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Research Article

Bacopa monnieri Extract as Augmentation Therapy to Enhance Memory, Learning, and Cognitive Function

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Abstract

Cognitive ability is the most crucial modifiable and effective aspect of the quality of life for the elderly population. The aging process affects processing speed, and substantial interindividual differences distinguish a person's cognitive ability. Based on existing knowledge, aging and cognitive decline are clearly not inevitable. Traditional expertise suggests that Bacopa monnieri (*B monnieri*) (BM), a neural tonic in Ayurvedic medicine, enhances mental performance, intelligence, and memory. Therefore, this review article focuses on BM's investigation into manageable medical comorbidities affecting cognitive function. This review is based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. *B monnieri* improves dementia, learning, and memory by reducing inflammation and oxidative stress levels, and could also enhance spatial and working memory impairment. *B monnieri* is suggested as an augmentation therapy for memory enhancement, which helps to improve attention, neural networks, long-term potentiation, and language function in daily tasks such as driving, navigating, climbing stairs, remembering numbers, and so on.

INTRODUCTION

Aging is associated with declines in the brain's ability to scavenge free radicals and produce antioxidants, which leads to a reduction in cognitive function, including attention, language skills, neuronal networks, and a decrease in synapse number, long-term potentiation (LTP), and impairments in working and spatial memory [1,2]. Deterioration of memory and learning performance, which includes processing speed and executive function, worsens with age, particularly in 50% of adults aged 64 and older. Additionally, the rate of decline varies among individuals and is linked to medical history and lifestyle factors (particularly dietary intake, immobilization, smoking, etc.). The evidence showed the imbalance between brain Aβ production and the clearance of these proteins. Additionally, the presence of neurofibrillary tangles is the most critical reason for brain aging and dementia. The aging process causes several changes in the brain, including enlargement of the ventricles, hyperintensities of white matter, reduction of gross brain volume, and decreases in frontal and temporoparietal volume. Furthermore, increased brain cortical atrophy has been demonstrated through neuroimaging studies. Cortical volume shrinkage is one of the most significant reasons for impairments in cognitive function, consequently reducing an individual's cognitive ability. Other factors contributing to memory decline include alterations in prefrontal cortex (PFC) activation and bilateral activation of this region in younger individuals [3-11]. Learning and memory are fundamental mental processes, and the brain (CNS and PNS) is responsible for these processes, referred to as "Mind," which encompasses thinking, feeling, wanting, perceiving, learning and memory, curiosity, wisdom, and is all manifested in an individual's behavior. Therefore, it is crucial in neuroscience studies. By addressing sources of individual behavioral experiences, these processes can change and facilitate learning to acquire memory. Experiences of individual behavior that affect memory include declarative/spatial memory (conscious awareness linked to events and factual information) and procedural/working memory (another form of memory derived from past experiences related to learned skills, enhanced through practice and training, such as playing tennis and rugby). The hippocampus and cerebrum are the most important declarative and procedural memory brain

areas. The hippocampus plays a crucial role in executive function, processing speed, intelligence, spatial processing, and path integration. Although the synapse, where nerve cells communicate, is a popular candidate site for memory storage. Additionally, altered transmission efficacy of synapses (referred to as synaptic plasticity) has been considered in memory studies [12,13]. *Bacopa monnieri* (BM) is a member of the family Scrophulariaceae and is commonly used as a nootropic for treating insanity, epilepsy, memory and learning impairments [14], anxiety, necrosis, cognitive dysfunctions, and promoting longevity. Also, it possesses antioxidant and neuroprotective properties [15], as well as anti-inflammatory, analgesic, antipyretic, antidepressant, antidepressant, antiulcerogenic agent, calcium antagonist, and antipyretic activities [16,17]. *B. monnieri* boosts protein kinase activity in the hippocampus, resulting in a nootropic effect. Research indicated that *B. monnieri* extract reduced cholinergic degeneration and exhibited cognition-enhancing effects in an animal model of Alzheimer's disease [18]. Also, *B. monnieri* prevented AChE activity, increased ACh levels, and protected neuronal cells from β-amyloid damage [19]. Furthermore, consuming *B. monnieri* extract lowered ROS levels and oxidative stress [20]. A clinical trial demonstrated that taking *B. monnieri* extract reduced oxidative stress and inflammation, leading to improved cognitive functions in Alzheimer's disease patients [21,22].

