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EVOLUTION OF PHYTONOTROPES: EMPHASIS ON BACOPA MONNIERI

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Memostim® is a phytonootropic agent, containing standardized BM extract (150 mg per capsule) and Ginkgo biloba extract (120 mg per capsule), providing the whole daily dose of both components. Memostim® is registered in United Kingdom and sold in United States under trade name Memoboost®.

As shown in a clinical trial of Memostim® (Memoboost®), its use in the patients with dyscirculatory encephalopathy (term, commonly used in Ukraine, which corresponds more widely used term "cerebral small vessel disease") during 3 months can ameliorate the clinical signs of this disturbance, particularly, increasing the level of neurotrophic factors (nerve growth factor-beta) up to 67%. Memostim® (Memoboost®) reduced manifestations of cognitive dysfunction, improving memory and attention. Positive influence of BM extract on the cognitive functions was followed by decreasing of manifestations of anxiety-depressive syndrome, as well increasing of the quality of life of the patients.

Bacopa is a very promising medicine for cognitive dysfunction, and has a favorable safety profile with a long history of use in humans. If you or your patients suffer from cognitive dysfunction, consider performing a study on their cognitive function before and after a period of Bacopa use (>1 month is required to notice statistically significant improvements in prior clinical trials). Dosing should not be on an empty stomach, which can result in gastrointestinal upset, as Bacopa is a pro-cholinergic agent. Bacopa should be taken with food. Absorption and bioavailability of the active constituents of Bacopa, such as the bacosides, may be enhanced by co-administering a lipid such as coconut milk / medium chain triglycerides, fish oil (EPA/DHA), avocado, or other fatty foods. Bacopa can be taken any time of day, but some users report improved sleep quality when dosed prior to bed.

Key words: bacopa Monnieri, Memostim®, cognitive dysfunction, dyscirculatory encephalopathy.

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One of the most studied and popular herbal remedies prescribed by the Indian Ayurveda system of medicine is *Bacopa monneri*. There have been >300 articles, meta-analyzes (which include more than 1,500 patients) have been published in international scientific journals about Bacopa monnieri ("BM"), including six rigorous clinical trials that found compelling evidence for improved cognitive function. I also wrote a scientific journal article reviewing the neuropharmacology of Bacopa monnieri describes about 150 scientific journal articles that report the molecular mechanisms of enhanced cognitive function and neuroprotection across animal species in the laboratory. In this brief article, I will summarize, for the general audience, some of the key points from that more technical discussion.

Bacopa monnieri (also known as brahmi, water hyssop, Bacopa monniera, and Herpestis monniera), is a creeping perennial with small oblong leaves and purple flowers, found in warm wetlands, and native to Australia and India. Commonly found as a weed in rice fields, BM grows throughout United States and the East Asia³ The entire plant is used medicinally.

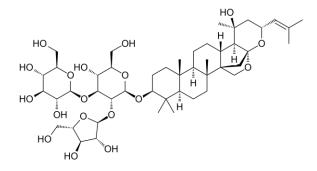
Background on Bacopa





Bacopa contains a combination of active compounds, not just a single molecule, and therefore cannot be patented. However, the most pharmacologically active compounds in Bacopa are structurally similar, known as 'bacosides' and can be standardized to a certain percentage of concentration within the plant extract and put in a pill — a process similar

to brewing tea and then dehydrating the liquid to leave only the dry powder containing water-soluble molecules from the tea.



Bacoside A3, one of the active molecules in Bacopa monnieri

Unlike the potentially addictive and forceful action of widely used psychostimulants, chronic and moderate administration of BM appears to *nourish rather than deplete* the brain, an action compatible with 1400 years of Ayurvedic study. BM was initially described around the 6th century A.D.

in texts such as the Charaka Samhita, Athar-Ved, and Susrutu Samhita as a medhya rasayana—class herb taken to sharpen intellect and attenuate mental deficits. The herb was allegedly used by ancient Vedic scholars to memorize lengthy sacred hymns and scriptures. BM is colloquially called Brahmi, after the Hindu creator-god Brahma, especially when combined with other alleged intellect-sharpening herbs like Centella asiatica (Gotu Kola) or Gingko biloba. BM is consistently found in the many Ayurvedic preparations prescribed for cognitive dysfunction, often combined with ghee (clarified butter) for absorption and other cognitive enhancing herbs.

