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Correspondence concerning this article should be addressed to Navneet Kumar, MD, 4610, Cimarron Drive, Bloomfield Hills, MI, USA. Zip 48032. Email: drnavneetkumar@gmail.com

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Effect of *Bacopa monnieri* on Cognitive functions in Alzheimer's disease patients

Shishir Goswami (1), Anand Saoji (2), Navneet Kumar (3) *, Vijay Thawani (4), Meenal Tiwari (5), Manasi Thawani (6)

(1) BAMS, Ayurvedacharya, 8, Bhande plot, Umred road, Nagpur, Maharashtra, India 440 024.

(2) MD, Lecturer, Psychiatry Department, Government Medical College & Hospital, Nagpur, Medical Chowk, Maharashtra, India 440003 (GMCHN).

(3) MD, Resident, Transitional Year, Providence Hospital & Medical Center, Southfield, MI, USA 48075.

(4) MD, Professor and Head, Pharmacology Department, VCSGGMSRI, Srikot, Srinagar, Pauri-Garhwal, Uttarakhand, India 246174.

(5) MBBS, GMCHN, India.

(6) MBBS, Jawaharlal Nehru Medical College, Sawangi, Wardha, India.

* Corresponding author; Email: drnavneetkumar@gmail.com

ABSTRACT

Background: Alzheimer's disease is a degenerative condition mostly affecting the elderly. It significantly affects the patient's quality of life. So far there is no proven effective therapeutic intervention for such patients. *Bacopa monnieri* is an indigenous plant which is found throughout India. It has been referred in Ayurveda since centuries as a "Medhya Rasayan" (nootropic). Studies have shown various effects of *Bacopa monnieri* among which is its inhibitory effect on the enzyme cholinesterase. This can result in decrease in the breakdown of acetylcholine, an important neurotransmitter whose decreased levels are seen in Alzheimer's disease.

Aims & Objectives: We conducted this study to evaluate the effect of *Bacopa monnieri* on cognitive functions in Alzheimer's disease patients.

Study Design: This was an open label, prospective, uncontrolled, non-randomized trial. Study population included all newly diagnosed patients of Alzheimer's disease in the Psychiatry Outdoor Patient Department between 60-65 years of age. Baseline scores on Mini Mental State Examination Scale (MMSES) were recorded for all patients. Subsequently all patients took 300 mg of *Bacopa monnieri* standardized extract (Bacognize®) orally twice a day for 6 months. MMSES scores were recorded again after the completion of study drug.

Results: Mean age of 39 patients who completed the study was 65.23 years. Study patients showed statistically significant improvements in various components of MMSES including orientation of time, place & person, attention and in their language component in terms of reading, writing & comprehension at the end of trial. The patients involved in this trial also reported improvement in their quality of life, and decrease in the irritability and insomnia.

Conclusion: The results of our clinical trial show that *Bacopa monnieri* standardized extract (Bacognize® 300 mg twice a day orally) for 6 months results in improvement in some aspects of cognitive functions in geriatric patients suffering from Alzheimer's disease. While the above results are encouraging given the improvement in cognitive functions in geriatric Alzheimer's disease patients, further studies that include a control group are required to validate these results.

Keywords: Brahmi, memory improvement, MMSES score, dementia, Bacognize®

Running head: BACOPA MONNIERI IN ALZHEIMER'S DISEASE

Introduction

Alzheimer's disease is a neurodegenerative disorder of uncertain cause and pathogenesis. It mostly affects the elderly. In mild cases it results in forgetfulness and as the disease progresses it affects both short and long term memory. It is commonest cause of dementia in elderly, responsible for approximately 60-80 percent of cases¹⁻⁴. It has significant effect on quality of life. Currently available treatments can modulate the disease course and ameliorate some symptoms but no proven effective therapeutic cure for Alzheimer has been identified to date.

