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2. A Review on the Neurocognitive and Neuroprotective role of Brahmi (Bacopa Monniera) Herb

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Abstract

Brahmi (Bacopa monnieri) is a perennial herb belong to the Scrophulariaceae family and is classified as "medhyarasayan" which means intellect or cognitive rejuvenation in Sanskrit that is especially advantageous in reducing cognitive impairments, improving memory and brain function. One such memory enhancer and a natural remedy for central nervous system dyfunction is Brahmi. The bioactive components present in Brahmi are alkaloids, flavonoids, glycosides, phytochemicals (betulinic acid and betulic acid) and saponins (bacoside A and baccoside B). Each chemical components plays a vital part in neuroprotection and therapeutic treatment of patients with memory loss. The neuroprotective properties of Brahmi have effective role in reduction of reactive oxygen species, neuroinflammation, and cognitive and learning behaviour enhancement. Brahmi has number of pharmacological advantages, including improving memory, treating Schizophrenia and Alzheimers' disease, exhibiting antiparkinsonian, anti-stroke, and anticonvulsant effect. The present review focus on the pharmacological role of Brahmi as a chemical constituent in different clinical studies. In recent years, enough stud has been conducted on the effectiveness of Brahmi in treating various disorders and now more researches are required in this field which will address the molecular aspects of Brahmi on various neurological disorder.

Keywords: Brahmi, Neurocognitive, Pharmacological effects, Alzheimers' Disease and Schizophrenia

Introduction

Neurocognitive diseases are a progressive disorder of the central nervous system, which is characterized by progressive loss of neurons (brain) and spinal cord that impedes cognitive and motor functioning in disease such as Alzheimer, Parkinson, Schizophrenia and related disorders (**Brettschneider *et al.*, 2015; Medina *et al.*, 2015**). The *Lancet Neurology* report predicted by 2021; more than 3 billion people globally will be suffering from neurological disorder. Neurological conditions are the main cause of illness and disability these days. Since 1990, the

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total number of illnesses, disability, and premature death brought on by these diseases are raised to 18%. More than 80% of neurological deaths and heath impairments take place in low- and middle-income countries, and there is a significant difference in the access to treatment facilities and professional availability (**WHO 2024**). Currently available pharmaceutical drugs slow down the progression of these disease, but unable to provide a permanent treatment (**Connolly *et al.*, 2014; Kumar *et al.*, 2015**). Numerous food supplements have been shown to increase brain activity as "Memory boosting food or health supplements". One such Ayurvedic traditional medicinal herb is Brahmi or *Bacopa monnieri,* a perennial creeping herb growing in the marshes and wetlands of North and South America, Australia, Africa, Asia and Eastern India for thousands of years. Brahmi was first mentioned in 6th Century A.D. in the Charaka Samhita, Atharva-Veda, and Susrut Samhita as the "medhya" which means intellect and "rasayana" which means cognitive rejuvenation in Sanskrit i.e., Brahmi is beneficial in enhancing memory, cognitive disability and brain function. Both Chinese and Indian traditional literatures mention its medicinal and therapeutic effectiveness. Bacoside-A and bacoside-B, alkaloids, glycosides, flavonoids, and other chemical substances all have been extracted from Brahmi etc (**Chakravarty *et al.*, 2003**). According to research done thus far, have revealed that Brahmi exerts variety of pharmacological effects in treatment of neurological diseases such as Alzheimer, schizophrenia, antistroke, anticonvulsant and antiparkinson potential. The present review focus on the pharmacological role of Brahmi as a chemical constituent in different clinical studies.

