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Efficacy and Tolerability of BacoMind® on Memory Improvement in Elderly Participants - A Double Blind Placebo Controlled Study

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Abstract: A randomized double blind placebo controlled study was designed to evaluate the efficacy and tolerability of BacoMind®, an enriched phytochemical composition from *Bacopa monnieri* on memory improvement upon chronic administration in elderly subjects as memory loss in elderly people is one of the leading health problems worldwide and its uncertain recovery with conventional therapies has paved way to elucidate the use of complementary and alternative system of medicine. Elderly individuals with mini mental state examination score of twenty four and above were enrolled. BacoMind® or placebo was given as a single oral dose of 450 mg daily for the duration of 12 weeks. The combination of well established battery of neuropsychological tests revealed that BacoMind® improved performance in tests associated with attention and verbal memory in elderly participants. Significant interaction effects between group and time were observed in digit span backward test ($p = 0.008$), list learning delayed recall test ($p = 0.014$), paired associates dissimilar delayed recall test ($p = 0.047$) and in visual retention-I test ($p = 0.035$). In conclusion, the study findings suggested that BacoMind® improved the cognitive functions such as attention and verbal memory in elderly individuals and was also found to be well tolerated.

Key words: BacoMind®, *Bacopa monnieri*, memory, efficacy, tolerability, elderly participants

INTRODUCTION

Cognitive impairment is an important clinical issue among elderly, reported as occurring in almost half of the population aged over 65 years (Small, 2002). The prevalence of dementia doubles every five years in senior population, so that by age 85 about 50% of the individuals develop some degree of cognitive impairment (Lyons *et al.*, 2001). Based on the severity, there are three main forms of memory loss viz., Age Associated Memory Impairment (AAMI), Mild Cognitive Impairment (MCI) and Dementia in the ascending order.

Due to the chronic and progressive nature of neurodegenerative disorders and poor satisfaction with the conventional therapy, the complementary and alternative systems of medicine seems to be promising and acceptable. Several Indian medicinal plants have claimed to improve memory function (Mukherjee *et al.*, 2007) and one such herb that holds great promise for the improvement of cognitive function is *Bacopa monnieri* Linn. (*B. monnieri*), known commonly as either Brahmi or water hyssop. *B. monnieri* is commonly available in India and has a long history of use as a traditional Ayurvedic medicine documented in the treatment of memory disorders, anxiety, epilepsy and insomnia (Russo and Borrelli, 2005).

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The historic use of *B. monnieri* has incited numerous preclinical and clinical studies as an effort to scientifically validate the claims. The acquisition and retention of memory (Singh and Dhawan, 1992, 1997; Vohora *et al.*, 2000) provided the scientific evidence for the neuropharmacological response on learning and memory. Kasture *et al.* (2007) reported that BacoMind™, an enriched phytochemical composition from *Bacopa monnieri*, significantly increased the discrimination index in both normal as well as scopolamine treated rats in object recognition test.

The memory enhancing effects were linked to the active constituents, saponins (bacosides) which have a facilitatory effect on memory retention (Singh *et al.*, 1988). It was postulated that *B. monnieri* contributed to cognitive function by its modulatory effects on cholinergic system and antioxidant effects on hippocampus, frontal cortex and striatum (Bhattacharya *et al.*, 2000). The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, restoration of synaptic activity and nerve impulse transmission (Singh and Dhawan, 1997). *In vitro* research revealed that *B. monnieri* exerted a protective effect against DNA damage in astrocytes (Russo *et al.*, 2003a) and human fibroblasts (Russo *et al.*, 2003b). Identification of phytoconstituent bacoside A, the putative bioactive component was found to be a mixture of four major saponins and an HPLC method together with an optimizing procedure was developed for the standardization and estimation of bacosides (Deepak and Amit, 2004; Deepak *et al.*, 2005).

BacoMind™ on single oral administration showed a median lethal dose of 2400 mg kg^{-1} b.wt. in Sprague-Dawley rats and did not show any marked and treatment related signs of toxicity on oral administration daily for 90 days up to a dose of 500 mg kg^{-1} b.wt. The no-observed adverse effect level (NOAEL) for BacoMind™, in the 90 day subchronic toxicity study was found to be 500 mg kg^{-1} b.wt. (Joshua *et al.*, 2007). No incidence of genotoxicity was reported with BacoMind™ treatment in Ames, Chromosomal aberration assay and Micronucleus test (Dipanwita *et al.*, 2008).

Clinical studies on *B. monnieri* for cognition improvement further supported the preclinical data. A double blind controlled study on the effect of a micro medicine derived from *B. monnieri* was reported to enhance memory (direct), arithmetic skill and some verbal factors in students of average intelligence (Abhang, 1993). Sharma *et al.* (1987) suggested *B. monnieri* as a useful agent for renovating and revitalising intellectual behaviour in children. A double-blind, placebo-controlled independent group design study showed that Keenmind, a standardized extract of *B. monniera* (300 mg) given for 12 weeks improved early information processing, verbal learning and memory consolidation in humans (Stough *et al.*, 2001). A pilot study was conducted to evaluate the safety and tolerability of BacoMind® in elderly volunteers. Each individual received 300 mg capsule for initial 14 days followed by 450 mg for the next 14 days as a single daily dose. Detailed clinical examination, routine haematology, serum biochemistry and urinalysis revealed no abnormalities. No signs of neurological adverse effects were reported. Also the safety evaluation of BacoMind™ in healthy volunteers, given one single capsule daily for 30 days (300 mg for first 15 days and 450 mg for next 15 days), did not indicate any untoward effects in detailed examination of clinical, haematological, biochemical and electrocardiographic parameters in pre and post treatment periods (Pravina *et al.*, 2007).