MATERIALS AND METHODS

This study was based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. Additionally, keywords used during the search include: "*Bacopa Monnieri*", "Cognitive function", "*B. monnieri* and Learning", "*B. monnieri* and cognitive A3, bacopaside II, bacopaside X, and bacopasaponin C), flavonoids (such as apigenin and luteonin), and additional phytochemicals (such as oroxindin, betulinic acid, betulic acid, wogonin, stigmastarol, beta-sitosterol) and amino acids (like alpha alanine, function", "*B. monnieri* and Alzheimer Disease".

RESULTS

Properties of Bacopa Monnieri

Active component: The primary chemical constituents of BM include alkaloids (like brahmine, herpestine, and hydrocotyline), glycosides (such as phenylethanoid, thanakunicide, and asiaticoside), triterpenoid saponins (including D-mannitol, Acid A, bacosides A, aspartic acid, glutamic acid, and serine), fatty acids, and tannins [23, 14,24]. BM's primary active chemical components are steroidal saponins and bacosides A and B, which are responsible for improving memory and learning [25]. Other components of BM include bacopasaponins D, E, and F, as well as alkaloids, phytosterols, and flavonoids [26]. It should be noted that BM extract is lipophilic and can dissolve in lipids, allowing it to cross the blood-brain barrier [27]. Bacosides improve kinase activity, restoring synaptic activity and nerve impulse transmission. Several mechanisms have been suggested for the neuroprotective and memory-boosting effects of BM, including free radical scavenging, increased antioxidant activity, and binding and detoxification of metal ions. Additionally, animal studies demonstrated another ability of BM, including antioxidant, adaptogenic, vasorelaxant, anti-inflammatory, metal ion chelating, cholinergic modulatory effects, and neuroprotective effects (like insomnia, epilepsy, amnesia, and memory deficits) [18]. One of the active components of BM is Bacosides, which have antioxidant and neuroprotective functions. Studies show that the triterpenoid saponins and Bacosides A and B, known as the "memory chemicals," enhance impulse transmission between neurons. Additionally, bacosides A1–A3, bacopasaponins A–G, and bacopasides I–V are reported in alcoholic BM extract [28]. Bacosides can regenerate the damaged neurons' repair ability, helping learn and remember new information. BM causes an increase in brain serotonin (a neurotransmitter promoting relaxation) secretion [28]. Studies show that bacoside decreases colchicine-induced cognitive deficits (intracerebroventricularly; icv) [29]. Other studies also indicate that administering bacosides significantly improves memory and learning *in vivo* [30]. The mechanisms of action relate to their effects on the CNS (central nervous system), scavenging of β-amyloid, and modulation of cholinergic densities and acetylcholine levels [31]. One study showed that the administration of bacoside A (10 mg/kg) improved the activities of ATPases (adenosine triphosphatases), inhibited lipid peroxidation, and maintained ionic equilibrium in the brains of rats exposed to cigarette smoke [32]. BM has medicinal properties related to the presence of triterpenoid saponins known as bacosides. Bacoside A, mainly responsible for the memory-boosting action of BM, is recognized as 3-(α-L-arabinopyranosyl)-O-β-D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene [33].

Mechanism of Action

The exact mechanism of action of BM has not yet been determined. Evidence suggests that BM possesses therapeutic potential for neurological disorders (such as enhanced cognition, learning, and memory) related to its ability to decrease NO-induced cellular adaptations [34], and enhance kinase activity, nerve impulse transmission,

