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Herbal Drug Interaction: A Special Reference to Medicinal Plant Brahmi

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Abstract: *From a very ancient time brahmi is used as medicine as raw and in other formulation. With Different herbs the mode of action of the brahmi plant is changed, so there is a lot of studies have been done to show the different dose of the brami with different herbal medicine have different mode of action. Here is a brief review about the herbal drug interaction of the brahmi with other medicinal plants and different drug dosing.*
Keywords: *Brahmi, Antioxident, Medicinal plants, Herbal drug interaction.*

I. Introduction:

The traditional use of *Bacopa monnieri* as an anti-anxiety remedy in Ayurvedic medicine isreinforced by both animal and clinical research. A one-month, restricted clinical trial of 35patients with established anxiety neurosis validated that administration of Brahmi syrup (30 mL daily in two divided doses, equivalent to 12 g dry crude extract of Bacopa monnieribring about in a significant decrease in anxiety symptoms[1,5,9], level of anxiety, level ofdisability, and mental fatigue, and an intensification in immediate memory span (Singh andSingh, 1980). Other ups and downs noted were increased body weight, decreased respirationrate, and decreased systolic blood pressure. In one up-to-date study, effects of a SBME (300mg/day) on cognitive performance[2], anxiety, and depression in the elderly wereappraised in a randomized, double-blind, placebo-controlled clinical trial with aplacebo run-in of 6 weeks and a treatment period of 12 weeks [3-5].In fifty-four participants aged 65 or older (mean 73.5 years), deprived of clinical signs ofdementia, were conscripted and randomized to *Bacopa monnieri*or placebo. Forty-eight (48) completedthe study with 24 in each group[4]. *Bacopa monnieri* participants were bring into being to have enhancedAuditory Verbal Learning Test (AVLT), overdue word recall memory scores relative toplacebo, decreased Center for Epidemiologic Studies Depression scale (CESD-10)depression scores, combined state plus trait anxiety scores[5], and heart rate over timecompared to that of placebo group. This study provided further evidence that BM has agood potential for safely enhancing cognitive performance in the aging[6-9].

Dosage

The day-to-day doses of *Bacopa monnieri*, generally acclaimed in traditional practice are 5-10 g ofnon-standardized powder, 8-16 mL of infusion, and 30 mL daily of syrup (brahmi)(Monograph, 2004) . Prescribed amount of a 1:2 fluid extract are 5-12 mL per day for adults and2.5-6 mL per day for children ages 6- 12[8]. For BME standardized to 20-percentbacosides A and B the measured quantity is 200-400 mg daily in divided doses for adults, and forchildren, 100-200 mg daily in divided doses. The acclaimed daily dose ofBacopin® (standardized to contain a minimum of 20% Bacosides A and B) for an adultis 100 mg - 3 times daily and children 50 mg - 3 times daily [7]. InIndia, the Ayurvedic doctors use it without any ill effects in children, pregnant ladiesand breast feeding mothers but no parallel studies of its use in children, pregnant andbreast feeding women regarding toxicity or herb-drug interactions, unlike modernpharmacological drugs are available, so its use may warrant precautions[9].

Herbal drug interactions

In vitro and animal studies have validated that the *Bacopa monnieri* extracts might potentiate theconsequence when taken with some synthetic drugs or it might have a protective upshot againstcertain drugs and their negative side effects[10-14]. *Bacopa monnieri*has been well-known in animal models todecrease the toxicity of morphine and phenytoin (Sumathy et al., 2001). In this studythe paraphernalia of an alcohol extract of *Bacopa monnieri* on morphine-induced hepatotoxicity in rats wasscrutinized, as restrained by lipid peroxide accumulation and antioxidant enzyme levels[12].Administration of *Bacopa monnieri*Extract with morphine was established to considerably decrease lipidperoxidation, in addition to amplified levels of antioxidant enzymes and glutathione inrat hepatic tissue, when equated to morphine alone. These results suggested aprotective effect for *Bacopa monnieri* on the hepatic antioxidant status in morphine-treated rats[13]. Inmice, *Bacopa monnieri* administration with phenytoin significantly reversed phenytoin-inducedcognitive impairment, as noted by improved acquisition and retention of memory[15]. In study, the passive avoidance response task (PA),

