeneration and chromatolysis) when compared with normal control group. Treatment with *B. monniera* significantly (p\0.05) improved behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of cerebellum. In conclusion, the present study suggests that *B. monniera* ameliorates the autistic symptoms possibly due to its antianxiety, antioxidant and neuro-protective activity (Sandhiya *et al*., 2012).

Zhou *et al*. (2009) [52] have shown that bacosides from the plant show nootropic activity against scopolamine-induced memory impairment. Limpeanchob *et al*. (2008) [30] have shown the neuroprotective effect of BM on Aβ induced cell death in primary cortical neurons which was thought to be mediated through antioxidant effect of BM. Uabundit *et al*. (2010) [53] reported that BM administration mitigated the memory impairment and the degeneration of neurons in hippocampus in ethylcholine aziridinium induced animal model of AD.

In addition, BM was found to be effective in improving neurotransmission and repairing of damaged neurons via enhanced regeneration of nerve synapses (Singh HK, 1997) [14, 54]. Administration of bacosides to mice attenuated

diazepam induced anterograde amnesia and improved memory as measured by the morris water maze test (Kishore and Singh, 2005) [55]. Molecular studies revealed that diazepam up-regulates the mitogen activated protein kinase, phosphorylated CREB, inducible nitric oxide synthase, cAMP response element binding protein (CREB) expression, cyclic adenosine monophosphate (cAMP) without affecting calmodulin levels, while BM supplementation significantly suppressed the diazepam induced impairment (Prabhakar *et al*., 2008) [56]. A study employed a number of convulsion inducing models including pentylenetetrazol, strychnine, hypoxic stress and pilocarpine to investigate the anticonvulsive activity of Brahmi in rats and mice. Brahmi was administered orally (50 and 55 mg/kg) in these animals, 2 and 4 h prior to receiving convulsive stimuli. It was found that the herb produced a significant anticonvulsant activity like benzodiazepines in different convulsion inducing models studied (Kaushik *et al*., 2009) [57].

Nemetchek *et al*. (2017) studied about the tea, infusion and alkaloid extracts of *Bacopa*, as well as Bacoside A, significantly inhibited the release of pro-inflammatory cytokines TNF-α and IL-6 from activated N9 microglial cells in vitro. In addition, the tea, infusion and alkaloid extracts of *Bacopa* effectively inhibited caspase 1 and 3 and matrix metalloproteinase-3 in the cell free assay. *Bacopa* inhibits the release of inflammatory cytokines from microglial cells and inhibits enzymes associated with inflammation in the brain. Thus, *Bacopa* can limit inflammation in the CNS and offers a promising source of novel therapeutics for the treatment of many CNS disorder. Brahmi also possesses antiepileptic property as evidenced by reducing the dopamine levels of dopaminergic neurons in the frontal cortex region of the rat brain (Jash and Chowdary, 2014) [59]. These observations suggest that Brahmi may possess the property to alleviate the positive symptoms of schizophrenia.

Aluminium-induced neurotoxicity is well known and different salts of aluminium have been reported to accelerate oxidative damage to biomolecules like lipids, proteins and nucleic acids. The present study investigated whether BM could potentially inhibit aluminium toxicity in the cerebral cortex. Male Wister rats (8 months old) were administered with $AlCl_3$ orally at a dose of 50mg/kg/day in drinking water for 1 month. Experimental rats were given $AlCl_3$ along with BM extract at a dose of 40 mg/kg/day. One group of rats was treated with l-deprenyl at a dose of 1mg/kg/day along with $AlCl_3$ treatment. It is observed that BM prevented accumulation of lipid and protein damage significantly, which resulted from aluminium intake. Decline in the activity of endogenous antioxidant enzymes associated with aluminium administration was also inhibited by BM extract. The potential of BM to inhibit Al-induced oxidative stress was observed to be similar to that of l-deprenyl, which was taken as standard. The potential of BM extract to prevent aluminium neurotoxicity was reflected at the microscopic level as well, indicative of its neuroprotective effects. These findings strongly implicate that BM has potential to protect brain from oxidative damage resulting from aluminium toxicity (Jyoti *et al*., 2006) [60].