neuronal synthesis, antioxidant activity, modulation of cholinergic neuron densities, β-amyloid scavenging properties, and modulation of frontocortical and hippocampal acetylcholine levels. also, BM has properties that protect against DNA damage in human fibroblasts and astrocytes [34]. BM extract has a rich source of saponin that increases several enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities in different brain areas such as the frontal cortex, striatum, and hippocampus of rats in a dose-dependent manner [35]. The effect of BM is related to age-associated cognitive decline in the elderly, and it's beneficial for certain types of dementia [36]. One study indicates that methanol fractions of the BM leaves (100 mg/kg) significantly reduced inflammation compared to the standard anti-inflammatory drug (aspirin). Additionally, the methanol fraction and the aqueous extract of *Bacopa monnieri* exhibit antimicrobial, antioxidant, and anti-inflammatory properties in rats [37]. Bacoside administration diminished the up-regulation of iNOS in the aged rat brain [38]. Moreover, neuroinflammation contributes to Aβ concentrations in AD brains [39]. Research studies showed BM causes signaling molecules, increasing those involved in synapse formation and maintenance [40], including raising the level of protein-kinase activity, neurotrophins, and phosphorylated CREB. These molecules contribute to synaptic plasticity by increasing the concentration of post-synaptic receptors, forming new dendritic spines, and regulating synapse proliferation and apoptosis through gene transcription [41]. Human studies showed that BM causes cognitive improvements, including enhanced immediate and delayed memory recall, processing speed, and sustained attention [42,43]. The study indicated that BM administration improved the level of wisdom and reminiscence in a scopolamine-induced memory deficit mouse model [44]. Another study found that BM extract administration (300 mg twice daily orally for 6 months) enhanced cognitive functions in geriatric patients with Alzheimer's disease [45].

Previous research

Clinical trials: A randomized, double-blind, placebo-controlled trial investigated 54 older participants without clinical signs of dementia who consumed 300 mg/day of BM tablet orally for 12 weeks. After that, participants were assessed using tests such as the delayed recall score from the Rey Auditory Verbal Learning Test (AVLT), the Stroop Task evaluate the ability to ignore irrelevant information, the Divided Attention Task (DAT), and the Wechsler Adult Intelligence Scale (WAIS) letter-digit test of immediate working memory. The results showed that BM has the ability to enhance cognitive performance in aging men [46], safely. The randomized, double-blind, placebo-controlled trial assessed cognitive tasks, life satisfaction, memory complaints, and mood after consuming BM combined with cognitive training (CT) for 3 hours weekly over 12 weeks in older men (aged 55 and above). Therefore, the neuroimaging outcomes improved the complexity of neuronal networks in older adults after BM supplementation and CT [47]. A randomized, double-blind study assessing changes in cognitive function in Indian school children receiving a combination of BM and micronutrient supplementation versus placebo. The spatial working memory "strategy" score significantly improved after 60 days [48]. One clinical study investigated the cognitive effects of a dietary supplement made from extracts of *Bacopa monnieri*, astaxanthin, phosphatidylserine, and vitamin E in subjects with mild cognitive impairment, through assessment of the Scale-Cognitive Subscale (ADAS-cog) test and the clock drawing test. The tests showed improvement in cognitive impairment among subjects with mild cognitive impairment [49]. A randomized controlled trial investigating the effects of a special extract of BM on hyperactivity and inattention in male children and adolescents measured with the Conners' Parent Rating Scale (CPRS) after 16 weeks. Additionally, cognition, mood, sleep, and EEG were assessed. The results demonstrated improvement in inattention, hyperactivity, and impulsivity symptoms in clinical and/or subclinical populations of children and adolescents [50]. A clinical study investigated the efficacy of Cognition Support Formula (the combination effect of BM, Ginkgo biloba, Panax ginseng, and alpha-lipoic acid) on cognition in older adults with cognitive impairment (CI) over 6 months through various tests, including cognitive (using CogState®), mood (using the Depression, Anxiety, Stress Scale (DASS-42) and Short Health Anxiety Inventory (SHAI)), and fatigue (using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)) tasks [51]. A randomized placebo-controlled trial investigated the efficacy of a standardized extract of BM on cognitive functions in medical students over 15 days. The results showed that BM administration improved cognitive functions and significantly increased serum calcium levels [52].

Animal study: Studies of the effect of BM in neuroscience studies are detailed in Table 1.

DISCUSSION

The most important aspect of longevity is needed to reveal many aspects of aging in individuals, while also addressing the rapidly growing aging population. Additionally, the challenges an aging population faces

Table 1: The effect of BM on improving neurological disease.