BM is traditionally used for various ailments but is best known as a neural tonic and memory enhancer. Numerous animal and *in vitro* studies have been conducted, with many evidencing potential medicinal properties. Several randomized, double-blind, placebo-controlled trials have substantiated BM's nootropic utility in humans. There is also evidence for potential amelioration of dementia, Parkinson's disease, and epilepsy.

Current evidence suggests BM acts via the following mechanisms—anti-oxidant neuroprotection (via redox and enzyme induction), acetylcholinesterase inhibition and/or choline acetyltransferase activation, β -amyloid reduction, increased cerebral blood flow, and neurotransmitter

¹ Pase et al. (2012) The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. *J Altern Complement Med*.

² Aguiar & Borowski (2013). Neuropharmacological Review of the Nootropic herb Bacopa Monnieri. Rejuvenation Research.

³ Barrett SC. Strother JL. Taxonomy and natural history of Bacopa in California. Syst Bot. 1978;5:408–419

modulation (acetylcholine [ACh], 5-hydroxytryptamine [5-HT], dopamine [DA]). BM appears to exhibit low toxicity in model organisms and humans; and while Bacopa has been used for centuries in Indian medicine however, long-term studies of toxicity in humans have yet to be conducted.

Bacopa has many potential medical applications, beyond cognitive enhancement. These include:

- anti-convulsant^{4,5,6}
- anti-depressant⁷
- analgesic⁸,⁹,¹⁰
- anti-inflamatory¹¹
- anti-microbial¹²
- anti-ulcerogenic¹³/anti-*H. pylori*¹⁴
- anxiolytic15
- adaptogenic¹⁶,¹⁷
- ⁴ Mathew J. Gangadharan G. Kuruvilla KP. Paulose CS. Behavioral deficit and decreased GABA receptor functional regulation in the hippocampus of epileptic rats: Effect of Bacopa monnieri. Neurochemical Res. 2011;36:7–16.
- ⁵ Khan R. Krishnakumar A. Paulose CS. Decreased glutamate receptor binding and NMDA R1 gene expression in hippocampus of pilocarpine-induced epileptic rats: Neuroprotective role of Bacopa monnieri extract. Epilepsy Behav. 2008;12:54–60.
- ⁶ Mathew J. Paul J. Nandhu MS. Paulose CS. Bacopa monnieri and Bacoside-A for ameliorating epilepsy associated behavioral deficits. Fitoterapia. 2010;81:315–322.
- ⁷ Sairam K. Dorababu M. Goel RK. Bhattacharya SK. Antidepressant activity of standardized extract of Bacopa monniera in experimental models of depression in rats. Phytomedicine. 2002;9:207–211.
- ⁸ Abbas M. Subhan F. Mohani N. Rauf K. Ali G. Khan M. The involvement of opioidergic mechanisms in the activity of Bacopa monnieri extract and its toxicological studies. Afr J Pharm Pharmacol. 2011;5:1120–1124.
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- ¹² Azad A. Awang M. Rahman M. Akter S. Biological and pre-clinical trial evaluation of a local medicinal plant Bacopa monnieri (L.) IJCRR. 2012;4: 92–99.
- ¹³ Sairam L. Rao C. Babu M. Goel RK. Prophylactic and curative effects of Bacopa monniera in gastric ulcer models. Phytomedicine. 2001;8:423—430.
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- ¹⁵ Bhattacharya SK. Ghosal S. Anxiolytic activity of a standardized extract of Bacopa monniera: An experimental study. Phytomedicine. 1998;5:77–82.
- ¹⁶ Bhatia G. Palit G. Pal R. Singh S. Singh HK. Adaptogenic effect of Bacopa monniera (Brahmi) Pharmacol Biochem Behav. 2003;75:823–830.
- ¹⁷ Chowdhuri DK. Parmar D. Kakkar P. Shukla R. Seth PK. Srimal RC. Antistress effects of bacosides of Bacopa monnieri: Modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res. 2002;16:639–645.

