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REVIEW ARTICLE

Validation of *Bacopa monnieri* as a nootropic drug: analysis of the existing preclinical and clinical data

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Abstract: Nootropics or smart drugs are compounds used as cognitive enhancers; known for their neuroprotective role. *Bacopa monnieri* was first chronicled in several ancient Ayurvedic texts. Scientific validation of ayurvedic herbs is important for their recognition and acceptance as standard drug. Several preclinical studies and few clinical studies have been conducted to validate the role of *Bacopa monnieri* as a nootropic drug. This review analyses the preclinical and clinical studies in order to validate its use as a drug for improving memory and learning. Furthermore, this review also tries to understand the mechanisms involved in enhancement of memory and learning.

Key words: Nootropic drugs, *Bacopa monnieri*, preclinical, clinical studies, clinical trials.

Introduction

Nootropics mediate their effects by increasing alertness, awareness, mental focus, motivation, creativity, memory and learning (Suliman *et al.* 2016, Soni *et al.* 2020). These drugs decrease burden of Aβ synaptic dysfunctions, inflammation, apoptosis and oxidative stress. The nootropics improve learning and memory through the blockage of Ca channels, inhibition of acetylcholinesterase (AChE) activities, increases the level of antioxidants and the increase in synaptic and mitochondrial response genes (Chiroma *et al*. 2019). *Bacopa monnieri* is a creeping plant found in warm, marshy wetland areas, including those of the Indian subcontinent, East Asia, Australia, and the United States. Bacopa has white to light purple flowers and small leaves. *Bacopa monnieri* was first chronicled in several ancient Ayurvedic texts including the Charaka Samhita (2500BC) the Sushruta Samhita (2300 BC) and Atharva Veda where clear reference was made to its action on the central nervous system (Nemetchek *et al.* 2017). In Ayurveda Brahmi is placed as one of the "medhya rasayana". Ancient Vedic scholars reportedly used *Bacopa monnieri* along with *Centella asiatica* for memorizing long sacred hymns (Aguiar and Borowski 2013). Scientific validation of ayurvedic herbs is important for their recognition and acceptance as standard drug.

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Methodology

The present review has been written after extensive literature survey from databases such as PubMed, Google scholar, nature journals, Cochrane Library, Web of science, Scopus, Hinari and Shodhganga. Research papers and review articles with high citations have been preferred and included in this review.

Nootropics

The term nootropic was coined by the Romanian Chemist and Psychologist Coeneliu E. Giurgea in 1972 (Satyanarayan *et al.* 2013). Those natural and synthetic substances that can hack the brain and increase its power are called as nootropics, and the process of brain hack is known as biohacking. There are three types of nootropics: synthetic, a lab created compound such as Piracetam, Modafinil and Adderall (Chiroma *et al*. 2019) Hybrid, the substances which are found in human body and also can make in laboratory such

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as L-tyrosine, 5-HTP (5- Hydroxiytryptophan), GABA and natural nootropics, such as *Bacopa monnieri*, *Ginkgo biloba*. Nootropics are mainly used for the treatment of Alzheimer's disease, narcolepsy (too much sleep), ADHD attention deficit hyperactivity disorder (who are unable to concentrate properly (Suliman *et al.* 2016). Nootropics must be prescribed by doctors because taking nootropics without prescription can also have side effects like headache, nausea etc.

General Mechanism of action of Nootropic drugs

Nootropic drugs that specially used to target AD and brain injuries. The proposed mechanisms of actions are based on the following six primary brain pathways:

1. Brain energy: Brain alone uses nearly one-fifth of the total energy consumption of the human body. Nootropics act via raising the metabolic activity of mitochondria thus aiding the transportation of fatty acid material into brain cells. It increases the cerebral uptake of oxygen and nutrients leading to supply of fuel for energy production for the brain.