Bacopa monnieri (synonyms – *Bacopa monniera*, *Herpestis monniera*), family Scrophuliaceae^{5,6}, also known as 'Brahmi', is an indigenous plant, found throughout India, Nepal, Sri Lanka, China, Taiwan, Vietnam and Florida, Hawaii and some other southern states of USA. It has been referred in Ayurveda since centuries as a 'Medhya Rasayan'⁶. *Bacopa* is a small tropical, creeping, succulent, marshy herb with short, petiolated, oblong leaves, rooting at nodes. Stem is 10-30 cm long, 1-2 mm thick, with soft, glabrous ascending branches. Leaves are 0.6-2.5cm long and 3-8mm broad. Flowers are blue or white with purple veins, axillary and solitary on long pedicels. Capsule is ovoid, glabrous, up to 5mm long. It has no distinct odor but taste is slightly bitter⁵. It has been used as a brain tonic for improvement of memory and concentration⁷ and for the treatment of mental illness and epilepsy⁶. *Bacopa*'s main chemical constituents include alkaloids brahmine, herpestine and nicotine, saponin monierin, hersaponin⁸, bacoside A1⁸, A2⁹, A3¹⁰ and B¹¹ and four saponin bacoside A1 to A4¹². It is known to be safe and well tolerated in humans^{13,14}. In a phase I study, bacoside A and B were found to be well tolerated in both single dose (20-300 mg) and multiple doses (100-200 mg) for 4 weeks by healthy human subjects¹³.

Many clinical studies of *Bacopa*'s actions on various systems have been published. *Bacopa* methanol extract has dose dependent free radical scavenging capacity and protective effect on DNA cleavage¹⁴. Its antioxidant property is postulated to be responsible for its antistress, immunomodulatory, cognition fascilatory, anti-inflammatory and anti-aging effects. Its anti lipid peroxidation property has been credited with memory enhancing and sedative actions. It is recommended for its efficacy in low doses for long term therapy rather than a single high dose¹⁵. *Bacopa* has been used to maintain youthful vitality and longevity. Ayurveda describes it as cold, bitter, astringent, digestive, carminative, laxative, diuretic, anti-inflammatory, depurative, bronchodilator, anticonvulsant and tonic for heart and nerves^{5,6}. Its anxiolytic action is comparable to benzodiazepine in animal models of clinical anxiety¹⁶. No significant motor deficits were seen with its anxiolytic doses.

Bacopa has been shown to reduce beta-amyloid deposits in the brain of animal models of Alzheimer's disease¹⁷. It has significant memory-promoting effect¹¹. It improves acquisition, retention and retrieval of learned tasks^{18,19}.

Brahmi Rasayan, an Ayurvedic preparation having *Bacopa* as the major ingredient, had anti-inflammatory actions in large oral doses in animal models of inflammation²⁰. Brahmi ghrita, an Ayurvedic formulation significantly improved latency in Elevated Plus Maze in rats²¹.

Another rodent study showed that *Bacopa* has inhibitory effects on the enzyme cholinesterase, thereby decreasing the breakdown of acetylcholine- an important neurotransmitter whose decreased levels are seen in Alzheimer's disease thereby leading to dementia²².

However the efficacy of *Bacopa monnieri* in geriatric age group having Alzheimer's disease has not been reported. Another clinical

trial done at Government Medical College and Hospital, Nagpur, India (GMCHN) by us showed effective improvement in memory of medical students²³. Thus the current trial was planned to see whether the drug is effective on the geriatric patients suffering from Alzheimer's disease.

Material & Methods

This was an open label, prospective, uncontrolled, non-randomized trial which was started after the approval of Institutional Ethics Committee.

Standardized extract of *Bacopa monnieri* (Bacognize[®]) was obtained from M/s Pharmanza Herbal Pvt Ltd., Gujarat, India. Aerial parts of *Bacopa monnieri* were collected from Banks of Howrah River, Kolkata, India. Herb was authenticated by Botanical Survey of India, Jodhpur, India. It was further confirmed by methods given in Indian Pharmacopeia. Plant material was washed with water. After discarding water the material was dried at 50 °C for 12 hours. Dry material was extracted with 4 volumes of methanol twice at 60 °C. The methanol extract was concentrated and the material was spray dried to get powder. The extract contained 45% *Bacopa* saponins when analyzed using UV spectrophotometer²⁴. The dosage form was also analyzed using HPLC-PDA (Shimadzu 1100 series). The analytical column (Phenomenex, LUNA C18 (2), 5u150X4.6) was used with mobile phase (MP) comprising of 0.1% Trifluoro acetic acid in Acetonitrile, 0.1% Trifluoro acetic acid in Water (35 : 65 v/v), under isocratic mode of separation. The injection volume was 20 µL, with run time 15 minutes, flow rate 1.5 mL/min and detector wavelength set at 205nm. Autosampler carry-over was determined by first injecting the highest calibration standard before a blank sample. Negligible carry-over was observed, as

indicated by the lack of *Bacopa* glycosides peaks in the blank sample. A 5mg/mL concentration sample of standardized *Bacopa monnieri* extract was prepared in methanol and analyzed. Standards for Bacoside A3, Bacoside II, Bacopaside X and Bacopasaponins C were obtained from Chromadex USA. Total of four bacosides were 11.38% by HPLC (Table 1 and Figure 1).