- anti-neoplastic 18, 19
- hepatoprotective²⁰
- immunostimulatory^{21,22,23}

One product available in Ukraine is called *Memostim**, which is a standardized extract of Bacopa and other cognitive enhancing agents.

An estimated 3.4 million people are affected by dementia in the United States,²⁴ most prevalently in the elderly. The elderly population (aged over 65) is expected to double by 2030, reaching 72 million, or 20% of the total U.S. population²⁵ Bacopa may benefit some patients with dementia and other forms of neurodegeneration.

Neuropharmacology of Bacopa

Bacopa is neuroprotective in studies of neurons or brain slices in a petri dish, as well as in animals like rodents. The experimental produce is as follows: scientists administer a toxin, like pesticides, cigarette smoke, and neurotoxins like mercury. Then, the scientists co-administer Bacopa monnieri, which results in reduced brain tissue damage and improved cognitive function in the animals. Many toxins, like the pesticide rotenone, which can cause Parkinson's disease, inflict harm by producing reactive oxygen species (ROS). These are 'free radical' compounds that can destroy the cell in a chain reaction. Bacopa extract itself is antioxidative, but more interestingly, Bacopa actually turns on the gene expression of enzymes that act as very powerful antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx).

Bacopa also reduces neuroinflammation — a process of hyperactive immune function (e.g., by microglia, the resident immune cells of the brain). This is similar to

¹⁸ Deb DD. Kapoor D. Dighe DP. Padmaja D. Anand MS. D'Souza P. Deepak M. Murali B. Agarwal A. In vitro safety evaluation and anticlastogenic effect of BacoMind on human lymphocytes. Biomed Environ Sci. 2008;21:7–23.

¹⁹ Elangovan V. Govindasamy S. Ramamoorthy N. Balasubramanian In vitro studies on the anticancer activity of Bacopa monnieri. Fitoterapia. 1995:66:211–215.

²⁰ Ghosh T. Maity TK. Das M. Bose A. Dash DK. In vitro antioxidant and hepatoprotective activity of ethanolic extract of Bacopa monnieri. IJPT. 2007;6:77–85

²¹ Yamada K. Hung P. Park TK. Park PJ. Lim BO. A comparison of the immunostimulatory effects of the medicinal herbs Echinacea, Ashwagandha and Brahmi. J Ethnopharmacol. 2011;137:231–235.

²² Samiulla DS. Prashanth D. Amit A. Mast cell stabilising activity of Bacopa monnieri. Fitoterapia. 2001;72:284–285.

²³ Russo A. Borrelli F. Bacopa monniera, a reputed nootropic plant: An overview. Phytomedicine. 2005;12:305–317.

²⁴ Plassman BL. Langa KM. Fisher GG. Heeringa SG. Weir DR. Ofstedal MB. Burke JR. Hurd MD. Potter GG. Rodgers WL. Steffens DC. Willis RJ. Wallace RB. Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology. 2007;29:125–132.

²⁵ Federal Interagency Forum on Aging-Related Statistics. Older Americans. Key Indicators of Wellbeing. 2012

autoimmunity, when the body's immune system destroys the rest of the body. Neuroinflammation is increased with age, brain trauma, bad diet and lifestyle, insufficient sleep, and other stressors. Bacopa monnieri has been shown to reduce neuroinflammation and calm down the brain's immune system.

Furthermore, Bacopa enhances blood flow in the brain, specifically vasodilation and neurovascular coupling. Brain aging may be caused in part by reduced blood flow, and vascular aging similar to cardiovascular disease elsewhere in the body. This type of reduced blood flow, when severe, is known as ischemia, and is a slow-moving version of a stroke – starving brain cells of oxygen and nutrients. Of all the organs in the body, the brain is the most metabolically active by weight – it's about 5% of body weight but consumes 20% of energy. Therefore, restrictions in blood flow and nutrients are very serious. Gingko biloba and vinpocetine are other natural agents that enhance cerebral blood flow.

