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Roles of Monnieri: Plays an important role in memory enhancement and neuroprotection

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A B S T R A C T

A well-known perennial creeping herb in Indian Ayurveda, Bacopa monnieri (Brahmi) contains a wealth of bioactive phytoconstituents that are linked to the treatment of a number of serious illnesses. This herb is well-known for its medicinal properties, especially as a nootropic and nerve medication. Bacopa monnieri has therapeutic value because it includes bioactive compounds like phenolics, tannins, alkaloids, and flavonoids. Bacoside A is a triterpenoid saponin that has been the subject of most investigation because of its capacity to improve memory and cognitive function. Bacoside A has been demonstrated to enhance the production of proteins and RNA, improve cerebral blood flow, guard against oxidative stress, and raise synaptic activity in specific brain areas. By enhancing antioxidant defense systems, lowering oxidative stress, and altering neurotransmitters, Bacopa monnieri demonstrates neuroprotective qualities.

The herb bacopa monnieri has a potent effect on neurological conditions like Parkinson's and Alzheimer's. Bacopa is frequently used to treat thyroid issues, anxiety, and mental health issues. The current study highlights the various health benefits of Bacopa monnieri and concentrates on several pharmaceutical initiatives.

Key Words: *Bacopa monnieri; Brahmi; Bioactive phytoconstituents; Nootropic; Memory enhancement*

Introduction

A curative herb Bacopa monnieri or popularly known as Brahmi, It include of the fresh stems and the newly harvested leaves of *Bacopa monnieri* Linn. and associated to family Scrophulariaceae is spread out around the Indian subcontinent in damp, moist swampy surroundings, and waterway banks sides. Different names of Bacopa monnieri In Bengali: brahmisaka In Assamese: Brahmi In Gujarati: Jalanevari Hindi: Brahmi In Tamil: Pirami In Telugu: Sambrani Aku In Kannada: Ujala Brahmi In Malayalam: Brahmi- Sak. About 100 variety exists, out of that 3 variety, that is to say- Bacopa monnieri, Bacopa hamiltoniana, and Bacopa procumbens are found in the Indian states. It is Indian cure, towards anxiety in addition to being a thought-improving action, it is too declared expected advantageous in the situation of cardiac, respiring, and neurological problems containing stress, sleeplessness etc. The leaves in addition to stems are cutted from the adult plant and are dehydrated in shade.

Brahmi Morphology

It's a tiny, creeping, succulent herb. They grow from creeping stems that establish roots at the nodes, and they are between 10 and 30 cm long. They are simple, oblong, and have a base that is narrower than the other end. The leaves measure around 2 cm by 1 cm in length, including the whole edges. The flowers are either white or blue. In the leaf axils, pedicels are solitary. Their petals are either pink or white with five lobes. Size grows in the persistent calyx and reaches up to 5 mm. The plant is succulent and fresh, but as it dries, it wrinkles and loses its flavor. It has a diameter of roughly 6-7 mm, is brown, and has longitudinal wrinkles. The stem is composed of cylindrical, glabrous pieces with noticeable nodes that are connected to a cluster of tortuous, brittle roots ventrally by vertically ascending branches. The internodes of the stem are about 1.0-1.5 cm in length, 3.0–4.0 mm in diameter, light yellowish-green, and have a purplish stain (3). It is whole, elliptical-oblong to lanceolate in shape, 0.6-2.5 cm in length and 3-8 mm in breadth, simple, opposite, crisscross., somewhat sessile, smooth, and has 1-3 nerves that are obscurely visible on its bottom surface. The color of the plant is mild green.

The flower, which has two linear bracteoles and is typically longer than the leaves, is light blue or white with a tinge of pink. {Ref- Labani Pal, B Jyotirmayee and Gyanranjan Mahalik, Efficacy and Pharmacological Activities of Bacopa monnieri : A Review}

Brahmi Location

It can be found all around India. The Andaman and Nicobar Islands are home to it. Kerala, the southernmost state of India, has all of its districts covered by it (5).It originates from Indochina, Sri Lanka, and India. There are 56 species in the genus that live in tropical and subtropical areas (6).Traditionally used in India, bacopa monnieri is a plant that grows along lakes and rivers.