maximalelectroshock seizures and locomotor activity were evaluated in mice.The mice received phenytoin (PHT, 25 mg/kg orally for 14 days). Bacopa monnieri (40 mg/kg for 7days) given along with phenytoin in the second week of the two-week regimensignificantly reversed PHT-induced impairment of cognitive function as determinedfrom the PA results[16]. Both acquisition and retention of memory were improved withoutaffecting the anti-convulsant activity of PHT in the study. These effects were found tobe independent of motor stimulation. The results suggested a potential corrective effectof Bacopa monnieriExtract in phenytoin-induced cognitive deficit [17]. It has also beenshown, albeit inconsistently; to have a slight sedative effect [18]. Both cold aqueous infusion and standardized 95% alcoholic Bacopa monnieriExtract potentiated the sleep, prolonging the hypnotic effect of sodium phenobarbitone in ratsin the study. This sedative action observed in rats was attributed to the saponin fractionbacosides. So a caution was raised when the same is administered in combination withother known sedatives.One in vitro study using guinea pig ileum isolates examined the effect of Bacopa monnieriExtract on druginducedmorphine withdrawal. Addition of 1,000 μg/mL Bacopa monnieriExtract to the tissue isolates,prior to injection of morphine significantly reduced the naloxone-induced withdrawaleffects in the study [19], an effect that was attributed to theanticholinergic and calcium antagonistic properties. The same researchers reported asimilar effect for brain mitochondrial enzyme activity of morphine treated rats[20]. Also, since Bacopa monnieriExtract appeared to stimulate T4 thyroid hormoneactivity in animals at high doses [21], it was theorized that it maypotentiate the activity of thyroid-stimulating drugs or inhibit the effect of thyroidsuppressantdrugs. An animal study has found that the effects of chlorpromazine, a drugsimilar to (perphenazine, prochlorperazine, thioridazine), were enhanced when a Bacopa monnieriExtract was given along with it [22]. So it was cautioned that peopletaking medications from these family of drugs mentioned above should be careful whiletaking Bacopa monnieri, until more information is available. Moreover, the benefits of Bacopa monnieri havebeen so good in anxiety and depression that it could be used alone for mild to moderateproblems[23]. However if is taken along with other synthetic drugs, a caution should betaken to monitor the response and the dosage.In addition to all pharmacological studies mentioned above, herb-drug and herb-herbinteractions of Bacopa monnieri need to be studied. In recent years, various case reports and clinicalstudies in herbal drug interactions have been published which provided a consistentevidence that the interactions between herbal medicines and synthetic drugs exist andcan have serious consequences [25-31]. Therefore, it is necessary to consider thepossibility of Bacopa monnieri-drug interactions and the need for exercising requisite precautionswhile co-medicating the herb extract with synthetic medications.

Memory: Memory is the ability of the brain to encode, store, and retrieve information. Encoding refers tothe initial perception and registration of information. Storage is the retention of encodedinformation over time. Retrieval refers to the processes involved in using stored information.Whenever people successfully recall a prior experience, they must have encoded, stored, andretrieved information about the experience [27]. Conversely, memory failure for example, forgettingan important fact reflects a breakdown in one of these stages of memory. Cognition refers to theprocesses through which information coming from the senses is"transformed, reduced,elaborated, recovered, and used". The term information, used here, refers simply to sensory inputfrom the environment that informs us about something that is happening there. Cognitiveprocesses are thus the mental processes involved in knowing about the world; as such, they areimportant in perception, attention, thinking, problem solving and memory[29]. Memory and learningare closely related, and the terms often describe roughly the same processes.Nootropics,popularly referred to as "smart drugs", "smart nutrients", "cognitive enhancers", "brainenhancers" and "memory enhancers", are a class of drugs that improve impaired humancognitive abilities (the functions and capacities of the brain). The term covers a broad range ofsubstances including drugs, nutrients and herbs that have purported cognitive enhancing effects[30-35].