In aged rats, Bacopa enhanced the concentration of key neurotransmitters involved in cognition, including dopamine, acetylcholine, and serotonin. Bacopa was also shown to be protective in animal models of epilepsy, Parkinson's, Alzheimer's, and other neurological ailments. Furthermore, Bacopa turns on' a critical gene called CREB, that is the master regulator of memory and learning, and the discovery of which won a Nobel prize for Eric Kandel in the year 2000.

The positive effect of BM extract on the cognitive functions of patients has been proven from the standpoint of evidence-based medicine. According to the results of a large meta-analysis of double-blind randomized placebocontrolled clinical trials, BM extract significantly improves patients' cognitive functions²⁶. Experimental studies have demonstrated the ability of BM to increase levels of nerve growth factor (NGF — peptide, which stimulates growth of nerve cells) in various brain structures: 47.5% in the hippocampus and 108.7% in the prefrontal cortex. Because NGF is a trigger for neuronal tissue repair, an increase in its level with BM extract was also accompanied by an increase in the release of other neurotrophins, in particular brain-derived neurotrophic factor (BDNF — another essential peptide, which ameliorates growth and repair of nerve tissue).

According to the majority of clinical trials of BM extract as a neurocognitive enhancing agent, the most effective daily dose ranges from 150 to 300 mg of standardized extract, as well there are a raw of trials, proving safety and tolerability of BM extract in higher doses.

The cognitive-enhancing properties of BM extract have been thoroughly proved in many clinical trials, involved persons of different ages. BM provided nootropic effect in the regime of taking daily doses ranged between 150 – 300 mg during the period of time from 6 to 12 weeks.

According to the results of the clinical trials, BM improved speed of information processing (particularly, visual information), learning rate and memory consolidation, minimized state of anxiety, with maximal effects evident after 12 weeks²⁷. BM significantly improved performance on the working memory factor, particularly, spatial working memory accuracy and speed²⁷. The study²⁸, engaged 76 adults aged between 40-65 years show a significant effect of the BM extract (300 or 450 mg/day) on a test for the retention of new information even after a significant period after the three months of trial. There was shown that BM extract decreases the rate of forgetting of newly acquired information. Moreover, Raghav et al.²⁹ reported improved mental control, logical memory, as well associate learning as measured on subsets of the Wechsler Memory Scale in participants aged 55 years and over with age-associated memory impairment in a 16-week trial (12 weeks on active treatment) with improvements maintained at 4 weeks post-treatment³⁰.

These results are consistent with the findings of Morgan A. et al.³⁰, where was found out that BM significantly improved memory acquisition and retention in healthy older persons aged over 55 years. Other studies with participation persons aged between 50-75 years with complaint of memory impairment for at least one year without any major cognitive deficit, revealed that BM given at the dose of 450 mg once daily for 12 weeks improved the cognitive functions such as attention and verbal memory. Besides, it was also found to be well tolerated³¹.

²⁶ Pase M.P. The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. J Altern Complement Med. 2012 lss. 18(7): 647-652.

²⁷ Stough C. et al. Examining the Nootropic Effects of a Special extract of Bacopa monniera on Human Cognitive Functioning: 90-Day Double-Blind Placebo-Controlled Randomized Trial. *Phytother. Res.* **22**, 1629–1634 (2008).

²⁸ Roodenrys S. et al. Chronic Effects of Brahmi (Bacopa monnieri) on Human Memory. *Neuropsychopharmacology*. **2002**. Vol. 27, No. 2, P. 279–281.

²⁹ Raghav S. et al. Randomized controlled trial of standardized Bacopa monniera extract in age-associated memory impairment. *Indian J Psychiatry.* **2006** Oct-Dec; 48(4): 238–242.

³⁰ Morgan A., Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. *J Altern Complement Med.* **2010** Jul;16(7):753–759.

³¹ Barbhaiya H. et al. Efficacy and Tolerability of BacoMind®on Memory Improvement in Elderly Participants - A Double Blind Placebo Controlled Study. *Journal of Pharmacology and Toxicology.* **2008**. 3(6): 425–434.