Season

June and September witness a large production of Bacopa monnieri. November, however, is a strong farming month for improved bacoside-A growth.

Climatic Condition

Bacopa monnieri is a marine-adapted plant. It can be found all across the world's tropical and subtropical regions. It is present in all of India's humid regions, which have decent sunshine length, temperatures between 30 and 40 °C, and relative humidity levels between 60 and 80 percent. The sandy soils have a pH between 7 and 8. Bacopa monnieri is able to tolerate water with a pH of between 6 and 7 (12).

Distribution

It is most likely a tropical Asian species called Bacopa monnieri that has spread throughout the tropics and subtropics. This species is found in Africa, the Arabian Peninsula, Australia, the Iberian Peninsula, the Americas, and the Caribbean (17). The Caiman Islands, Portugal, Spain, and Singapore are a few of the nations where it has been introduced (18). The tropics and subtropics of the world, including Sri Lanka, India, Nepal, China, Taiwan, Vietnam, and Pakistan, are home to Bacopa monnieri. It is also found in the Mediterranean Basin, Florida, Hawaii, and the southern states of the United States. Among the Indian states where it is found are the Nicobar Islands, Andhra Pradesh, Bihar, Delhi, Goa, Gujarat, Kerala, Assam, Karnataka, , Orissa, Manipur , Punjab, Rajasthan, Tamil Nadu, and West Bengal.

It has been noticed in Northern and Southern Oman, the United Arab Emirates, Saudi Arabia, Bahrain, Kuwait and Socotra, Venezuela, Haiti, Honduras, Ecuador, El Salvador, French Guiana, Grenada, Guadeloupe, Guatemala, Haiti, Honduras, India, Indonesia, Jamaica, Kuwait, Madagascar, Malaysia, Mexico, Mozambique, Nicaragua, Nigeria, Oman, Pakistan, Panama, Philippines, Puerto Rico, Saint Lucia, Saudi Arabia, Somalia, South Africa, Sri Lanka, Swaziland, Taiwan, and the Province of China (North Yemen, Socotra, South Yemen) (19).

Cultivation

Vegetative propagation, or cutting plants, is important for Brahmi cultivation (11, 27). Temperature for Sowing: 25–30°C. Positioning: 1300–1400 meters. 33–40°C is the temperature required, 50–100 cm of rain required, Temperature for Harvesting: 20–25°C.

Soil Condition of Brahmi

Although it may thrive in damp conditions, well-drained soil is ideal for its growth. It even tolerates clogged drains. It has the most pleasant effects in alluvial marshes. Wetlands, canals, and other waterways are ideal habitats for it. It requires acidic soil to thrive at its best (28). In India, this creeping herb can be seen growing alongside canals and other bodies of water. It thrives in soils with poor drainage. The plant likes acidic soil for good growth (29).

Sowing Time

Mid-June or mid-July is the ideal time to plant. The roots are chopped into little pieces, which make for perfect transplant material. Seedlings are then replanted 20 x 20 centimeters apart. This is a swampy, moisture-loving plant that requires a plenty of water (31).

Field Landing

Establishment of Land

The weeds need to be plucked in order to properly prepare the field. Once the ground has a smooth texture, it should be ploughed two or three times. Five tones of farmyard manure per acre should be applied to the soil as part of the preparation.

Irrigation Methods

After the rainy season, field irrigation must be provided. In the winter, the area needs to be rinsed for twenty days.

Intercultural Methods

Weeding

It's important to weed every day. Every ten or fifteen days, after planting, it should bed one. Although hand weeding is more critical, it is preferred for the crop.

Fertilizer

It is essential to add farmyard manure (five tonnes per hectare) along with the soil during the land preparation process. Per hectare of land, it has to be provided with 100 kg of nitrogen, 60 kg of phosphorus pentoxide, and 60 kg of potassium

oxide. After planting bacopa monnieri in the ground or a container, fertilizer is added. This promotes quick and healthy growth. Twenty kg/hectare of zinc sulphate (ZnSo4) is frequently required in places exhibiting deficiencies, such as the Punjab and Uttar Pradesh plains (31).