Smart drugs can basically do three different things to your brain: minimise the damage to thebrain and the natural deterioration of one's brain functions, repair some of the damage alreadydone or enhance brain functions above usual levels[36]. Human nervous system deteriorates with agethrough natural ageing process and sometimes due to drinking or smoking. This deterioration isusually caused by an oxidation process, which destroys brain cells and form free radicals thatcause further havoc in one's brain[37]. Even though brain cells likely cannot regenerate, it is possibleto deactivate free radicals and repair some of the other damage (such as low levels of electriccurrent transmitting chemicals in the brain). And this is can be achieved with smart drugs andsome nutrients, such as vitamins, antioxidants, amino acids, choline and lecithin[38]. Since timeimmemorial, plants have played an integral part in the development of human civilization. Today,interest in the plant products has increased around the globe for health as well as beauty-care.Many plant-based medicines are known to be economic and are found to be free from sideeffects. In India, plant based indigenous knowledge and traditional medicines are being used invarious cultures and tribes[37-42]. The tribal healers inhabiting different remote pockets of India are thereal powerhouse of such knowledge. They perform several healing practices in order to curevarious health disorders. Brahmi, an Ayurvedic herb is known for its effectiveness in enhancingthe memory and promoting the alertness[43]. Brahmi, also known as Bramhi, improves the brain cell

functions and henceused in various mental conditions. Bacopa is also helps you to increase the long and short termmemory[40, 21. 15, 7, 51, 109].This herb has also deals with other health disorders such as brain, memory, mentaldeficiency, learning capacity, depression and stress.This herb is also very effective for heartdiseases and restlessness and also helps to reduce the hair fall problem[49, 70, 3, 33, 115].

Natural memory enhancers

These natural memory enhancers come in three main forms:

Herbs and nutrients: Ginkgo Biloba; phosphatidylserine, a nutrient from soybeans; andpregnenolone, a naturally-occurring hormone; are just a few of the natural supplements that somesuggest can boost your memory[44]. Together they are believed to increase oxygen circulation to thebrain, block against free radicals and promote neural growth.

Foods: Eating the right diet may also increase and help retain your memory's capacity. Leafygreens and cruciferous vegetables like broccoli, cabbage, spinach and Swiss chard arerecommended by some researchers, as are berries, plums, and cherry tomatoes. The Omega-3fatty acids found in fish like salmon, herring, and anchovies are also thought to help memoryretention [45].

Physical acts: challenging your brain with simple exercise can also help your memory accordingto some scientists[47]. Try showering and dressing with your eyes closed, play crosswords or Sudokuin the morning paper, or take a class on an activity or topic you are unfamiliar with, Alone or incombination, these natural memory enhancers may stem the tide of memory loss and maybe evenbring a little back[43, 39].

Herbal formulations for enhancing memory power

- Mix Bacopa monnieri (Brahmi) powder with Saraca indica (Ashoka) bark powder in equal amounts. Administer 5g of this formulation to the patient everyday. This formulation is said to be effective for improving mental clarity, confidence, intelligence and memory recall.
- Eating half cooked Trigonella foenum-graecum (Methi) curry is known to be beneficial for increasing memory power.
- One teaspoon of Asparagus recemosus (Satavari) root powder taken with milk everyday works as an effective memory enhancer.
- To enhance memory power, Kantilla asiatica (Mandukparni) leaves powder (5g), Evolvulus alsinoides (Shankhpushpi) powder (5g), Prunus amygdalus (Badam) seeds (2 nos.) and Elettaria cardamomum (Elaichi) fruit (1 no.) are crushed in water. It should be boiled in milk and taken for 6 months.
- Nardostachys jatamansi (Jatamansi) whole plant powder, Acorus calamus (Ghodavach) rhizomes powder and Centella asiatica (Mandukparni) leaves are taken in equal amount and administered to the patient with honey. This formulation also helps strengthen memory.
- Powder Glycyrrhiza glabra (Mulaithi) roots, Asparagus recemosus (Satavari) roots, Centella asiatica (Mandukparni) and Evolvulus alsinoides (Shankhpushpi) in equal amounts. One teaspoon powder with milk works as memory enhancer.
- Seeds of Saraca indica (Ashoka) should be chewed with Piper betel (Paan-patta) leaf for three weeks for improving intelligence.