2. Brain chemicals: Nootropics may optimize neurotransmitters by various mechanisms. Some of them are supplying brain chemical precursors, promoting neurotransmitter synthesis, enhancing receptor sensitivity, inhibiting neurotransmitter breakdown. Certain nootropics, such as L- tyrosine naturally and directly engage neurotransmitter pathways by means that essentially qualify them as nootropic neurotransmitter nutrition.

3. Cerebral blood flow: Nootropics may support cerebral circulation by promoting nitric oxide activation and relaxation of blood vessels, inhibiting homocysteine and oxidative damage on blood vessels, making blood cells less "sticky" and thus less likely to clump (Sukumaran *et al.* 2019).

4. Brain wave: Nootropics most notably L-theanine can raise certain brain waves. Alpha brain waves are often targeted for promoting alert-yet-relaxed mind states that can be beneficial for productivity, creativity or simply chilling out. L-theanine influences brain function by having an effect on attention and alertness in healthy people with high anxiety (Akiko Higashiyama 2011).

5. Neuroprotection: Nootropics may support neuroprotection by increasing the brain's antioxidant capacity, helping to fight formation of irregular protein clusters, clearing brain tissue of neurotoxins, protecting the brain against the negative effects of stress (Abdul Manap *et al.* 2019).

6. Brain regeneration: Nootropics may support neuroregeneration by boosting natural brain-boosting growth factors, such as NGF, providing raw neuronal building block materials, like chlorine, maintaining brain cell membrane flexibility and plasticity, one of the more exciting neuroregenerative nootropics on the scene, Lion's Mane Mushroom has been the centre of recent clinical research for its potential in naturally increasing neurotrophic NGF activity.

Bacopa monnieri

Ayurveda is the traditional medicine system of India in which many herbs and natural products have been described for CNS disease and therapy which is more than 5000 years old. Ayurveda has classified selected plants as 'medhya rasayan' (medhya = intellect or cognition and rasayan = procedure or preparation and rejuvenation in Sanskrit) (Chaudhari *et al.* 2017) means brain tonic or nootropic which is specifically beneficial in boosting memory, preventing cognition deficits and improving brain function (Russo and Borrelli, 2005). Such plant products have been used in herbal and traditional medicine because they provide better therapeutic benefits in central nervous system disorder with cognitive impairment and memory deficit compared to pharmaceutical drugs (Kongkeaw *et al.* 2014). A natural plant for memory booster and central nervous system function is *Bacopa monnieri* (Brahmi). *Bacopa monnieri* belongs to the family scrophulariaceae (Chaudhari *et al.* 2017) and it is also known as water hyssop, Brahmi, Bramabhi, and Nirbrahmi, is a creeping plant found in warm, marshy wetland areas, including those of the Indian subcontinent, East Asia, Australia, and the United States (Aguiar and Borowski 2013). Bacopa has white to light purple flowers and small leaves and the genus *Bacopa* has approximately 100 species of aquatic herbs distributed apart from India in Nepal, Sri Lanka, Taiwan, China and certain parts of USA (Shinomol and Muralidhara 2011). Bacopa has

been used medicinally for thousands of years by Ayurvedic physicians, the practitioners of the traditional system of medicine of India. Brahmi is a Sanskrit word derived from "Lord Brahma" or "Brahman". Lord Brahma is the divinity responsible for all of the creative forces in the world (Russo and Borrelli, 2005). Brahmi literally means the energy (or "Shakti") of Brahma. Thus, Brahmi has a lot to offer to the medical world (Shinomol and Muralidhara, 2011). Brahmi is often recognized by different names in different regions and languages. In Sanskrit, it is called Saraswati (Goddess of learning, knowledge and wisdom or the essence of the self), Somavati (containing soma or), Indravalli (energy of Lord Indra). In Hindi, it is known as Brahmi (knowledge of Brahma or supreme reality). In Gujarati, it is known as Jala-Brahmi Jalanevari or Kadavi luni (the better herb). In English, it is called herb-of-grace, Bacopa or Water hyssop. It is known as Jia ma chi xian in Chinese. Following is the Sanskrit text from BhavprakdsaVarg-Prakarana describing actions and uses of Brahmi:

ब्राम्ही ब्रह्मण्डूकी च
ब्राम्ही कपोतवंगा च सोमवल्ली सरस्वती ।
मण्डूकपर्णी माण्डूकी त्वाष्ट्री दविया महौषधी ॥
ब्राम्ही हमि रसा तक्ति लघुर्मेध्या च शीतला ।
कषाया मधुरा स्वादुपाकायुष्या रसायनी ॥
स्वर्या स्मानदतप्रिदा कुष्ठपाण्डुमहास्रकासजति ।वषिशोथज्वरहरतिदवन्मण्डूकपर्णनी ।२८४॥

The description is as such: Brahmi, kapotvadka, somvalli and Saraswati are various names of brahmi. Mandukaparni, manduki, twashtri, divya, mahaaushadhi are various names of mandukaparni. Brahmi has cold potency, astringent and has bitter taste. It is light in nature, brain, tonic and rasayan and good for improving voice and memory. Brahmi is used for skin disorders, anemia, and hyperglycemia, bleeding disorder, cough inflammation and fever. The entire plant is used for the medicinal purpose (Singh and Dhawan 1982).

Key benefits of this medha rasayana are:

- It is a nootropic which helps in improving chemicals/neurotransmitters which are related to the processes of thinking, learning and memorizing
- Increases cognitive capability
- Leads to a calm and composed mind which in turn increased clarity of thought
- Helps in memory consolidation.
- It is an antioxidant neuro-protector
- Reduces unnatural age-related brain deterioration
- Helps in treatment of psychosis, epilepsy and anxiety.
- Relieves nervous irritation or agitation.
- Treats fever and also used as diuretic and aphrodisiac

Chemical composition of *Bacopa monnieri*

Bacopa monnieri contains alkaloid (brahmine, nicotine and herpestine), saponins (saponins are a class of bioorganic compounds found in particular abundance in plant kingdom), sterols (β- sitosterol and sigma-sterol), d-mannitol, betulinic acid. The main constituent of *Bacopa monnieri* is triterpene saponins of dammarane class, which have been named bacosides bacosaponins. There are two types of saponins; jujubogenin and pseudojujubogenin which differ from a sugar unit in the glycosidic chain (Aguiar and Borowski, 2013) and the chemical compound that has neuropharmacological properties and pseudojujubogenin moieties, known aglycone units. The major chemical unit that is responsible for neuropharmacological effects of *Bacopa monnieri* is bacoside A and B. Bacoside A is actually a mixture of four major components, ie. Bacoside II, Bacopside A_3, Bacosaponin C and an isomer of Bacosaponin C. Moreover, new saponins Bacopaside I, II, III, IV, V have been isolated from the plant.

Preclinical studies on *Bacopa monnieri*

The use of *Bacopa monnieri* in cognition and neuroprotection has been well documented (Abdul Manap *et al.* 2019). XoanThi Le *et al* conducted study to clarify the anti-dementia effects of *Bacopa monnieri*, using an animal model of vascular dementia, and also to investigate the constituent(s) contributing to the actions of *Bacopa monnieri*, using an *in vitro* model of ischemia; his team reported the protective effect of *Bacopa monnieri* on the models, bacopaside I (25 μM) exhibited potent neuroprotective effects against drug induced neuronal cell damage (XoanThi *et al.* 2015).

Bacopa monnieri has been shown to exhibit anti-inflammatory effect by inhibiting the release of inflammatory cytokines from microglial cells as well as enzymes associated with brain inflammation. Thus, Bacopa can limit inflammation in the central nervous system, and offers a promising source of novel therapeutics for the treatment of many central nervous system disorders (Nemetchek *et al.* 2017).

Mixture of *Bacopa monnieri*, *Ginkgo biloba,* and *Lavandula angustifolia* significantly enhances memory and learning behaviour more than by each extract individually in scopolamine-induced amnesic mice. Moreover, it shows that *Bacopa monnieri* is the most potent in action to enhance memory and learning in chronic treatment, as compared to *Ginkgo biloba* and *Lavandula angustifolia*, which may further be evaluated for their compounds as lead molecules with targeted therapies (Rehman *et al.* 2021).