Chemical Constituents of Bacopa Monnieri

Bacopa monnieri extract contains bacosides, which are triterpenoid saponins. There are twelve recognized analogues of the bacoside family. More recently, novel saponins known as bacosides I–XII have been discovered. Brahmin, nicotine, herpestime, D-mannitol, apigenin, her saponin, monnierasides I–III, cucurbitacins, and plantain side B have all been documented as alkaloids. Alkaloids, saponins, and sterols are the compounds that give bacopa its medicinal properties. Numerous active ingredients, including the saponins d-mannitol and her saponin, acid A, and monnierin, as well as the alkaloids brahmine and herpestime, were identified in India more than 40 years ago. Numerous bacosides and Bacopa saponins, as well as betulin, stigmasterol, and betasitosterol, have also been discovered as active components.

These include Alkaloids like aspartic acid, glutamic acid, β-sitosterol, betulinic acid, D-mannitol, α-alanine, brahmine, nicotinine, herpestine, bacosides A and B, saponins A, B, and C, triterpenoid saponins, stigmastanol, and serine and pseudojubogenin glycoside. are among the ingredients found in BM. Bacoside A and B, two saponin glycosides found in leaves, hydrolyze in acid to form triterpenoid aglycones known as bacogenin A and B, respectively. Brahmic acid and asiatic acid are also present.

Balance of neurotransmitters, including serotonin.is maintained by the Bacosides.

Treatment with BME Controls Serotonin Synthesis

Previous research showed that enhanced tryptophan hydroxylase (TPH) mRNA expression increased 5-HT metabolism and TPH activity, which may have a significant impact on synaptic 5-HT activity [63, 64]. Additionally, it is known that the 5-HT is vitally absorbed by the serotonin transporter (SERT) through transit across the presynaptic membrane [65]. The subject of whether BME's elevated 5-HT level affects TPH2 and SERT levels is raised. Interestingly, Charles et al. [35] showed that TPH2, SERT mRNA expression was up and stayed that way for a week after the BME treatment.

The enhanced expression of SERT may regulate the duration and intensity of serotonergic activity at the synapse, as well as the reuptake of released 5-HT. This may be one of the mechanisms that enhance learning and memory processing and aligns well with established principles in multiple models [66,67]. Alongside these studies, an in silico analysis showed that bacosides (A, A3) may alter TPH2 activity through their interaction with TPH2, which could be one of the processes behind increased 5-HT generation.

5-HT Receptor Activation by BME Therapy

It has previously been discovered that 5-HT produced synaptically acts via a variety of receptors [69]. The downstream signaling cascade that controls synaptic plasticity is either favorably or negatively regulated by activated receptors [70–72]. In light of these findings, the expression of 5-HT receptors (5-HT1A, 5-HT2A, 5-HT4, 5-HT5A, 5-HT6, and 5-HT7) after BME treatment was examined.. Interestingly, 5-HT3A receptor expression was higher than that of any other receptor. It is the sole metabotropic receptor, and endogenous 5-HT may promote its expression, so enabling the hippocampus-dependent task [73,74]. Therefore, the role of 5-HT3A in hippocampus-dependent learning might be assessed using the 5-HT3 antagonist 1-(m-chlorophenyl)-biguanide (mCPBG), which effectively decreases the retention of the conditioned response [75] in both short- and long-term memory.

The 5-HT3 antagonist mCPBG has facilitated our understanding of the role of the BME-induced 5-HT3A receptor in hippocampus-dependent learning and its modulation of other neurotransmitters. Remarkably, BME therapy lessened mCPBG's antagonistic effects. Alongside the 5-HT3A receptor's overexpression, behavioral task improvement was observed when mCPBG and BME therapy were combined. Given the interaction of multiple neurotransmitters implicated in the learning and memory network, the role of the 5-HT3 receptor in the activation/inhibition of other neurotransmitter systems may be significant [77–80].

