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Neuroprotective Potential of Bacopa monnieri: A Comprehensive Study

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Abstract
This study synthesizes behavioural 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 evidencing potential medicinal properties. 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. Current evidence suggests Bm acts via the following mechanisms—anti-oxidant neuroprotection (via redox and enzyme induction), acetyl cholinesterase inhibition and / or choline acetyltransferase activation, b-amyloid reduction, increased cerebral blood flow, and neurotransmitter modulation (acetylcholine [ACh], 5-hydroxytryptamine [5-HT], dopamine [DA]). Bm appears to exhibit low toxicity in model organisms and humans; however, long-term studies of toxicity in humans have yet to be conducted. This review will integrate molecular neuroscience with behavioural research.
Keywords: Bacopa monnieri, Dementia, Parkinson's disease, acetylcholinesterase, b-amyloid.

Introduction:

An estimated 3.4 million people are affected by dementia in the United States (Plassman et al. 2007) most prevalently in the elderly. The elderly population (aged over 65) is expected to double by 2030. reaching 72 million, or 20% of the total U.S. population (Federal Interagency Forum on Aging-Related Statistics, 2012). Bacopa monnieri (Bm) shows great clinical potential in attenuating dementia via several mechanisms, most notably dose-dependent acetylcholine potentiation and free radical scavenging. Alzheimer's disease (AD) is a chronic neurodegenerative disease of undetermined etiology, seen in the elderly albeit rarely before 60 years except when its inheritance is autosomal dominant (Ballard et.al., 2011; Ryman et al., 2014). Combined presence of amyloid beta (Aß) and tau (τ) stands out as the hallmark of progressive AD and the basis of most disease-modifying therapy (Scheltens et al., 2016; Akiyama,2016). Initial stage of disease is characterized by the impairment of recent memory which is followed by impairment of cognitive abilities, vocabulary, and concepts (Markowitsch &S taniloiu, 2012). Early impairment of recent memory is due to involvement of median temporal lobe and hippocampus which controls recent memory (Scoville & Milner ,1957). Subsequently, involvement of other areas of brain may manifest as sleep disturbances, problems in judgment, psychological changes, pyramidal and extrapyramidal motor signs (Alzheimer's Association, 2010). According to World Alzheimer's Report 2015, global prevalence of dementia rose from 30 million (2010) to 46.8 million and global expenditure on dementia rose from US$ 604 million (2010) to US$ 818 million (2015). In India, the prevalence of dementia was 33.6 in every 1,000 people of which 54% were cases of AD (World Alzheimer Report 2015).

Currently, the effects of aging on cognitive function have become a prominent area of research. It is well established that aging is associated with a gradual impairment of cognitive function (Nandy, 1997). Age-related cognitive ability decline varies considerably across individuals and across cognitive domains. Various cognitive domains show different susceptible to aging. The basic cognitive functions most affected by age are speed of processing, memory, spatial ability, and reasoning (Hughes, 2010). Since the cognitive function is a key success factor in life, the strategy to sustain or prolong this function is one of the ultimate goals in care for the elderly. Therefore, the development of cognitive enhancers has been focused on in research.

Due to the lack of effective disease-modifying treatments, findings on pharmacological or nonpharmacological strategies to slow disease progression are of significant importance. In addition, the failure of potential pharmaceuticals in human clinical trials has highlighted the need for research into early diagnosis. The lack of effective treatments and pharmaceuticals has led to the assessment of alternative therapeutics, such as nutraceuticals. For example, many antioxidants may enhance cognitive ability (Calabrese et al., 2003; Emilien et al., 2000; Kontush & Schekatolina, 2004). Nutraceuticals have an effect on various neurodegenerative diseases as they modulate signaling pathways (Maity et al., 2019). Nutraceuticals are nutrients, herbals, and dietary supplements that can help in maintaining physical wellbeing, work against

various diseases, and ensure a better quality of life. Bacosides from Bacopa- monnieri (B monnieri) are examples of valuable therapeutic agent for neurological diseases (ND) due to their anti-inflammatory, antioxidant, and Aß This review presents current clinical studies and scientific evidences that document the therapeutic potential of B monnieri extracts (BME) such as bacosides in ND.