Trial recruitment ran for a period of six months. Psychiatrist for the trial diagnosed new patients of Alzheimer's disease from Psychiatry OPD, GMCHN above the age of 50 years, of either gender. The patients were screened for hypertension and diabetes. Patients and accompanying relative were informed about the details of the trial. All their queries were satisfactorily answered. Well informed, written consent was taken from the patients in the presence of the psychiatrist who ensured that the patient was competent to give his/ her consent. The treatment schedule was explained in detail to both the patient and the caretaker. The patients were then administered Mini Mental State Examination Scale (MMSES) for baseline scores. We used MMSES as it is a simple test for cognitive functions, which we felt is fit for our study as this is the first human study being done to gather data regarding effect of *Bacopa monnieri* on Alzheimer's disease patients. Patients were then asked to take orally one tablet of *Bacopa monnieri* extract (Bacognize[®]) 300 mg, twice daily for 20 days and return back for review with the medicine bottle. During compliance review pill count was done and patients and their caregivers were asked regarding any type of change seen in their life. Compliance issues were also addressed during each visit. Such reviews continued for total duration of drug administration of 180 days. 80% medicine consumption was considered as compliant. MMSES was re-administered after completion of the total run- in phase. Statistical analysis

was done using Wilcoxon Signed Ranks test with the help of institutional statisticians using SPSS v12 software.

Results

Total 50 patients gave consent for the trial during the recruitment period. Of them 2 patients died before the completion of trial and 9 patients were lost in follow up. Thus 39 patients completed the trial, of which one was illiterate and hence could not participate in the design component of the MMSES. However this patient was considered for evaluation for other parameters of MMSES. 15 participants were male while the rest 24 were female. All these 39 patients were compliant.

The mean age of study patients was 65.23 ± 6.67 years (Table 2). Mean ages of men and women in the trial were 63.63 ± 5.2 years and 67.80 ± 8.06 years respectively. Mann-Whitney test showed no significant difference between them with respect to age.

Statistical analysis revealed that the patient showed significant improvement ($p < 0.001$) in their MMSES scores after drug administration. MMSES component analysis showed that patients had significant improvements in orientation of time, place and person and attention component. Language component of the test also showed improvement in terms of reading, writing and comprehension (Table 3 and Figure 2).

Other components of MMSES like registration, recall and design were statistically insignificant on pre-post drug comparison.

Furthermore we stratified the patients into two groups with respect to gender. Statistical analysis showed that women showed more statistically significant improvements in orientation, attention and language components of MMSES as compared to men (Table 4).

During the trial, patients and their caregivers also reported improvement in their quality of life, increase in the memory power, decrease in irritability and sleeplessness, and some even reported positive changes in their behavior towards the family.

Discussion

The effects of *Bacopa monnieri* are time tested. The physicians from ancient time have used *Bacopa monnieri* for different psychological disorders including dementia and insomnia. It is reported to improve the quality of health and increase memory in all age groups.

Researchers are trying to find effective medicines for Alzheimer's disease. But so far none of the studies have shown an effective herbal medicine alternative to improve cognitive functions in Alzheimer's disease. Recently a study tested apple juice, but the trial showed that it only improved behavioral but not cognitive symptoms in Alzheimer's disease patients²⁵.

The results of our clinical trial are highly encouraging. It shows improvement of various components of cognitive functions in geriatric patients suffering from Alzheimer's disease who took *Bacopa monnieri* for six months.

We realize that we used a very crude yet simple measure for cognitive functions (MMSES). But since this is the first study to test *Bacopa monnieri* in Alzheimer's disease patients we thought that it would provide valuable data needed for further detailed studies.

Other limitations of our study include open label study design and lack of control, randomization and control of other confounding factors.

But still we feel that this is the first human study which showed improvement in cognitive functions in Alzheimer's disease patients receiving *Bacopa monnieri* extract. Elaborate

objective and subjective tests which can assess multiple cognitive domains would be highly useful in future studies. Also studies need to be done to compare *Bacopa monnieri* with the established medications for Alzheimer's disease. These detailed studies need to be done in future to fully evaluate the potential of *Bacopa monnieri* in Alzheimer's disease patients.

The patients involved in this trial also reported improvement in their quality of life, decrease in irritability and insomnia. But since these were incidental findings, it is desired that further exploration needs to be done for proving these scientifically so that Alzheimer's disease patients can have a potential natural alternative available for their illness.