In addition to interacting with other neurotransmitters implicated in learning and memory, the increased 5-HT3A receptor may also modulate the serotonergic system [58, 67, 81]. Because 5-HT3A is a heteroreceptor, it has been shown that mCPBG activation increases GABA and DA levels while blocking ACh release [74]. 5-HT3 receptor activation in dopaminergic neurons may promote DA release [82,83], and mCPBG increases synaptic dopamine levels by blocking dopamine absorption through its binding to the dopamine transporter [84]. However, BME's anticholinesterase activity [40] and other regulatory mechanisms also play a role in memory enhancement [33, 85] and ACh level regulation. The fact that it had no effect on the Glu level is remarkable. This implies that the 5-HT3A receptor may not colocalize with glutamate neurons in the hippocampus [59]. The modifications that have been seen are proof that BME works through the 5-HT3A receptor to facilitate long-term and intermediate types of memory.

Protein Kinases-CREB Pathway Activation

Adenyl cyclase in neuronal cells produces more cyclic adenosine monophosphate (cAMP) in response to serotonin stimulation, according to a seminal study published in 1976 [86]. A later study by Castellucci et al. [87] found that cAMP stimulation phosphorylates proteins, particularly cAMP-dependent protein kinase or protein kinase A (PKA), which in turn promotes the downstream signaling cascade. PKA that is cAMP-dependent splits into catalytic and regulatory subunits upon activation. The catalytic subunit of PKA promotes the activation of mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK1/2) [88,89]. It has been shown that activation of protein kinases (MAPK/ERK) can phosphorylate the crucial transcription factor CREB, a positive regulator of memory consolidation [90–93]. These events led us to investigate whether the 5-

HT3A receptor activation brought on by BME treatment controlled synaptic plasticity via the cAMP response element bi nding (CREB) protein signaling pathway and protein kinase. It is important to highlight that BME treatment raised ERK1/2 phosphorylation and gives the many types of memory that have been found a physiological and functional explanation [42]. One would anticipate concurrent alterations in the expression of CREB and CREB-targeted genes as well as functional repercussions if p-ERK activity were to rise or fall [94–97]. The production of synaptic proteins, which are necessary for the consolidation of long-term memory (LTM) [99–102] and are known to be involved in processes related to synaptic plasticity in the hippocampus [98], is regulated by the activation of p-CREB1. Both total and phosphorylated CREB protein levels were increased in those who received BME, according Preethi et al. [39]. The fact that BME prevented the mCPBG-mediated reduction of CREB phosphorylation when given before m-CPBG treatment offered more proof of its function in the regulation of the PKA-CREB pathway.

BME-mediated activation of CREB regulation via MicroRNA-124

New protein synthesis is necessary for the establishment of long-term memory [103,104], and it is controlled by mRNA transport and translation [105]. Currently, a number of studies have suggested that microRNAs (miRNAs) are among the factors that control gene expression [106,107], which may be controlled by the amount of miRNA or the manufacture of miRNA. The regulation of miRNA production is mediated by two molecules, Dicer and Ago2 [108]. Since 5-HT stimulation has been demonstrated to downregulate miR-124 expression during 5-HT-induced synaptic facilitation [109], it is important to note that there is an interaction between the two. Therefore, we hypothesized that BME therapy might change the molecules involved in the production pathway of miR-124 as well as the degree of miR-124 expression. We next discovered that BME treatment decreased the levels of Ago2 mRNA, protein, and Dicer [39]. Dicer reduction has been shown to improve synaptic plasticity [110], and Ago2 activation is necessary for the development of the miRNA-induced silencing complex (miRISC) [111]. Additionally, this study showed that in BME-treated patients, lowering Dicer and Ago2 directly decreased miR-124 levels. On the other hand, mCPBG treatment of 5-HT activity resulted in increased levels of Dicer, Ago2, and miR-124 [39]. It has been hypothesized that CREB would be up regulated as a result of miR-124 down regulation [109]. Even though 5-HT has been shown to increase Creb1 mRNA levels [112], new research has suggested that miR-124 may bind to Creb1 3′UTR directly and control CREB expression [109, 113]. In fact, the miRNA is reciprocally controlled by increased CREB [109,114]. This finally promotes synaptic plasticity by controlling the activation of immediate early genes [115–118]. These cellular occurrences show that BME may fine-tune transcription factors by controlling the transcriptional regulators.