Bacopa monnieri (L.)

Bacopa monnieri (L.) (Bm) is an important medicinal plant in Indian traditional Ayurvedic medicines. It is a small perennial herbaceous plant commonly known as 'Brahmi', belonging to the family Scrophulariaceae. It is a renowned Indian medicinal plant that has been used as a memory booster in the Ayurvedic medicinal system for more than 3000 years (Gohil & Patel, 2010)

Traditional Aspects of Bm

Traditional Aspects of Bm According to World Health Organization, traditional medicine is defined as "the sum total of knowledge, skills and practices based on the theories, beliefs and experiences of different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses."(World Health Organization,2008) Many population in the developing countries have reverted to the use of traditional plants in maintaining their health and wellbeing (Robinson& Zhang, 2011). In this age where migration has taken a leap, immigrants tend to bring traditional plants from their country of origin to use as supplements. This has caused the promotion. These plants or plant compounds are known as complementary or alternative medicines in non-native countries. Notably, B monnieri, otherwise known as Brahmi and Aindri (Sanskrit) is classified into the Scrophulariaceae family and found throughout the Indian subcontinent in moist soil, humid, and muddy environments (Satyavati et al.., 1976) The genus Bacopa has 146 aquatic herbal species dispersed throughout the subtropical regions of the globe, including Nepal, India, Sri Lanka, Taiwan, China, and Vietnam, as well as Florida and other US southern regions. Although it can be seen in the United States, these plants are perceived as weeds in rice fields and abundantly grown in wetlands and marshes of warmer districts (Barrett& Strother, 1978). Brahmi is a succulent herb commonly grown in subtropical nations up to 1500m altitude. Brahmi, which is traditionally known as "medhyarasayana," which means brain tonic or nootropic, or in Sanskrit word, referring to intellectual, cognition, and rejuvenation because it enhances the brain's cognitive properties, is popular among Ayurveda practitioners, who use it to treat various ailments.

Bm Bioactive constituents

The main nootropic constituents of Bm are believed to be dammarane types of triterpenoids saponins known as bacosides, with jujubogenin or pseudo-jujubogenin moieties as aglycone units (Sivaramakrishna et al., 2005). Bacosides comprise a family of 12 known analogs (Garai et al., 2009). Novel saponins called bacopasides I–XII have been identified more recently (Chakravarty et al., 2001; Chakravarty et al., 2003). The alkaloids brahmine, nicotine, and herpestine have been catalogued, along with D-mannitol, apigenin, hersaponin, monniera sides I–III, cucurbitacins and plant ainoside B (Chatterji et al., 1965; Chakravarty et al., 2008; Kawai&Shibata, 1978; Bhandari et al., 2007; Phrompittayarat et al., 2007; Deepak et al., 2005, Kregel& Zhang 2007; Valko et al., 2007). The constituent most studied has been bacoside A, which was found to be a blend of bacoside A3, bacopacide II, bacopasaponin C, and a jujubogenin isomer of bacosaponin C (Deepak et al., 2005). These assays have been conducted using whole plant extract, and bacoside concentrations may vary depending upon the part from which they are extracted. In one BM sample, Rastogi et al. found this bacoside profile—bacopaside I (5.37%), bacoside A3 (5.59%), bacopaside II (6.9%), bacopasaponin C isomer (7.08%), and bacopasaponin C (4.18%).66 The complete assay of BM is an ongoing effort.