Furthermore since *Bacopa monnieri* has shown beneficial effects in Alzheimer's patients, it can be tried in future studies in other types of dementias, like multi infarct dementia or Lewy Body Dementia, thereby shedding new light on this age old "Medhya Rasayan".

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Conflict of Interest

Authors have no conflict of interest in this trial. No funding was obtained for this trial. Raw data of this trial or the results have not been made available to the pharmaceutical company which supplied the medicines.

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Table 1: HPLC Analytical data of standardized *Bacopa monnieri* extract (Bacognize®) used in the trial

ANALYTES	RESULT	UNIT
Bacoside A3	4.57	%w/w
Bacopaside II	2.13	%w/w
Bacopaside X	1.70	%w/w
Bacopasaponin C	2.98	%w/w
Total Bacopasaponin [Identified]	11.38	%w/w
Total Bacopasaponin [Identified + unidentified]	15.57	%w/w

Table 2: Age distribution of study patients

	n	Mean age (years)	SD
Men	15	67.8	8.06
Women	24	63.63	5.2
Total	39	65.23	6.67

Table 3: Effect of standardized *Bacopa monnieri* extract (Bacognize®) on Mini Mental State Examination Scale (MMSES) (mean score \pm standard deviation)

MMSES component	Pre Drug	Post Drug	'p' value[#]
Orientation (n=39)	5.33 \pm 2.27	6.9 \pm 2.4	<0.001*
Registration (n=39)	2.77 \pm 0.63	2.64 \pm 0.78	>0.05
Attention (n=39)	1.82 \pm 1.83	3.15 \pm 2.44	<0.001*
Recall (n=39)	2.18 \pm 0.82	2.03 \pm 1.18	>0.05
Language (n=39)	6.33 \pm 1.78	8.41 \pm 2.57	<0.001*
Design (n=38)	0.74 \pm 0.44	0.71 \pm 0.46	>0.05
Total Score	19.15 \pm 4.54	23.85 \pm 7.61	<0.001*

#On comparing pre and post drug scores of MMSES of patients receiving *Bacopa monnieri* by using **Wilcoxon Signed Ranks test**.

*Statistically significant.

Table 4: Gender analysis of effect of standardized *Bacopa monnieri* extract (Bacognize®) on Mini Mental State Examination Scale (MMSES) (mean score \pm standard deviation)

MMSES component	Pre Drug	Post Drug	'p' value#
Orientation			
Men (n=15)	5.33 \pm 1.77	7.13 \pm 2.36	<0.01*
Women (n=24)	5.21 \pm 2.57	6.75 \pm 2.42	<0.001*
Registration			
Men (n=15)	2.87 \pm 0.52	2.67 \pm 0.82	>0.05
Women (n=24)	2.71 \pm 0.69	2.62 \pm 0.77	>0.05
Attention			
Men (n=15)	1.47 \pm 1.64	3.13 \pm 2.97	<0.05*
Women (n=24)	2.04 \pm 1.94	3.17 \pm 2.12	<0.01*
Recall			
Men (n=15)	2.27 \pm 0.70	1.60 \pm 1.30	>0.05
Women (n=24)	2.12 \pm 0.90	2.29 \pm 1.04	>0.05
Language			
Men (n=15)	6.07 \pm 1.83	8.27 \pm 3.10	<0.01*
Women (n=24)	6.50 \pm 1.77	8.50 \pm 2.24	<0.001*
Design			
Men (n=15)	0.80 \pm 0.41	0.73 \pm 0.46	>0.05
Women (n=23)	0.70 \pm 0.47	0.70 \pm 0.47	>0.05
Total Score			
Men (n=15)	19.00 \pm 3.34	23.53 \pm 8.77	<0.05*
Women (n=24)	19.25 \pm 5.22	24.04 \pm 6.98	<0.001*

On comparing pre and post drug scores of MMSES of patients receiving *Bacopa monnieri* by using **Wilcoxon Signed Ranks test**.

*Statistically significant.