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Calabrese et al.³² demonstrated, that patients older than 65 years, taking BM extract 300 mg/day for 12 weeks were improved in delayed recall memory and Stroop task reaction times over the course of the study, as well displayed a decrease in depression and combined state plus trait anxiety scores. The daily dose was well tolerated with very few adverse events

Apart from normalizing cognitive function in the elderly and persons with declined cognitive functions, it was demonstrated that efficiency of attention, freedom from distractibility, and working memory improved significantly with the use of BM extract on a group of individuals with already high cognitive abilities (medical students aged 19-22 years)³³, as well in schoolchildren aged 6-8 years BM showed improvement in immediate memory, perception, and reaction performance without any side effects³³.

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encephalopathy (term, commonly used in Ukraine, which corresponds more widely used term "cerebral small vessel disease") during 3 months can ameliorate the clinical signs of this disturbance, particularly, increasing the level of neurotrophic factors (nerve growth factor-beta) up to 67%. Memostim® (Memoboost®) reduced manifestations of cognitive dysfunction, improving memory and attention. Positive influence of BM extract on the cognitive functions was followed by decreasing of manifestations of anxietydepressive syndrome, as well increasing of the quality of life of the patients.

Considering the current evidence for BM clinical efficacy and international practice of its use as a cognitive-enhancing agent, I strongly recommend paying special attention of Ukrainian doctors on the phytonootropic complex Memostim® (Memoboost®), containing standardized BM extract (150 mg per capsule) and Ginkgo biloba extract (120 mg per capsule).

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ЕВОЛЮЦІЯ ФІТОНООТРОПІВ: АКЦЕНТ НА БАКОПІ МОНЬЄ

Себастьян А. Брунемайєр

доктор філософії (PhD) з біохімії старіння в Оксфордському університеті (стипендіат Кларендона), магістр за напрямком «управління бізнесом в галузі біології», а також магістр за напрямком «молекулярні нейронауки» Амстердамського університету (стипендіат Amsterdam Excellence Scholar)

«Мемостім®» — це фітоноотропний засіб, що містить стандартизований екстракт бакопи Моньє (150 мг) та гінкго дволопатевого (120 мг), що забезпечує всю добову дозу обох компонентів. «Мемостім®» зареєстрований у Сполученому Королівстві та продається в США під торговою назвою «Memoboost®».

Як було продемонстровано у клінічному дослідженні препарату «Мемостім®» («Memoboost®»), його застосування у пацієнтів з дисциркуляторною енцефалопатією (термі, який зазвичай використовується в Україні, та відповідає більш широко вживаному терміну «церебральна хвороба дрібних судин») протягом 3 місяців, полегшує клінічні прояви цього порушення, а також збільшує рівень фактора росту нервів-В до 67%. «Мемостім[®]» («Метоboost[®]») зменшував прояви когнітивної дисфункції, покращував пам'ять і увагу. Позитивний вплив екстракту бакопи Моньє на когнітивні функції супроводжувався суттєвим ослабленням проявів тривожно-депресивного синдрому, а також підвищенням якості життя пацієнтів.

Бакопа Моньє представляє собою перспективний засіб для осіб з когнітивною дисфункцією, маючи при цьому сприятливий профіль безпеки, що підтверджений тривалою історією використання в медичній практиці. Якщо Ви або Ваші пацієнти страждаєте на прояви когнітивної дисфункції, раціональним підходом є оцінка когнітивної функції до та після періоду використання БМ (для відчутних змін необхідним ϵ застосування > 1 місяця, як було продемонстровано у попередніх клінічних дослідженнях). Уникайте прийому / призначення БМ натщесерце, оскільки внаслідок прохолінергічної дії БМ можливими є шлунково-кишкові розлади. Бакопу Моньє слід приймати з їжею. Всмоктування та біодоступність біологічно-активних компонентів бакопи Моньє, таких як бакозиди, можна підсилити шляхом одночасного прийому ліпофільних продуктів, таких як кокосове молоко / тригліцериди середнього ланцюга, риб'ячий жир (ЕРА / DHA), авокадо або інші жирні продукти. Бакопу Моньє можна приймати в будьякий час доби, разом з тим, деякі користувачі повідомляють про поліпшення якості сну за умови прийому безпосередньо перед

Ключові слова: бакопа Моньє, «Мемостім®», когнітивна дисфункція, дисциркуляторна енцефалопатія.