Chronic cigarette smoke exposure enhances oxidative stress, thereby disturbing the tissue defense system and bacoside A was found to protect the brain from the oxidative damage through its antioxidant potential in a study (Vani *et al.* 2015).Some of the chemical constituents of extract of *Bacopa monnieri* are lipophilic (Ramasamy *et al.* 2014)**.** Furthermore, Bacosides are believed to repair damaged neurons by enhancing kinase activity and neuronal synthesis linked with the restoration of synaptic activity, culminating in the improvement of nerve impulse transmission (Stough *et al.* 2001). Antidepressant and anxiolytic effects have been reported in animal studies (Bhattacharya and Ghosal 1998, Sairam *et al.* 2002)**.** However it is the memory enhancing effects of EBm that have generated the most attention (Simpson *et al.* 2015).

In 1996 a special extract of BM was launched by the Indian Government's Central Drug Research Institute, Lucknow, termed CDRI 08(21)**.** A special extract of BM (CDRI-08) restores learning and memory by regulating expression of the NMDA receptor subunit GluN2B in the brain of scopolamine-induced amnesic mice (Rai *et al.* 2015)**.**

Interestingly, in a recent study, *Bacopa monnieri* was found to be effective in management of anhedonia via preclinical and a clinical evaluation (Micheli *et al.* 2020). In another recent study *Bacopa monnieri* was found to have protective effect on organs against injury induced by ischemia (Ozlu *et al.* 2021). *Bacopa monnieri* showed neuroprotective effect also through the up regulation of 5-HT (2C) receptor in epileptic rats (Calabrese *et al.* 2008). Clinical trial is required to validate the effect on actual patients on epilepsy.

Regarding the toxicity studies of *Bacopa monnieri*, the acute and chronic toxicity studies of *Bacopa monnieri* extract on using rats suggested no toxicity of this herbal extract even at 5000 mg/Kg body weight. The behavior and health of animals were found to be normal throughout the study (Sireeratawong *et al.* 2016)**.**

Clinical studies of *Bacopa monnieri*

Clinical trials of any drug are important for advising and treating patients. The literature survey for clinical trials of *Bacopa monnieri* found only 14 trials. Out of these, results of three trials have not been published yet. These clinical trials have been conducted in order to validate the role of *Bacopa monnieri* as a nootropic drug as well as its effects on diseases of the brain such Alzheimer's, Parkinson, depression etc.

In a study conducted on the effect of *Bacopa monnieri* on human memory, it was revealed that retention of the new information was significantly enhanced (Roodenrys *et al.* 2002). *Bacopa monnieri* capsules were given to 37 healthy adults at 300 mg for person under 90 kg and 450 mg for person above 90 kg. However; no significant improvement was observed in other cognitive parameters such as measures of short-term memory, working memory, attention, or the retrieval of information from long-term memory. In the same study, depression, anxiety and stress were found to be unaffected. On the contrary, Calabrese *et al* (2008) reported improved depression and anxiety scores along with enhanced cognitive performance in elderly people aged more than 65 years. In another study conducted on healthy older Australians Bacopa significantly improved memory acquisition and retention (Morgan and Stevens 2010). Satyanarayan *et al.* (2013) however reported no significant effect on cognition parameters such as memory and anxiety in healthy

adults upon giving single daily dose of 450 mg of Brahmi extract.

In a study conducted on geriatric patients of Alzheimer's disease showed that *Bacopa monnieri* standardized extract (Bacognize 300 mg twice a day orally) for 6 months showed improvement in some aspects of cognitive functions as measured by MMSE scores (Mathur *et al.* 2016).

Stough *et al* (2001) reported that extract of *Bacopa monnieri* 300 mg significantly improved speed of visual information processing measured by the IT task, learning rate and memory consolidation measured by the AVLT and state anxiety compared to placebo, with maximal effects evident after 12 weeks.