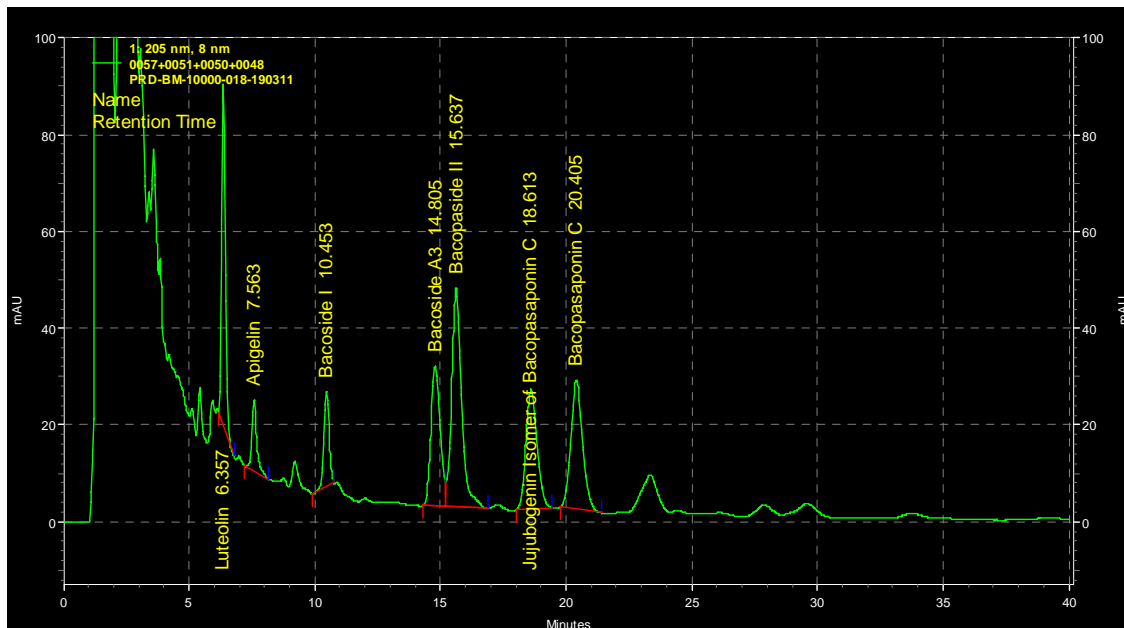


Figure 1: HPLC Fingerprint of standardized *Bacopa monnieri* extract (Bacognize[®]) used in the trial

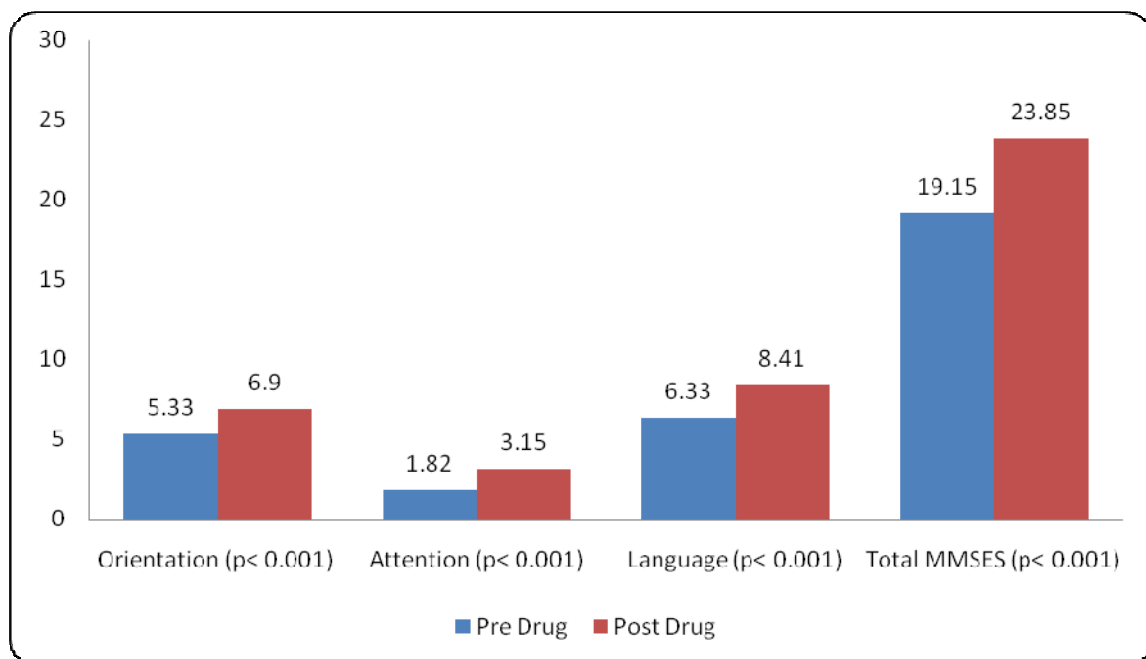


Figure 2: Effect of standardized *Bacopa monnieri* extract (Bacognize[®]) on different components of Mini Mental State Examination Scale (MMSES) (n= 39)