The anti-dementic activity of BM was tested against scopolamine-induced behavioral deficits. BM treatment for 7 days significantly attenuated the dementic effect in vivo and showed a dose-dependent inhibitory effect on acetylcholinesterase (AchE) activity suggesting that BM has potent cognitive enhancing properties (Das *et al*., 2002) [31]. In another study, administration of BM for two weeks, reversed the depletion of acetylcholine, the reduction in AchE activity and the decrease in binding of muscarinic cholinergic receptor in the frontal cortex and hippocampus, induced by neurotoxins (Bhattacharya, 2000) [22]. Like animal studies, clinical studies have provided significant evidence regarding the action of BM on cognitive function (Kidd, 1999; Pravina *et al*., 2007) [62, 63]. However, the mechanism of the pharmacological actions needs to be elucidated.

Dave *et al*. (2014) [64] standardized the extract of *B. monnieri* (SBME) which significantly reduced the subtests scores of ADHD symptoms, except for social problems. The symptom scores for restlessness were reduced in 93% of children, whereas improvement in self-control was observed in 89% of the children. The attention-deficit symptoms were reduced in 85% of children. Similarly, symptom scores for learning problems, impulsivity and psychiatric problems were reduced for 78%, 67% and 52% of children, respectively. It was observed that 74% of the children exhibited up to a 20% reduction, while 26% of children showed between a 21% and a 50% reduction in the total subtests scores. Standardized extract of *B. monnieri* was found to be effective in alleviating the symptoms of ADHD and was well tolerated by the children.

The cognition-facilitating effect has been attributed to two active saponins present in the ethanol extract of BM *viz*., bacosides A and B (Singh HK, 1997) [14, 54]. The composition of bacoside A and bacoside B have been established as a mixture of four triglycosidic and four diglycosidic saponins, respectively (Deepak *et al*., 2005; Sivaramakrishna *et al*., 2005) [65, 66].

BM ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats. Early prenatal or post natal exposure to environmental insults such as valproic acid (VPA), thalidomide and ethanol could induce behavioral alterations similar to autistic symptoms. Treatment with *B. monniera* significantly improved behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of cerebellum (Suruchi Chandra, 2013) [67]. Pretreatment with *B. monnieri* extract offsets 3-nitropropionic acid induced mitochondrial oxidative stress and dysfunction in the striatum of prepubertal mouse brain (Shinomol, 2011) [68].

Negi *et al*. (2000) [69] reported significant memory enhancing effect of phytocomposition containing *B. monnieri* in children with Attention Deficit Hyperactivity Disorder (ADHD). Further, safety aspect of *B. monnieri* extract, no mutagenic effect was observed in Ames test (Dipanwita *et al*., 2008) [70] and no incidence of genotoxicity was also reported as well (Giri and Khan, 1996) [71]. A no-observed adverse effect level of 500mg/kg/day was established in subchronic oral toxicity study for 90 days (Joshua *et al*., 2007) [63]. So the BM extract can be provided to the children below the age of ten with ADHD symptoms.

Bhalerao *et al*. (2013) [73] revealed that the *Brahmi ghṛitam* is an Ayurvedic formula that contains four medhya herbs. Medhya herbs have a positive effect on the central nervous system (CNS). This Ayurvedic polyherbal formulation contains four medhya plants *viz*., Brahmi (*Bacopa monneri*), Vaca (*Acorus calamus*), Kustha (*Sassurea lappa*) and Sankhapuspi (*Convolvulus pluricaulis*) and is processed in Goghrtam (Ghee prepared from cow's milk). Of these, two of the ingredients of the formulation *viz*., Sankhapuspi and Brahmi have been earlier evaluated in different behavior

disorders and have shown promising results. The study was carried out in two phases. The first phase (pilot, exploratory) was conducted to confirm the selected dose and dosage regimen of *Brahmi ghrtam*, whereas in the second phase (therapeutic, confirmatory) *Brahmi ghrtam* was compared with methylphenidate, the standard of care in ADHD. In the pilot, exploratory study at Tilak Ayurved Mahavidyalaya (TAV), *Brahmi ghrtam* showed almost 66% decrease in total ADHD score. The ADHD score after completion of the study was significantly reduced when compared to baseline. The effect was slightly pronounced on the inattention symptoms when compared to impulsivity symptoms although both symptoms showed statistically significant improvement when compared to baseline.