Bm pharmacological activities

It is used in traditional medicine to treat various nervous disorders, digestive aid, improve learning, memory, and concentration and to provide relief to patients with anxiety, and skin disorders; specific uses include the treatment of asthma, insanity and epilepsy (Jyoti & Sharma,2006; Calabrese et al., 2008; Kamkaew et al., 2013). The Bacopa herb, also called nootropic herb, helps in the repair of damaged neurons, neuronal synthesis, and the restoration of synaptic activity, and improves brain function. Bm contains alkaloid brahmine, nicotinine, herpestine, bacosides A and B, saponins A, B and C, triterpenoid saponins, stigmastanol, ß-sitosterol, betulinic acid, D-mannitol, stigmasterol, α-alanine, aspartic acid, glutamic acid, and serine and pseudo jujubogenin glycoside (Devishree et al., 2017). The plant possesses a wide variety of pharmacologically active principles including memory enhancing, tranquillizing, sedative, antidepressant, antioxidant, cognitive, anticancer, antianxiety, adaptogenic, antiepileptic, gastrointestinal effects, endocrine, gastrointestinal, smooth muscle relaxant effects, cardiovascular, analgesic, antipyretic, antidiabetic, antiarthritic, anticancer, antihypertensive, antimicrobial, antilipidemia, anti-inflammatory, neuroprotective, and hepatoprotective activities (Russo& Borrelli, 2005; Sinha &Saxena, 2006; Ramasamy et al., 2015).

In a 90-day oral administration trial in rats, Bm exhibited a no-observed adverse effect level (NOAEL) of 500 mg/kg and a median lethal dose (LD50) of 2400 mg/kg (Tripathi et al., 1996). The standard experimental human dose is between 150 and 3000 mg equivalent per day. The most common clinical side effect of Bm is mild gastrointestinal upset, but long-term clinical trials are lacking. Several research groups formulate bacoside standardized Bm extract for clinical use, and the herb is widely used in India, the United States, and Australia. Bm has been applied in rodents and cell culture for the following uses, which will not be detailed in this review: anti-convulsant (Mathew et al., 2011; Mathew et al., 2010) anti-depressant (Sairam et al., 2002) analgesic (Abbas et al., 2011; Afjalus et al., 2012) anti-ulcerogenic(Sairam et al., 2001)anti-H. pylori (Goel et al., 2003) anxiolytic (Bhattacharya& Ghosal, 1998),adaptogenic(Bhatia et al., 2003), anti-neoplastic (Deb et al., 2008) hepatoprotective (Ghosh et al., 2007) immunostimulatory (Yamada et al., 2011).

Neuropharmacological Activity

Bm has been studied extensively in animal models and in vitro. While Bm is implicated in the treatment of anxiety, epilepsy, and other neurodegenerative disorders, this review will concentrate on cognition, learning, and memory. The clinical studies cited focus on memory, omitting other facets of cognition like fluid intelligence or creativity. Past clinical studies were not longitudinal, typically lasting only 12 weeks. The long-term effect of Bm on humans is unknown, but animal models suggest considerable protection against age-related neurodegeneration rather than progressive toxicity or tolerance formation. Putative mechanisms of action.

Neuroprotection by Antioxidant activity:

Acetylcholinesterase inhibition, choline acetyltransferase activation, b-amyloid reduction, increased cerebral blood flow, and monoamine potentiation and modulation. Anti-oxidant/neuroprotection. Oxidative stress (OS) occurs when free radicals (chemical species with unpaired electrons, produced during normal metabolism) overcome the cell's homeostatic defense mechanisms (Kregel& Zhang, 2007) Protective, free radical–quenching enzymes include superoxide dismutase, catalase, glutathione peroxidase (GPx), glutathione reductase (GSR), and others. Anti-oxidant compounds also play a key protective role, including vitamins A, C, E, and myriad phytonutrients (particularly phenols) (Valko et al., 2007). OS plays a role in many diseases, even aging itself (De Grey,1999), by degrading ligands, peroxidizing lipids, disrupting metabolic pathways, denaturing proteins, and breaking DNA strands (Maxwell, 1995). The brain is especially susceptible to OS because it is metabolically active, possesses high levels of pro-oxidant iron, and is composed of unsaturated lipids (prone to lipid peroxidation) (Arivazhagan et al., 2002). Furthermore, the blood–brain barrier prevents many exogenous anti-oxidants from quenching reactive oxygen species (ROS) in the brain (Gilgun-Sherki et al., 2001), Anbarasi et al. (2006) assessed the neuroprotective role of bacoside A against 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, GPx, 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.