Chemical Constituents

Brahmi contain several organic compounds and volatile elements (alkaloids and triterpene saponins) which have strong effect on the body (**Daniel** 2005). Bacosides are triterpenoid saponins of the dammarane class that include with aglycone units of jujubogenin or pseudo-jujubogenin moieties, and are best distinctive compound present in *Bacopa monnieri.* **Chakravarty** *et al.,* 2003 has also identify other saponins, Bacopasides I-XII. Along with apigenin, D-mannitol, hersaponin, curcubitacin, plantainoside B, and monnierasides I-III, the alkaloids brahmine, nicotine, and herpestine have also been classified (**Chakravarty** *et al.,* 2008). In particular, bacoside A-a mixture of bacoside A3, bacopacide II, bacopasaponin C, and a jujubogenin isomer of bacosaponin C, has been the most researched component. When whole plant extract of *Bacopa monnieri* was utilized, Rastogi *et al.,* found varied concentration of bacopaside (6.9%), bacoside A3 (5.59%), bacopaside I (5.37%), bacopasaponin C isomer (7.08%), and bacopasaponin C (4.18%) (**Sivaramakrishna** *et al.,* 2005). **Figure 1** shows the flowering image of Brahmi herbal plant.

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Figure 1 Flowering image of *Bacopa monnieri* herbal medicine extensively used for boosting brain health and also has various pharmacological importance (Source: https://www.shutterstock.com/search/brahmi-plant)

Pharmacological Significance of Brahmi (*Bacopa monnieri*)

Alzheimer Disease

Alzheimer is a neurodegenerative disorder characterized by loss of memory and erratic behaviour. Though the effectiveness of meditational drug for Alzheimer is limited, however there is currently no cure for Alzheimer's disease. Peptide Aβ plays a vital role in Alzheimer toxicity and progression, as it forms insoluble amyloid fibrils inside extracellular senile plaques or neuritic (**Abdul, M *et al.,* 2019**). This is later progress into dementia, cognitive declination, neuronal deterioration and synaptic dysfunction (**Khan *et al.,* 2014**).

Cell membrane contains unsaturated fatty acids, with high metabolic rate and low antioxidants activity. Brain is particularly suspectable to free radical damage. Even though, human body has a number of free radicals scavenge mechanisms including enzymatic (superoxide dismutase (SOD), glutathione reductase and catalase) and non-enzymatic (vitamin A, E, C, selenium, glutathione (GSH) and coenzyme Q10, whose antioxidant properties guards against free radical damage to neuronal tissue). However, imbalance between antioxidant mechanisms and free radical species causes free radical damage in older population which leads aging and cognitive decline (**Chaudhari *et al.,* 2017**). Brahmi hold antioxidant properties and enhances the concentration of GSH, glutathione peroxidase, catalase and SOD and also as free radical scavenging agent. Therefore, administrating Brahmi to certain doses may have potential effect as preventive medicine for cognitive and age-associated memory loss in Alzheimer's population (**Chaudhari *et al.,* 2017**).

A study conducted by **Benson** *et al.,* (2014) on double-blind, cross over and placebo study to evaluate the assess the impact of Bacopa extract formulation (KeenMind-CDRI 08) on 17 healthy participants. The cognitive effects were evaluated using a multitasking framework that includes activities like mental arithmetic test, letter search, stroop, and visual tracking in

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computer screen. State Trait Anxiety Inventory (STAI) and the Bond-Lader VAS were used to assess the mood of the participants. Finding suggested that participants experienced some adaptogenic and nootropic effects with B. *monnieri*. In another study, non-randomized, uncontrolled, and open label clinical trial was done to assess the effect of B. *monnieri* on cognitive function of newly diagnosed Alzheimer patients (60-65 years). After recording baseline scores of all patients, 300 mg of Bacognize (B. *monnieri extract*) was administered two times a day for 6 months. After 6 months of treatment cognitive functions of Alzheimer patients showed significant improvements (**Goswami** *et al.,* 2011). A double-blind randomized study was conducted on depression, anxiety, and cognition ability of elderly using B. *monnieri* extract. The subject belongs to 65 years and above with no signs of dementia. Supplementing 300 mg/kg tablet of B. *monnieri* was effective in improving cognition after various assessment (**Calabrese** *et al.,* 2008). In another study, effect of B. *monnieri* was observed in age-associated memory impairment. Result revealed that during the course of 12-weeks of treatment, B. *monnieri* considerably produced positive impact on memory and learning (**Raghav** *et al.,* 2006). Additionally, a clinical trial investigated the cholinergic, monoaminergic functions, attention, working memory, and cognitive processing on elderly participants. Treatment with Bacopa extract was given to both male and female participants for 12 weeks. Bacopa extract showed positive impact on memory and cognitive function since it has inhibitory effect on acetylcholinesterase (**Peth-Nui** *et al.,* 2012).