Natural memory enhancer herbs

Memory is the ability of an individual to record sensory stimuli, events, information, etc., retainthem over short or long periods of time and recall the same at a later date when needed. PoorMemory, lower retention and slow recall and are common problems in today's stressful andcompetitive world[48-55]. Age, stress, emotions are conditions that may led to memory loss, amnesia,anxiety, high blood pressure, dementia, to more ominous threat like schizophrenia andAlzheimer's diseases. The nature provides a new opportunity to regain one's full mental capacity.A number of herbs traditionally employed in the Indian System of Medicine "Ayurveda", haveyielded positive results.Brahmi (Bacopa monnieri)Brahmi is perhaps the most investigated of all herbs for its memory enhancement properties[56].Now it is certified that brahmi has several chemicals that promote the protein synthesis processin the nerve and the brain cells, which is directly responsible for developing the mental capacityof the brain. Brahmi can make a person think clearer, and hence the memory becomes more vivid[57-58].In India, brahmi is used in countless forms to improve mental capacity for school-going children.Brahmi also increases the grasping power of the brain, due to which people can understand andassimilate information easily.In adults, brahmi helps in relaxing and soothing the cells of the brain, and brings it to a normalstate of functioning. Thus, brahmi is a valuable anti-anxiety agent and an antidepressant. Brahmioil is quite often used to massage the head. This sort of massage immediately puts the mind atrest and the mental abilities rise drastically after its use[59-65]. Prolong stress ultimately caused brain fatigue and initiate a huge ways for the decreased directly not related to brain bur regulated by brain as shown in figure 1.

How Bacopa boost memory

The Bacosides help in restoring the synaptic activity of neuron. On receiving the signals from the sensory organs, the receptors in each neuron of the hippocampus trigger an electric pulse, mediated through a change in protein composition. The pulse is transmitted to the next neuron through the synapse[66]. The process continues till the bonds between the neurons become strong and the memory are created as in fig 2. However, continuous electrical activity wears out the synapses, impairing new memory creation and causing loss of Memory[67-68].

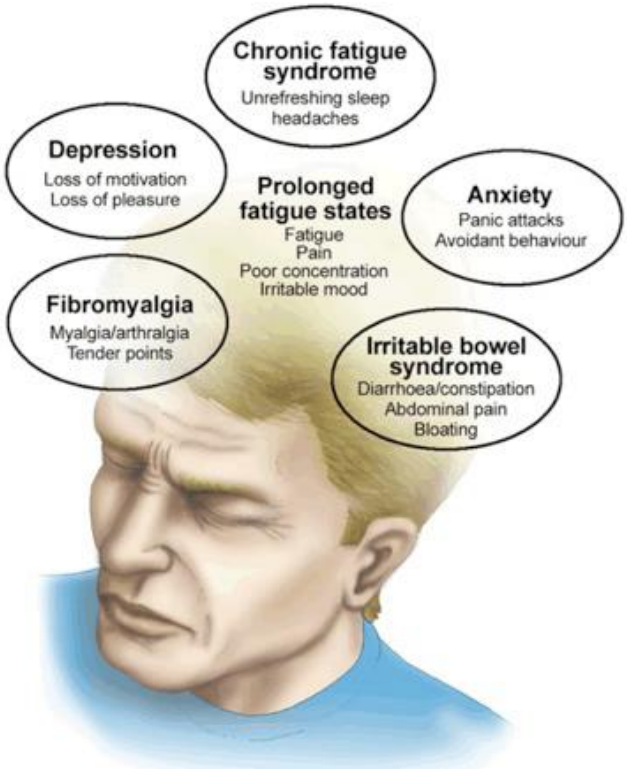

Figure 1: the stress factor and their consequences

Mechanism of memory:

In the left and right temporal sides of the brain hippocampus is situated which works for the signal processing sent to the brain through the senses into the memory templates, subsequently stored in other parts of the brain, which creates a long term remembrance. Due to a rapid alteration in protein composition the signals are changed into electrical impulses in the nerve cells. Through synapses, these impulses happen across neurons by connecting them. Such progression remains in flow in anticipation of the bonds between the nerve cells build upand memory is developed [69]. Neurotransmitters facilitate the normal synaptic activity. Each neuron is a single nerve cell having single or more axons that drive signals to the dendrites. As soon as a signal is transmitted through an axon point, vesicles combine with its membrane and by rupturing of the vessels into the synaptic space the neurotransmitters are released. The axons reabsorb some of the neurotransmitters and the enzymes in the synapse neutralize the other neurotransmitters resulting into the ending of the signals [69]. Thus, the memory is affected by the failure in any part of normal synaptic activity which is generally happens in old age, hence, creation of new memory is impaired and memory failure happens [70]. Reports suggested that the bacoside facilitate in repairing of the damaged neurons due to addition of muscles to kinase protein involved in the replacement of old neurons by synthesizing new ones [71], thus, depleted synaptic activity is renovated and memory is enhanced [72-81].

Mode of action of the Bacoside

1. Learning: An early study employed a sleep deprivation model to investigate the effect of Brahmi on the learning process in rats. When deprived of sleep, the levels of the stress hormone, serotonin, increased. There was also an increase in glutamate levels, while GABA (gamma amino butyric acid), a chemical involved in the transmission of nerve impulses, showed marked reduction [82]. Discrimination learning was significantly reduced following sleep deprivation stress. Brahmi significantly reduced the levels of stress hormones following sleep deprivation and improved discrimination learning in the animals. The authors concluded that Brahmi helps to regulate the altered levels of biogenic amines following stress, thereby improving learning, [83].

2. Memory: An important feature of memory formation in various animal species is its progression from a short-lived labile form to a long lasting stable form, probably by consolidation through a multiphasic pathway [72]. During this period of consolidation, memory can be disrupted by administering agents that induce amnesia. Electroconvulsive shock, hypothermia and hypoxia are conditions that induce retrograde amnesia non-invasively. Other chemical agents (e.g. diethyl-dithio-carbamate) could induce temporary amnesia [84]. Earlier studies on the processing of memory have revealed that memory consolidation involves both serial and parallel processing of information [85].