Baco Mind, a standardized bacopa bioactive compound formulation derived from BM and used as a memory enhancing agent, was evaluated for toxicity studies to confirm its safety (Joshua *et al*., 2007; Pravina *et al*., 2007) [63]. Baco Mind, on single oral administration, had a median lethal dose of 2400 mg/kg in rats (Joshua *et al*., 2007) [63]. A subchronic oral toxicity study for 90 days in rats at the dose levels of 85/210/500 mg/kg did not reveal any evidence of toxicity with respect to clinical signs, neurological examination, weight gain, or hematological parameters. Necropsy and histopathological examination did not reveal any deteriorative changes (Joshua *et al*., 2007) [63]. The LD_{50}s of orally administered BM extracts in rats were 5 g/kg (aqueous extract) and 17 g/kg alcoholic extract (Singh and Dhawan, 1982) [25].

Administration of bacopaside 1 for six days at the doses of 3/10/30 mg/kg showed amelioration in neurological deficit, cerebral infarct volume and edema in a rat model of transient focal ischemia by improving cerebral energy metabolism and by antioxidant actions (Liu *et al*., 2013) [75]. Bacopa and its constituents (bacosides) prevented behavioral impairment and GABA-receptor dysfunction in epileptic rats (Mathew *et al*., 2011) [76]. The anti-aging effect of BM in astrocytes through the activation of protective mitochondrial autophagy could mitigate pollution and aging-related neurological disorders (Saha, 2020) [23].

The neuronal dendritic growth stimulating property of BM has also been reported, which may be responsible for its memory enhancing effects (Vollala *et al*., 2011) [77] and also his another study examined the effects of standardized extract of BM on behavioral changes of Wistar rats when administered the extract for various durations and in varying doses. They divided the animals into 2, 4 and 6 week treatment groups. Rats in each of these groups were divided into 20mg/kg, 40mg/kg and 80mg/kg dose groups (n = 8 for each dose). After the treatment period, the rats, along with age matched normal and gum acacia control rats, were subjected to spatial learning (T-maze) and passive avoidance tests. The data were compared with those of age matched control rats. The results showed improvement in spatial learning performance and enhanced memory retention in rats treated with BM extract. The results of T-maze tests in rats treated with lower doses of BM (20 mg/kg) for a 2 weeks period were not significantly different than those from the normal control group rats. However, rats treated for 2 weeks in the higher dose groups (40 and 80 mg/kg) showed significant improvement in their learning behavior. These results clearly indicate that oral administration of BM extract improved learning and memory in rats (Vollala *et al*., 2010) [78]. In this study the effects of *B. monnieri* mimic those of the positive control (imipramine 20 mg/kg) which acts primarily as a sigma-1 ligand (Brimson *et al*., 2020; Muller, 1999) [79].

Other studies have also shown that chronic unpredictable stress (CUS) induced reductions in brain derived neurotrophic factor (BDNF), AKT (Protein kinase) and cyclic-AMP response element binding (CREB) expression are reversed by *B. monnieri* treatment indicating sigma-1 receptor activation (Ji *et al*., 2017) which is hypothesized to be involved in the activities of antidepressant drugs (Brimson *et al*., 2020) [79]. However, there has not been a study directly investigating the role of the sigma-1 receptor in the antidepressant activities of *B. monnieri*, although it does seem to be a possible target (Hazra, 2017) [82].

In a double blind, placebo controlled trial of 38 healthy volunteers (age 18-60 years), a single dose of 300 mg of *Bacopa monnieri* extract (containing 55% combined bacosides A and B) did not cause any significant change in cognitive function at two hours (Nathan *et al*., 2001) [83]. However, bacopa administration (300 mg for subjects under 90 kg and 450 mg for subjects over 90 kg, equivalent to 6 g and 9 g dried rhizome, respectively, for six weeks) in a double blind, randomized, placebo controlled trial, showed significant improvement in retention of new information in 40 to 65 years old healthy adults (Roodenrys *et al*., 2002) [84].