Schizophrenia

Schizophrenia is a neuropsychriatric disorder that produce positive and negative symptoms in human body. Positive symptoms include hallucination, delusions, thought disorder, increased motor functions, and perpetual disturbances. The later includes social withdrawal, amotivation, anhedonia deficits, and cognitive disabilities (**Piyabhan** *et al.,* 2019). Till date, antipsychotic treatments mainly Dopamine receptor subtype 2 (D2) antagonist, have so far been successful in reducing both positive and negative effects, but have failed to alleviate the cognitive deficits associated with Schizophrenia (**Leucht** et a., 2013). However, antipsychotics treatment can have a several adverse effects, such as Parkinson's disorder. Therefore, developing a novel drug that enhances cognitive functioning while minimizing side effect is crucial. Previously, also **Piyabhan** *et al.,* 2013 measured the density of vesicular glutamate transporter type 1 (VGLUT1) in same area of brain and found that the rats induce with Schizophrenia had significantly lower levels of VGLUT1 transporter expression. Treatment with Brahmi upregulate the expression of VGLUT1 transporter to normal level thereby proving effective against Schizophrenia. According to **Jash** *et al.,* (2014) Brahmi has anti-epileptic property, as it has shown to reduce dopamine levels in dopaminergic neurons in the rats' frontal cortex region. Results implies that Brahmi able to ameliorate the positive symptoms of Schizophrenia.

Parkinson disease

The second most prevalent neurodegenerative disease is Parkinson's disease. The primary cause of this disease is the death of dopamine-producing neurons. Since the motor activity is typically linked with neurotransmitter dopamine; thus, loss of dopaminergic neurons leads to muscle rigidity, bradykinesia (difficulty in initiating movements) and tremors. Moreover, it

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affects sleep, personality, cognition, behaviour, and mental state resulting into depression and anxiety (**Cheng** *et al.,* 2010). In addition to improving memory, Brahmi has been shown to be beneficial in treating Parkison's disease. **Siddique** *et al.,* (2014) investigated the impact of CDRI-08 (KeenMind) in transgenic Drosophila fruit flies (a model of Parkison's disease) that replicate normal human alpha synuclein in their neuros. Several parameters were assessed to investigate the impact of Brahmi in the brain of fruit fly such as climbing skills, activity pattern, apoptosis, and oxidative stress. Results showed Brahmi reduces behavioural deformities, reduce oxidative stress and neural cell death in the brains of Parkison disease fruit fly model. In another study **Krishna** *et al.,* 2019 assess the influence of B. *monnieri* on behaviours considered to reflect anxiety-like state, motor ability, and biochemical analysis in brain regions of paraquat (PQ) and herbicide exposed rats. Supplementing B. *monnieri* extract (300mg/kg) for 3 weeks showed improvement in exploratory behaviour, gait abnormalities and motor impairment of PQ-induced rats. Additionally, the striatum's dopamine levels decreased, MTT and mitochondrial succinate dehydrogenase (SDH) activity was restored. In 2011, **Jadiya** *et al.,* evaluate the effectiveness of Brahmi in Caenorhabditis elegans model of Parkinson disease. Exposure with Brahmi plant reduced the alpha synuclein accumulation, dopaminergic cell death and restored lipid content and thus, evidence suggest Brahmi can be considered as a possible anti-Parkinson disease medication.