Subject	Title aim	Dosage of Brahmi/day	Duration	Results
Male adult Wistar rats [53]	epilepsy	180 mg/kg, oral	one week	*Bacopa monnieri* exhibited anti-seizure activity in the PTZ model and increased the seizure threshold in the experimental model of generalized tonic-clonic seizures.
Cultures [54]	memory	8.9 μM BA	14 days	Increase the 90% survival rate.
In Vitro and In Vivo [55]	Neuromodulatory	5 mg/kg BM	10 days	The antioxidative property of BM may be partly responsible for its neuroprotective action.
Mice [56]	Cognitive Deficits	50 mg/kg BM	15–30 days	BME ameliorates TMT-induced cognitive dysfunction mainly via protecting the hippocampal neurons.
Rat [57]	Alzheimer's disease	100 mg/kg, oral	15 days	a potential natural source of bioactive compounds, and maybe beneficial in treating Alzheimer's disease.
Mice [58]	anhedonia	50–200 mg /kg BM	one week	*B. monnieri* extract may be effective for the management of anhedonia.
Rat [59]	The brain and kidneys of diabetic rats	50, 125, and 250mg/kg BM	15 days	*B. monnieri* modulates antioxidant activity and enhances the defense against ROS-generated damage in diabetic rats.
Rats [60]	neuronal dysfunction	BA: 100, 200, and 400 mg/kg and Bacosine (BS: 5 and 10 mg/kg)	30 days	Improves the neuronal dysfunction in Streptozotocin-induced diabetic neuropathy.
Patient [61]	Alzheimer's Disease	300 mg/kg, oral	twice a day for 6 months	improvement in some aspects of cognitive functions in Alzheimer's disease patients.
Mice [62]	Parkinson's disease	48 mg/kg	2 weeks	Novel treatment strategy for PD treatment; significantly increased spontaneous locomotor activity.
Rats [63]	dementia	50 mg/kg	15 days	Prevents colchicine-induced dementia by an anti-inflammatory action.
Rats [64]	Memory Loss and Learning Deficit	100, 200 mg/kg BM, 5 mg/kg Rivastigmine	42 days	significantly improved Memory and learning in AlCl3 (100 mg/kg p.o.) for induction learning deficits and amnesia in animals.
Rats [65]	dendritic arborization of the hippocampal	20, 40, and 80 mg/kg BM	two weeks	did not show any significant change in hippocampal CA3 neuronal dendritic arborization
Rat [66]	learning and memory	BM, Brahmi Ghrita (BG) Acorus calamus L., Convolvulus pluricaulis Choisy, Saussurea lappa DC.	One week	Brahmi Ghrita enhances learning and memory analogously to the standard drug (piracetam) in normal rats.
Mice [67]	Spatial Memory	120 mg/ kg BM containing 55.35% bacosides	One week	*Bacopa monniera* Attenuates Scopolamine-Induced Impairment of Spatial Memory in Mice.
Rats [68]	Memory Dysfunction	40 -80 mg/kg BM and 20mg/kg Melatonin	Continued daily up to the day 13	*Bacopa monniera* Attenuates Okadaic Acid-Induced Memory Dysfunction in Rats.
Mice [69]	Amnesic Mice	120mg/kg BM, CDRI-08 extract	One week	Expression of Neuronal and Glial Plasticity Markers in the Brain of Scopolamine-Induced Amnesic Mice.
Mice [70]	Neuromodulatory	40, 80 or 120 mg/kg	from postnatal day (PND) 3-10	Restore the activities of antioxidant enzymes in the frontal cortex and the hippocampus.
Wistar Rats [71]	Cold Stress	40 mg/kg	one month	Results indicate that when BM extracts are administered orally, they produce a neuroprotective effect in cold stress-induced hippocampal neurodegeneration of rats.
Zebrafish [72]	Parkinsonism	6×10^{-4} M BM Stabilized Platinum Nanoparticles		Improve mitochondrial complex I and antioxidant activity.

related to cognitive decline may affect the quality of life and mortality rate [73,74]. There are two types of strategies for spontaneous memory performance: internal (e.g., rehearsal, visual imagery) and external (e.g., using a calendar, taking notes). Older mature individuals proportionately use more external strategies than younger mature individuals. Additionally, cognitive reserve (CR) is believed to reduce the relationship between cognitive decline and brain changes by fostering compensatory cognitive processes. also, studies show that high CR individuals exploit additional brain regions associated with better memory task performance [75-77]. Cognitive vigor or power during the elderly period of life is weakened by either "normal cognitive aging" or neurodegenerative diseases that lead to dementia, primarily the progression of Alzheimer's disease (AD) and vascular dementia. These unavoidable phenomena also affect cognitive vitality, which can be modifiable or managed daily [78,79]. Research indicates that stimulating agents, including environment, estrogen, aerobic exercise (running), and herbal drug consumption, promote neurogenesis in the neocortex of rats, mice, and adult primates [80-83]. One aspect of cognitive function impairment that results from the aging process is executive function – the cognitive processes principally associated with the brain's prefrontal cortex, which instructs purposeful, goal-directed behavior. These functions include interference control, planning, shifting, updating, inhibition, dual-task coordination, and