CDRI08 a special extract of *Bacopa monnieri* was developed by CDRI Lucknow in 1996 has been used in several clinical trials. In a study conducted by Benson et al. (2014), reported positive cognitive effects 1 hour and 2 hours post CDRI08 consumption. Positive mood effects and reduction in cortisol levels were also observed suggesting stress lowering effect of *Bacopa monnieri.* The Australian Research Council Longevity Intervention (ARCLI) is currently running a clinical trial to investigate effect of CDRI08 (a special preparation of *Bacopa monnieri*) on cognitive performance in a group of aged people (Simpson *et al.* 2015).

According to a recent review paper published in *Nature* Journals, in a meta-analysis on the effect of *Bacopa monnieri* as a nootropic, antidepressant and neuroprotective effects, *Bacopa monnieri* was able to show only modest improvement in memory loss however, in a cocktail with other plant extracts significantly reduce the effects of Alzheimer's disease and depression (Brimson *et al.* 2021). Only limited studies establish the role of *Bacopa monnieri* as a memory enhancer and memory retainer as well as neuroprotective drug, more clinical studies are required to firmly validate the role of *Bacopa monnieri* as a nootropic drug. Sukumaran *et al.* 2019 have depicted the neuroprotective effects of *Bacopa monnieri* and its antioxidant, anti-inflammatory and anti-apoptotic activity.

Mechanisms of learning and memory

Sukumaran *et al.* 2019 have explained the mechanisms involved in the protective and cognition enhancing effects of *Bacopa monnieri*. Following are the various mechanisms thought to be involved in the memory and learning enhancer of the *Bacopa monnieri*.

Synaptic plasticity

Learning and memory depend upon any change in the efficiency of the synapse called synaptic plasticity. The molecular basis of synaptic plasticity is quite complex. Approximately 40 important neurotransmitters have been discovered thus far. Some of the best known are acetylcholine, norepinephrine, epinephrine, histamine, gamma-aminobutyric acid (GABA), glycine, serotonin, and glutamate. The complex interplay of various molecules such as neurotransmitters released, postsynaptic activation of various receptors and activation of neighbouring structures can lead to strengthening and weaning of synaptic connections. Strengthening of a synapse is called long term potentiation (LTP) and weaking of synapse is called long term depression (LTD) in the hippocampus (Sukumaran *et al.* 2019). The LTP and LTD in the hippocampus is the model used to study learning and memory. The molecules which play important role in LTP and LTD have been identified as different types of glutamate receptors, calcium-signalling molecules and the neurotrophin brain-derived neurotrophic factor (BDNF) (Au *et al.* 2016).

The Hippocampal NMDA receptor-dependent plasticity is adequate for episodic memory that involve influx of Ca2+ via ligand-activated Ca2+ channel causing early induction of LTP (Chaudhari *et al.* 2017)). In a report, *Bacopa monnieri* reversed the down regulated NMDA receptor and calmodulin dependent kinase II. The Brain Derived Neurotrophic Factor (BDNF) is key molecule involved in synaptic plasticity associated with learning and memory (Holcomb *et al.* 2006). *Bacopa monnieri* was shown to enhance the BDNF (brain-derived neurotrophic factor) mRNA in the hippocampus leading to enhanced cognitive performance (Sukumaran *et al.* 2019) along with enhanced CREB (cyclic AMP-responsive element binding protein) and BDNF (brain-derived

neurotrophic factor) mRNA in the hippocampus.

Cerebral blood flow

Cerebral ischemia can lead to the decline in learning and memory function. The levels of AChE, GABA, SOD, and MDA along with change of the content of certain amino acids in the brain are associated with cerebral ischemia and hence the decline of the learning and memory.