Antistroke effects

Few studies have been conducted by authors to investigate the protective role of Brahmi in treating brain stroke. Due to insufficient oxygen supply the blood flow in cerebral arteries reduces leading to ischemic brain or brain stroke condition. To explore whether Brahmi exerts any effect on cerebral blood flow (CBF) **Kamkaew** *et al.,* (2013) observed this parameter in animal model. Treatment was given for a period of 8 weeks with 40 mg of Brahmi and thereafter CBF was measured. Brahmi was found to be effective in increasing CBF by 25% in rats without affecting blood pressure. In another study, **Rehni** *et al.,* (2007) examine how the herbal plant Brahmi impact ischemia and reperfusion induced brain injury in mice model. The results showed that Brahmi play the protective effect in reducing infarct size in the ischemic-brain and ameliorating memory impairment in plus maze task. Ischemic-reperfusion induction causes an increase in infarct size and impairs short-term memory and motor balance. **Saraf** *et al.,* (2010) evaluated the effect of Brahmi on ischemic-induced brain injury in a rat model by supplementing the treatment group with Brahmi at doses of 120, 160, and 240 mg/kg and performing various biochemical and behavioural analyses. Finding shows Brahmi play a protective role in reducing infarct size in the ischemic brain and ameliorate memory impairment in plus maze task. Additional, rats subjected to ischemic insult shows Brahmi enhance muscle coordination and catalase activity. Significant decrease was observed in the levels of nitrite, nitrate and rate of lipid peroxidation. These finding suggests that Brahmi protects the brain against damage brought by ischemia insults.

Anticonvulsant Effects in treatment of Epilepsy

Epilepsy is a neurological disorder of the brain, characterized by seizures and brief episodes of involuntary movement that may affect a partial or generalized part of body as well as

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occasionally results in loss of consciousness and control over bowel or bladder motion. A group of brain cells experiences excessive electrical discharges during seizures episodes. Seizures can vary from the briefest muscle jerks or lapses of attention to severe, and protracted convulsions. The frequency of seizures can vary from less than one per year to several seizures per day. Epilepsy has associated with social stigma, fear, prejudice, misunderstanding, and discrimination for ages. Today, this stigma persists in many countries and negatively affects the the quality of life for people with disease and their family (**WHO 2024**).

In recent years, the quest for herbal remedies and formulations that could be used to treat epilepsy has attracted a lot of attention. One such popular herbal plant is Brahmi known to improves memory, nervous function, and lessens convulsion. In a study conducted by **Paulose** *et al.,* 2008 assessed the role of NMDA receptor 1 gene expression and metabotropic glutamate-8 receptor (mGluR8) in pilocarpine-induced epilepsy and neonatal hypoxia. During epilepsy, mGluR8 gene are downregulated whereas in hypoxic neonates, NMDAR1 shows increase gene expression. In order to investigate the neuroprotective efficacy of Brahmi, epileptic rats were treated with B. *monnieri* extract, while rats that had been exposed to hypoxia supplemented with glucose, oxygen and epinephrine. Results shows that treatment with Brahmi dramatically reverse the mGluR8 gene expression to normal. Glucose supplementation together with oxygen supply in hypoxic neonates restored the NMDAR1 expression to normal. These findings imply that Brahmi may have a neuroprotective role in glutamate-mediated excitotoxicity during seizures in pilocarpine-induced epilepsy. In another study, the anticonvulsant effect of Brahmi was examined by **Kaushik** *et al.,* (2009) in a number of convulsions inducing rats and mice models including pentylenetetrazol, strychnine, hypoxic stress and pilocarpine. Brahmi was orally administered at a dose of 50 and 55 mg/kg from two to four hours before receiving convulsive stimuli. Result suggests that Brahmi exerts strong anticonvulsant activity similar to benzodiazepines in various convulsion inducing rats. According to **Khan** *et al.,* 2008 and **Krishnakumar** *et al.,* (2009a, b, 2015) reported CRDI-08 (KeenMind) ameliorate pilocarpine induced epilepsy via controlling NMDA receptors and 5-Hydroxytryptamine receptor 2C (5-HT2C) and in cerebral cortex region. In epileptic state the expression of 5-HT2C receptor and IP3 (signal transduction molecule) are elevated. On other hand, NMDA receptors show a downregulated in the brain, and metabotropic glutamate-5 receptor and glutamate-aspartate transporter shows an upregulation leading to glutamate mediated excitotoxicity. Finding shows that treatment with Brahmi regulates the neurotransmitter balance during seizures in pilocarpine induced epilepsy by reversing IP3 content, 5-HT2C, and NMDA receptor expression and to normal and thereby.