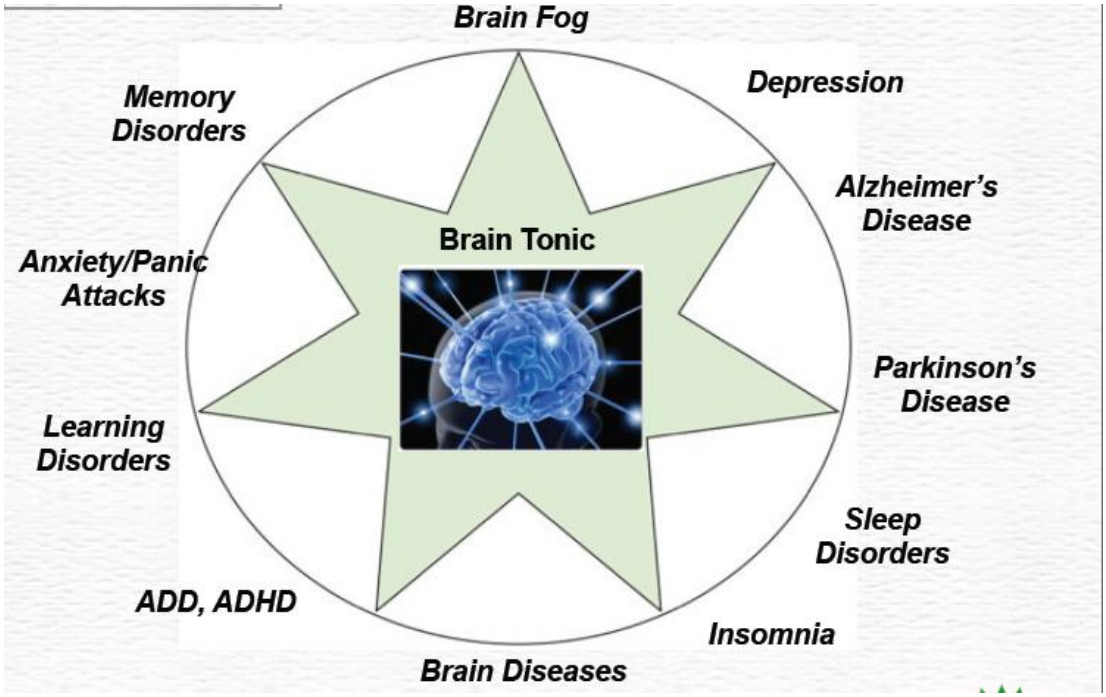

Figure 2: Brain tonic and their mode of action.

Drug preparation of Bacopa:
Preparation: Bacopa is available as an extract in tablet form, tincture, potency and a powder.
Parts used: Leaves, Stems, Root.
Suggested Use: Mix 1 to 2 teaspoons with juice, yogurt or add to your favourite smoothie. It can be used as a decoction and tea.
Actions: Brain tonic, nervine, sedative, antispasmodic, alterative, diuretic, astringent.
Combination: Combined with Ginkgo and Lecithin to improve cognitive function.
Safety And Side Effects: Women who are taking estrogen replacement therapy or who are on birth control pills should not use Brahmi[99-103].

Drug dosing in bacopa:
Bacopa monnieri (linn) is reputed nerve tonic in Ayurvedic literature. Hence, its effect on learning and memory performance of rats has been studied in different conditional schedules, extracts and doses. In a shock motivated brightness-discrimination reaction, the brahmi-treated group showed better acquisition, improved retention and delayed extinction[85-98].
Similarly, in an active conditioned flight reaction, the drug treated animals showed a shorter
reaction time than the controls ($P<0.01$).also, in continuous avoidance response, the drug treated group performed better than the controls ($p< 0.01$-0.05).Their findings are in confirmity with the Ayurvedic claims and with the present study, indicating that *Bacopa monnieri* can improve the performance of rats in various learning situations. Banerjee 1963,[90-100], have found two saponins, bacoside A and B, to improve the performance of rats in several learning tests, same as conducted by Singh and, Dhawan. A new minor triterpene saponin was obtained from *Bacopa monnieri.*
Tripathi and Singh (1996) [101-112] have done clinical evaluation of Smrtisagararasa inschizphrenia patients. Efficacy of Smrtisagararasa, a herbo-mineral preparation containing *Bacopa monnieri* and other drugs in dose of 250 mg tablet given three times a day with honey has shown improvement in memory after three months treatment.

Gupta et.al., (1997) [103]studied activity of Bacopa monnieri in slowing down the memory loss in aged rats. Brahmi in crystalline form in the dose of 1mg/100 g body weight was administered once a day between 9 and 10 AM. Animals were tested in passive avoidance, step through behaviour and concluded brahmi offset this latency and led to improvement at the geriatric level (15 and 21 months).

Sharma et.al., (1984)[84] have studied the efficacy of *Bacopa monnieri* in revitalizing intellectual function in children. To study the memory enhancement effect, the drug was given inboth sexes. Whole plant-extract with dose of 1.05 g/kg by oral route and found to be active.