In a comprehensive study, Rastogi et al. (2012) 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). 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 behavioural effect was modelled using the tail-suspension depression test,

showing an antidepressant effect in accordance with past research (Sairam et al., 2002) This study demonstrated the efficacy of Bm in preventing lipofuscin accumulation and enhancing acetylcholine synthesis, monoamine modulation, and inhibition of lipid peroxidation.

Cerebral blood flow and vasodilation:

Adequate perfusion of blood to capillary beds within the brain is of highest importance. Otherwise, deficits of oxygen and nutrients will ensue alongside the build-up of cytotoxic waste. Diminished cerebral blood flow is implicated in various pathologies, including dementia (de la Torre, 2012). Kamkaew et al. (2013) compared the effect of daily oral Bm (40 mg/kg oral) and Gingko biloba (60 mg/kg oral) on cerebral blood flow (CBF) in rats. Rats treated with Bacopa monnieri saw a significant 25% increase in CBF, although Gingko biloba increased CBF by 29% (albeit at a 20-mg higher dosage) in their 8-week trial. Chronic oral Bm administration had no effect on blood pressure, whereas intravenous infusion decreased diastolic blood pressure 31 mmHg with 40 mg/kg of ether extract, correspondingly decreasing CBF by 15%. Bm appears to act as a vasodilator by releasing NO from the endothelium and inhibiting calcium fluctuations in and out of the sarcoplasmic reticulum (Kamkaew et al., 2011).

Neurotransmitter potentiation

Adaptogens enable the body to better cope with the deleterious mental and physical consequences of stress. Rhodiola rosea, and Panax ginseng are classic adaptogens. Others include Ocimum sanctum (Sweet Holy Basil or Tulsi), Withania somnifera (Ashwaghanda), Astragalus propinquus, Ganoderma lucidum (Reishi mushroom), and many others (Winston & Maimes, 2007) Bm also exhibits adaptogenic qualities. One putative action of the adaptogen is modulation of neurotransmitter production, release, and synaptic concentration. Sheikh et al. (2007) evaluated Bm's adaptogenic effect in acute stress and chronic unpredictable stress-induced fluctuations of plasma corticosterone and monoamines in the rat cortex and hippocampus. Panax quinquefolium (PQ) was used as a positive control. Immobilization stress resulted in significant elevation of plasma corticosterone levels, which was significantly reduced by Bm at oral doses of 40 and 80 mg/kg, comparable to oral PQ at 100 mg/kg. Treatment with Bm attenuated stress-induced changes in levels of 5-HT and DA in the cortex and hippocampus but was ineffective in normalizing noradrenaline (NA) levels in the acute stress model, whereas PQ treatment significantly attenuated all assayed neurochemical effects of acute stress. In the chronic stress model, pre-treatment with BM and PQ significantly elevated levels of NA, DA, and 5-HT in the cortex and NA and 5-HT in the hippocampus compared to controls. Prevention of NT depletion is the cornerstone of adaptogenic stamina enhancement, both physical and mental. Charles et al. (2011) found Bm extract up-regulated tryptophan hydroxylase (TPH2) and serotonin transporter (SERT) expression in rats.

Dementia and cognitive dysfunction:

Dementia is a global loss of cognitive ability. Aging is a major risk factor for dementia, which includes various types, such as vascular dementia, frontotemporal degenerative dementia, Lewy body dementia, and Alzheimer disease. Dementia results secondarily from many neurodegenerative disorders. The exact etiology of Alzheimer dementia is uncertain and controversial, but there is a general consensus about some of the factors that may be involved. Free radical-induced OS is one such.Factor (Munch, et al., 2002) It is unclear whether OS is primary to the disease process or a secondary by-product, but the presence of OS does appear to play a major role in illness severity (Reddy, 2007) Cell loss, impaired energy metabolism, dystrophic neurites, DNA damage, b-amyloid plaques, and neurofibrillary tangles are also thought to play key roles (Shankar et al., 2008) Researchers have also put forward the hypothesis that Alzheimer disease is at least partially mediated by insulin resistance, leading some to brand the condition "type 3 diabetes."(de la Monte& Wands,2008) Deficits in ACh are also often seen in dementia patients, and the dominant therapeutic agents are AChE inhibitors (Francis et al., 1999) Despite some controversy, cigarette smoking appears to increase dementia risk (Rusanen et al., 2011) Despite containing nicotine itself, Bm protects against nicotine-induced lipid peroxidation and mutagenicity in mice. Aqueous Bm extract (50 mg/kg i.p.) restored anti-oxidant enzymes SOD, CAT, and GPx in the liver. Bm treatment also significantly decreased the incidence of micro-nucleated polychromatic erythrocytes (micro-nucleation is a product of chromosome damage). Hepatic glutathione, alkaline phosphatase, and glutathione-S-transferase levels were brought to normal values, indicating hepatic protection (Vijayan &Helen 2007).

Scopolamine (SC) is a powerful muscarinic ACh antagonist that impairs long-term potentiation (LTP) and memory (Ovsepian, 2004) Saraf et al. (2001) found that Bm extract (120 mg/kg oral, 55.35% bacosides) effectively reversed SC-induced anterograde and retrograde amnesia (Morris water maze) in mice. Another group of researchers isolated specific triperpenoid saponins from Bm and evaluated their reversal of SC-induced amnesia in mice, finding potential in bacopaside I and XI and bacopasaponin C (Zhou, et al., 2009).

Learning and memory

Bm may have a potential application to enhancing cognition in healthy subjects. Singh and Dhawan (1987) administered rats an ethanolic whole plant Bm extract (40 mg/kg orally) for

3 or more days and evaluated cognitive performance using shock-motivated brightness discrimination reaction, active conditioned flight reaction, and continuous avoidance response tests. The Bm-treated group showed significantly better acquisition, improved retention, delayed extinction, and faster reaction times than controls. Vollalaet al.(2011) studied the effect of Bm on the dendritic morphology of neurons in the basolateral amygdala, a region implicated in learning and memory. In another study, Vollala et al. (2010) found highly significant improvement in learning and memory in rats administered. Rajan et al. (2011) investigated the effect of Bm on serotonergic receptor 5-HT3A expression as well as ACh and 5-HT levels during a hippocampal-dependent learning task.

The anticonvulsant phenytoin adversely affects cognitive function. Vohora et al. (2000) combined Bm with phenytoin on passive-avoidance, maximal electroshock seizures and locomotor activity in mice. Phenytoin (25 mg/kg p.o. for 14 days) adversely affected cognitive function in the passive avoidance task. Bm extract (40 mg/kg p.o. for 7 days) significantly reversed phenytoin-induced memory impairment. Both memory acquisition and retention showed improvement without affecting phenytoin's anti-convulsant activity, supporting Bm use as an adjuvant for epileptics and possibly a nootropic for non-epileptics. Prisila et al. (2012) found that 80 mg/kg p.o. Bm extract (55% – 5% bacosides) protects against D-galactose (D-gal)-induced brain aging in rats in a contextual-associative learning task. Bm-treated individuals showed highly significantly more correct responses and less latency than control and D-gal–treated rats.

Conclusion

Bm demonstrates immense potential in the amelioration of cognitive disorders, as well as prophylactic reduction of oxidative damage, NT modulation, and cognitive enhancement in healthy people. Biomedical research on Bm is still in its infancy, but preliminary results such as these have begun to open the research floodgates. It is critical that much longer-term studies be conducted Bm in combination with other substances, as is prescribed by the Ayurvedic system, may result in synergistic effects and should also be investigated. The social implications of cognition-enhancing drugs are promising but must be appropriately tempered with ethical consideration as researchers enter the brave new world of neural enhancement.

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