In a clever set of experiments, in the frontal lobe and hippocampus area as well as the change of the content of some amino acids, are in support of this, an investigation to study the effect of regional cerebral blood flow (rCBF) in special brain areas, on adult male healthy Sprague- which demonstrated that, reduced rCBF impaired the learning and memory function as well as its molecular mechanism (Kong *et al.* 2008). As mentioned earlier, the ability of *Bacopa monnieri* to have an effect on AChE, GABA, SOD, and MDA levels may be the reason behind increased cerebral blood flow.

Stress resilience and proteostasis

Newborn neurons are continuously generated in hippocampus of adult animals. This phenomenon called adult Hippocampal neurogenesis is related to the development of memory and learning. It can improve both memory acquisition and maintenance. Hippocampus has a significant role in processing and remembering spatial and contextual information, by converting 'short term memories' to 'long term memories' while briefly storing them prior to eternal storage in the cortex (Suk-yu *et al.* 2015). Heat shock protein 70 (Hsp70) is expressed under stress and protects stress induced protein denaturation. In stress induced hippocampal animal model, *Bacopa monnieri* was found to regress the expression of Hsp70 significantly pointing towards enhanced performance of *Bacopa monnieri* in learning and memory through stress re-silence. Moreover, the study also promised that *Bacopa monnieri* supports in surviving with the combined hypoxic, hypothermic and immobilization stress by modulating the activity of P450s and SOD, in addition to the expression of Hsp70 (Sukumaran *et al.* 2019).

Cholinergic markers

Acetylcholine is a neurotransmitter having critical role in memory formation, retention and alertness; low levels may lead to memory impairment (Bardal *et al.* 2011 and McQuiston, 2014). In hippocampus the acetylcholine helps in the construction and recovery of memories in the concentration dependent manner.

Acetylcholine is synthesized from acetyl CoA and choline in a reaction catalysed by choline acetyl transferase enzyme in the pre synaptic nerve terminal (Orta-Salazar *et al.* 2012). In a review *Bacopa monnieri* is hypothesized to restore acetyl choline levels via acetylcholine boosting mechanisms involving activation of acetyl transferase enzyme (Čolović *et al.* 2013) and not via inhibition of acetyl cholinesterase activity (Čolović *et al.* 2013).

The acetylcholinesterase responsible for termination of acetylcholine neurotransmission is another cholinergic marker along with acetylcholine and acetylcholinetransferase. Various studies have depicted the protective role of *Bacopa monnieri* by modulating activities of these enzymes (Yang *et al.* 1998, Holcomb *et al.* 2006, Saini *et al.* 2010).

Glutamatergic markers

Glutamate has an excitatory effect on neurons and is the most abundant free amino acid in brain (Zhou and Danbolt 2014). It has a role in learning and memory, but can also excite cells to death causing excitotoxicity (Yang *et al.* 1998). The neurotoxicity induced by glutamate is believed to be involved in the development of neurodegenerative disorders in which cognition is impaired.

Serotonergic markers

Serotonin commonly known as a feel-good hormone is a neurotransmitter of the central nervous system and its increased levels in the hippocampus has a possible role in the long-term potentiation and enhanced memory and learning. A study on the role of *Bacopa monnieri* on epileptic rats revealed upregulation of serotonin receptors together with increased expression of serotonin and increased levels of IP3 in the hippocampus (Yadav

2013 and Meneses 2014). *Bacopa monnieri* has shown improved memory retention by increased serotonin levels by increasing expression of tryptophan hydroxylase-2 (TPH2) mRNA (Charles *et al.* 2011).

Conclusion

In India, *Bacopa monnieri* has been used since ancient times as a medhya rasayana to improve memory, concentration and general brain functions. Many scientific studies have been performed to validate its role as a brain tonic as well as its neuroprotective effects on neurogenerative diseases such as Alzheimer's, Parkinson's, epilepsy, depression etc. Plenty of preclinical data is available to establish the neuroprotective and cognition enhancing effects of *Bacopa monnieri*; however, clinical data is scarce. Many clinical trials did not show any significant effect. Results of some clinical trials are not published yet. Therefore, in order to authenticate the beneficial uses of this herb, more and extensive clinical trials are required.

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