The chemical constituents responsible for the facilitatory effect of brahmi on learning schedules were identified-as a mixture of two saponins designated as bacoside A and B.[85] The bacosides significantly improve the acquisition, consolidation and retention in the shock motivated brightness discrimination response, active conditional avoidance response and produce a dosedependent, facilitation of discre!ion between aversive (LILI) and palatable fluid in conditioned taste aversion response. Bacosides also attenuated the retrograde amnesia produced by immobilization induced stress, ECS and scopalamine. They also enhanced protein kinase activityand produced an increase in protein in hippocampus.[85]

Bacosides were also found to be safe in regulating pharmacological and toxicological studies and were well tolerated by normal healthy male human volunteers in single dose (20-300 mg) and multiple doses (100 and 200 mg) administered for 4 weeks in double blind placebo controlled and non cross over regulatory phase-1 clinical trial[86, 87].

Effects on learning and memory performance of rats have been studied in two parameters by administering an aqueous (0.3% carboxy methyl cellulose) suspension of aqueous and methanolic extract of leaf, stem and whole plant with dose 100 mg/kg and 50 mg/kg (P.O.) for 5days[88].Both the parameters, retention in elevated plus maze and retention in passive avoidance step through behaviour were performed better in drug treated animals. 100 mg/kg methanolic and water extracts of leaf and stem improved latency and retention (P< O.Ol). In both the parameters, methanolic extract treated group performed better than the water extract treated group. Observations showed that extract of leaf and stem have more significant activity as compared to whole plant extract and out of these, methanolic and water extracts of stem are more significant than leaves.50 mg/kg methanolic and water extracts performed better but found to be less significant when compared to 100 mg/kg dose (P<O.Ol - 0.05). The activity of leaf and stem extracts were significant upto 9th day, which was not observed in whole plant extract [89].Retention in passive avoidance study with 100 mg/kg dose of leaf and stem extracts showed long term activity, while retention in elevated plus maze is helpful for short term memory.

Substituents and Adulterants

Bacopa monnieri is often substituted and confused with Centella asiatica since both the plants are considered as 'Medhya rasayanas' (brain tonic) in Ayurveda and possess the same vernacular name Brahmi [27]. However, these plantsdiffer in their therapeutic properties and chemical constituents. In ancient Sanskritwritings, B. monnieri was known as Brahmi, Jala-brahmi or water-brahmi whereas the name Mandukaparni was assigned to C. asiatica [66]. Brahmi is used totreat specific mental disorders such as insanity and epilepsy [89],while Mandukaparni is a general rejuvenative tonic which improves mental health[90].

The Charak Samhita considers them as promoters of cognitive functions, but itsuggests that Brahmi is superior to Mandukaparni [17]. Chemically both species are rich in saponins, Bacoside A and B from B. monnieri and Made cassoside and Asiaticoside from C. asiatica (Sukhdev, 2006). The Sushruta Samhita also defines the properties of the herbs wherein Brahmi belongs to tikta rasa (bitter), while Mandukaparni belongs to kasaya rasa (astringent) [112].

Mandukaparni is cooling, making it better for pitta whereas Brahmi is warming, indicated in kapha/vata. Mandukaparni is also indicated in skin issues and for wound healing, whereas Brahmi has additional properties for helping throat and lung infections [113].

Ayurvedic preparations

B. monnieri forms the basis for many commercial Ayurvedic preparations like Brahmi ghrita (in clarified butter), Sarasvatarishta (a decoction used as brain tonic),Brahmi rasayana (a rejuvenating formulation), Brahmitaila (medicated oil) and Brahmi Sarbat/ Brahmi Panaka (a cooling drink usually used in summer) available in Indian markets due to its therapeutic values (37, 85). Other commercial formulations containing extracts of the herb include Brahmi Vati (tablet containing powders of Brahmi, other herbs and minerals), Brahmi Capsules, Memokriti Capsules, Brain-Act Capsules, Baco Mind, Brain-Fit (Herbal Fit for Brain),Memory Booster, Mind Power, More Memory Capsules, etc.

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