Discussion

The present review discusses about the pharmacological benefits of Brahmi on various animal and clinical models. Brahmi can be a promising substitute in treatment of Schizophrenia, Alzheimer disease, and conditions with antiparkinsonian, anti-stroke, and anticonvulsant properties. In Alzheimer disease, Brahmi has shown to exerts antioxidant activity by improving the concentration of GSH, CAT, SOD, and glutathione peroxidase and lowering the damage caused by free radical species in older people leading to improve cognitive ability, boosting

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working memory, attention span and cholinergic functions of rapid transmission of message to cerebral cortex (acetylcholine). Administration with Brahmi has shown to upregulate the levels of NMDAR1 and VGLUT1 gene expression in different parts of brain and shown to have neuroprotective role against Schizophrenia. Brahmi also possess anti-epileptic property to lower the dopamine levels in the frontal cortex of brain, improving positive symptoms of Schizophrenia. Brahmi has also shown anti-Parkinson activity by improving behavioural deformities, gait abnormality, motor coordination and lower alpha-synuclein accumulation and prevent dopaminergic cell death in Parkinson induced model. Further, supplementing Brahmi from 40mg to 240mg/kg body weight has shown protective role against cerebral blood flow and also ameliorate memory dysfunctioning, improving muscle coordination and antioxidant levels in rat models. Moreover, Brahmi has shown to have anticonvulsant activity by reversing the expression of 5-HT2C, NMDA receptor, IP3 to normal levels and lowering the excessive activation of glutamate receptor leading to neuronal damage and cell death and thereby managing the neurotransmission during seizures in epilepsy-induced models.

Conclusion

The Indian traditional system of medicine "Ayurveda" has been known for recognized since 5000 years and has discovered number of herbs and natural products for treatment of disease and disorders affecting the central nervous system. Ayurveda-based drug discovery has promise quicker and less time-consuming alternative to the western pharmacological drugs which lesser side effects. In Hindu traditional knowledge system, since brain is the primary organ for intellectual and creative capability, any product that improves the brain health is known as Brahmi. The term "Brahmi" refers to "bringing knowledge of the Super Reality". Research equivocally shows that Brahmi (B. *monnieri*) possess all the quality necessary to impart neuroprotection, improve cognition, memory, learning ability, protection against acute and chronic stress, improved neurotransmission, improvement in epilepsy-induced cognitive deficits, anti-Parkinson and anti-stroke effect. Similarly, the biological property exerted by Brahmi includes antioxidant and mitochondrial protection, anxiolytic property (reduce anxiety), protection against neuotoxicity, improves neuronal morphology, inhibits phospholipases, and stimulate neuronal proliferation. The requirement of such herbs is considered highly relevant for ever-increasing number of neurological disorders among adults and children. Being a natural product, Brahmi has been shown to have no adverse effects and to be supported by traditional medicine system which accelerates the application into human clinical trial. Still, more researches are required in this field which will address the molecular aspects of Brahmi on various neurological disorder.

Conflict of Interest

The authors declare no conflict of interest and no financial support was provided during the entire course period.

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