Stough *et al*. (2001) [83] reported significant improvement in verbal learning, memory consolidation and faster information processing following BM administration (containing 55% combined bacosides) for 12 weeks at a dose of 300 mg daily in a double blind, placebo controlled study in healthy volunteers (age 18-60 years, n = 46; Stough *et al*., 2001) [83]. Because the effects were not observed until after five weeks of treatment, delayed onset of action may be attributed to bacopa's antioxidant properties and/or its effect on the cholinergic and other systems (Stough *et al*., 2013) [86]. In another randomized, double blind, placebo controlled trial of 54 elderly participants over 70 years of age without clinical signs of dementia, bacopa treatment enhanced auditory verbal learning test results and delayed word recall memory scores relative to placebo (Calabrese *et al*., 2008) [87]. In subjects over 55 years of age with memory impairment, a standardized 125 mg of bacopa extract was given twice daily for 12 weeks in a double blind, placebo controlled manner. There was a significant progressive improvement in mental ability, memory and associated learning during the 12 weeks of therapy (Raghav *et al*., 2006) [88]. A recent meta-analysis suggested that *Bacopa monnieri* has the potential to improve cognition (Kongkeaw *et al*., 2013) [89].

Bacopa monnieri showed the anti-Parkinson activity in many experimental models of Parkinson's Disease (PD). Standardized extract of bacopa protected rat dopaminergic cell lines against paraquat/diquat and 1-methyl-4-phenyl-pyridinium iodide (MPP (+)) induced toxicity by scavenging free radicals, preserving mitochondrial activity and restoring tyrosine hydroxylase levels (Singh *et al*., 2012, 2013) [37, 91]. The alcoholic extract of bacopa treatment for three weeks showed a neuroprotective effect in the 6-OHDA rat model of parkinsonism (Shobana *et al*., 2012) [92]. In another study, bacopa decreased α-synuclein aggregation, ameliorated dopaminergic neurodegeneration and restored the lipid content, exerting anti-parkinsonian effects in a transgenic *Caenorhabditis elegans* model (Jadiya *et al*., 2011) [93]. The neuroprotective effect of bacopa has also been demonstrated against paraquat and rotenone induced oxidative stress, neurotoxicity and lethality in *Drosophila melanogaster*

(Hosamani and Muralidhara, 2009, 2010) [94, 95]. In an animal model of cerebral ischemia, aqueous extract of bacopa attenuated the ischemia reperfusion induced brain injury (Rehni *et al*., 2007) [96]. In another study, pretreatment with bacopa improved cognitive function and ameliorated cerebral injury in the transient in tracarotid artery occlusion rat model of stroke through its antioxidant actions (Saraf *et al*. 2010) [97, 98].

The following authors have also shown that bacopa reversed scopolamine induced amnesia via modulation of protein kinase C (PKC) and phosphorylated cAMP response element binding protein (pCREB) (Saraf *et al*., 2010) [97, 98] and improved scopolamine induced impairment in spatial memory in mice (Saraf *et al*., 2011) [99]. Bacopa and its constituents (bacosides) prevented behavioral impairment and GABA receptor dysfunction in epileptic rats (Mathew *et al*., 2010) [100].

Saga *et al*. (2020) concluded that BM significantly reduced the mitochondrial apoptosis induced by Benzo[a]pyrene (B[a]P); ROS, especially those released from mitochondria, play an important role in inducing apoptosis (Hekimi *et al*., 2016; Kim *et al*., 2017) [102, 103]. Therefore, the status of mitochondrial reactive oxygen species (ROS) generation was analyzed with B[a]P in the presence of BM. The MitoSOX staining data showed that BM reduced the levels of mitochondrial ROS in B[a]P treated cells to prevent mitochondrial dysfunction. All these data suggest that BM effectively fulfills a cytoprotective role against B[a]P mediated apoptosis in immortalized primary fetal astrocytes (IMPHFA).

Conclusion

This review article hasten the rising scientific substantiation on cognitive and neuropharmacological enhancement effects of *Bacopa monnieri* in humans. Numerous research studies indicated the natural compounds from *Bacopa monnieri* that serve as nootropic agents. Treatment with *B. monniera* significantly improved behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of cerebellum (Suruchi Chandra, 2013) [67]. The neuro psycho nutraceuticals producing companies have been endowed massive resources in the identification of natural nootropics, which could possibly alleviate debilitating disorders and slow the onset of mental retardation, though their full potential is yet to be determined and harnessed. The present review premeditated about the Natural nootropic *Bacopa monnieri* to alter the concentration of existing and to increase the activity of neurotransmitters induced by phytochemicals which improve synaptic transmission.

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