working memory; all of these are routine and substantial performance measures, applied to both fundamental and straightforward activities (such as daily living and grooming) and more complex relational activities (such as managing personal finances or improved living). The performance of cognitive functions is significant and serves a distinct purpose; it integrates basic, routine, and daily activities. Effective performance also relies on the proper functioning of inhibitory functions (the ability to suppress an irrelevant stimulus or inappropriate reaction) and working memory function (the temporary storage of information for learning and completing tasks). Moreover, cognitive function processes are particularly linked to age-related neurodegenerative diseases, such as Alzheimer's disease [84,85]. On the other hand, self-regulation is one of the most significant cognitive functions of goal-directed behavior, which means managing thoughts, feelings, and behaviors (including the capacity to plan, think flexibly, and inhibit inappropriate actions). Additionally, self-regulation, alongside brain health, is crucial in today's modern community, which encompasses suppressing or encouraging factors directly linked to health. Consequently, both open-skilled physical activity and closed-skilled task-switching often involve repetitive body movements, which require more cognitive effort from individuals. Activities that better engage cognitive effort, such as swimming, running, or yoga, are not dependent upon rapid changes in the environment but are predictable and self-directed [86,87]. Reasoning that cognitive disabilities could be relevant to malnutrition and weakness among the institutionalized elderly population, particularly in non-developed and developing countries. A Brazilian epidemiological study involving 60-year-old individuals showed that hemoglobin levels and the anemia index are inherently associated with the indicators of frailty (Fried phenotype criteria) [88]. Moreover, excessive consumption of Western diets that are high in lipids (e.g., SFA or Saturated Fatty Acids) and low in carbohydrates (with minimal vegetable intake) is linked to the prevalence of obesity, cardiovascular disorders, cancer, and diabetes [89]. Loss of endothelial homeostasis during aging is associated with nutritional factors, oxidative stress, and inflammation. Cognitive impairment patients who suffer from dietary interventions, especially when combined with loss of mobility, chewing, and digesting food, are also affected in preparing complex meals [90,91]. Circadian Cycle Regulation (CCR) and high dietary calorie content precautions are associated with longevity [92, 93]. Studies show that B*. monnieri* alone, along with specific herbal drugs, possesses synergistic effects. For example, a cohort study of elderly subjects investigated the consumption of one capsule per day for 8 weeks [94]. For more details, these supplements contain *B. monnieri, L-theanine*, Crocus sativus, copper, folate, vitamin B, and vitamin D (320 mg, 100 mg, 30 mg, 2 mg, 400 µg, 450-9 µg, and 25 µg, respectively). Subsequently, the patients' symptoms were evaluated using the Mini-Mental State Examination (MMSE), Perceived Stress Questionnaire (PSQ) Index, and Self-Rating Depression Scale (SRDS) tests, with results indicating improvement in cognitive decline, perceived stress, and depression. Another supplement containing *B. monnieri* (100 mg/kg) alongside rivastigmine (5 mg/kg) improved memory impairment in the aluminum chloride (AlCl3) rat model [95]. The aluminum chloride (AlCl3) rat model also caused memory and learning impairment, which was investigated using the Morris water maze and Elevated Plus Maze (EPM) tasks. Thus, *B. monnieri* and rivastigmine possess a synergistic mechanism of action to prevent neuronal damage and improve cholinergic neurotransmission [95,96].

CONCLUSION

Studies have shown that *B. monnieri* could enhance memory, learning, and cognitive function. Additionally, specific inappropriate behavioral habits can lead to a lack of brain concentration and promote aging behaviors. Aging, which is often associated with neurological diseases such as Parkinson's, Alzheimer's, and diabetes, should be managed under the supervision of specialists. Recently, research has been conducted on using nanoparticles from medicinal plants, demonstrating their positive effects.

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