BME Treatment Regulates CREB Phosphorylation

Unlike protein kinases, protein phosphatases (PPs) are dephosphorylating enzymes that dephosphorylate molecules like CREB [119]. PPs are essential for regulating the phosphorylation processes that impede memory and learning, age-related cognitive decline [121,122], and encourage forgetting [120]. Numerous PPs are known to be expressed in the brain. The most likely options are Ser/Thr phosphatases (PP1, PP2), which reduce the transcription of CREB-targeted genes [120, 126, 127] by blocking CREB phosphorylation [123–125]. BME treatment significantly reduced hippocampal PP1α and PP2A levels, which appears to be the reason for the observed BME-mediated enhanced memory [42]. According to this study, BME plays a role in controlling CREB phosphorylation, which promotes the transcription of genes targeted by CREB that are involved in memory formation. Additionally, it supported earlier research showing that blocking PPs can enhance memory formation [120, 124, 125, 128–130]. The exact process by which PPs are suppressed hasn't been studied yet, though.

Role of Bacoside

Bacosides have the potential to improve nerve impulse transmission by repairing damaged neurons and reviving synaptic function.

Bacosides can enhance cognitive abilities such as memory, learning, focus, attention span, and concentration.

Antioxidant enzymes such as glutathione peroxidase, catalase, and SOD can all be made more active by bacosides.

Bacosides have the ability to alter SOD, cytochrome P450, and Hsp70 activity.

Bacosides have the ability to control the surface expression of different neuroreceptors, decrease oxidative stress, and stimulate the production of antioxidant enzymes.

Experimental Autoimmune Encephalomyelitis (EAE), a preclinical form of Multiple Sclerosis (MS), can be prevented from progressing by bacosides.

Bacosides B aid in the healing of injured neurons and the restoration of synaptic function.

Monoamines such as serotonin, dopamine, and noradrenaline can be decreased in the brain by bacoside B.

Attention span, focus, concentration, learning, and memory are among the cognitive abilities that Bacosides B can enhance.

.In organs including the liver and brain, bacogenin A and other bacosides contribute to the development of a robust antioxidant environment. To achieve this, they scavenge free radicals.

Lipid peroxidation suppression and antioxidant enzyme activation

Bacogenin A controls the mRNA translation and surface expression of neuroreceptors such as GABAR, NMDAR, and AMPAR.

Bacogenin A influences the cholinergic, dopaminergic, and serotonergic pathways, which may improve memory.

Bacogenin A helps the central nervous system (CNS) work correctly by controlling GABA receptor activity in the cerebellum.
Acetylcholinesterase is inhibited by Bacogenin A.
In injured neurons, Bacogenin A increases kinase activity.

Pharmacological Activities of Bacopa monnieri
It shows several activities by crude extract

1. Antioxidant
2. anticonvulsant,
3. analgesic,
4. antiallergic,
5. antifungal,
6. cardiac depressant, and
7. cardio-tonic
8. Anticancer activity
9. Thrombolytic activity
10. Antidepressant activity
11. Acetylcholinesterase activity
12. Antimicrobial
13. Antiinflammatory

Conclusion
The bacosides in bacopa extract have been shown to enhance cognitive function through the modulation of several neurotransmitters. This review, however, concentrated on studies that give the serotonergic system a lot of attention. These studies covered their receptors and related signaling cascades, which are known to be involved in synaptic plasticity and memory enhancement, beginning with an in silico approach to 5-HT level alternation. These investigations offer molecular proof of a potential BME mechanism affecting the serotonergic system and related pathways.

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