The present study was planned with the primary objective of evaluating the clinical efficacy of BacoMind®, on impaired memory in elderly individuals. The secondary objective was to evaluate the safety and tolerability of BacoMind® in elderly individuals.

MATERIALS AND METHODS

Study Design

The study utilized a randomized double blind placebo controlled study with two parallel arms as BacoMind® and placebo treated groups. Institutional Ethical Committee (IEC) approval was obtained. The study was conducted as an outpatient procedure between May 2004 and February 2005.

Test Substance

BacoMind®, an enriched phytochemical composition of *B. monnieri* developed by Natural Remedies Pvt. Ltd., (patent pending) was standardized to the content of the following bioactive constituents viz., bacoside A_3 (>5.0% w/w), bacopaside I (>7.0% w/w), bacopaside II (>5.5% w/w), jujubogenin isomer of bacopasaponin C (>7.0% w/w), bacopasaponin C (>4.5% w/w), bacosine (>1.5% w/w), luteolin (>0.2% w/w), β-sitosterol-D-glucoside (>0.3% w/w) and apigenin (>0.1% w/w). It was further standardized using the following *in vitro* bioassays viz., lipoxygenase inhibition assay ($IC_{50} < 600$ μg mL^{-1}), ABTS radical scavenging assay ($IC_{50} < 100$ μg mL^{-1}), DPPH assay ($IC_{50} < 200$ μg mL^{-1}) and butyrylcholinesterase inhibition assay ($IC_{50} < 3000$ μg mL^{-1}).

Participants

A total of 65 (42 males and 23 females) individuals aged between 50-75 years (age mean±SD; 64.98±9.37) were enrolled for the study following informed written consent. Demographic information of subject is presented in Table 1. The participants were recruited strictly based on the selection criteria.

Inclusion Criteria

Elderly persons aged between 50-75 years with complaint of memory impairment for at least one year without any major cognitive deficit based on Mini Mental State Examination (MMSE) were deemed suitable.

Exclusion Criteria

Individuals with any pre-existing physical or psychiatric disorders were not included. Persons with alcohol and drug addiction liabilities were excluded. Participants with any severe infections in past 30 days or with significant renal, respiratory, cardiac, gastro-intestinal, hepatic, endocrine or haematological disorders were not selected. Individuals with severe cognitive problems like dementia, functional disability, post vascular cerebral symptoms or any neurological deficit were excluded from participation. Individuals with neuroimaging evidence of vascular or hippocampal shrinkage / atrophy or with any other medical conditions which in the view of the investigator would make the patient not participate fully, were also excluded.

Procedure

The study was conducted for a total duration of 24 weeks, wherein the test medication was administered for the first 12 weeks; thereafter, medication was discontinued and a subsequent duration of 12 weeks was kept as withdrawal period. Detailed clinical examination including neuropsychological testing along with routine laboratory investigations were conducted on week 0 and week 12. On 24th week clinical examination along with the battery of neuropsychological tests were repeated.

Allocation of participants was based on randomization table. The study investigator, who was responsible for enrollment of the participants was blinded to the treatment and assigned the test substance to the participants. Study medication (BacoMind® or placebo) was provided in coded bottles. Each capsule of BacoMind® contained 450 mg of standardized extract of *B. monnieri*. The placebo medication matched the test substance in every aspect except for the presence of actives. All the participants were instructed to take one capsule of BacoMind® or placebo with a glass of water after the breakfast as a single dose daily for the duration of first 12 weeks. There was no restriction placed on routine activity or diet during the study period. Patients were permitted to continue the concomitant medication under the supervision of investigator. A regular follow up was done every fortnight upto 12 weeks and a final follow up was conducted on 24th week. In each follow up visit, along with medical examination the participants were enquired about compliance of medication, adverse events and willingness to continue the participation. If confirmed, they were provided the next

container of 14 capsules. The compliance of study medication was ensured by counting the remaining capsules in the container along with the recording in the medication compliance card (MCC). Individuals taking 85% of study medication up to 12 weeks of treatment were considered to be compliant with therapy.

Neuropsychological Tests

Each participant was initially subjected to MMSE only at baseline, followed by the battery of neuropsychological tests on all three occasions.

MMSE was developed by Indo-US-Cross-National Dementia Epidemiology Study and was scored in the range of 0-30 scale. MMSE was conducted at week 0 to assess the baseline cognitive functions and to detect any intellectual deficits in participants. The elderly individuals with minimum score of 24 and above indicating cognitive fitness were chosen as lesser scores were indicative of probable cognitive impairment such as dementia, Alzheimer's disease, etc. A combination of well established battery of auditory and visual neuropsychological tests was chosen to evaluate the attention, memory and speed of information processing. The memory tests were designed by Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, modified for geriatric population. The construction and standardization of these tests were based on Rey's Auditory Verbal Learning Test (RAVLT) (Rey, 1964) and Weschler Memory Scale - I (WMS - I). All the tests were explained to the participants by the psychologist and uniformity in timing was maintained in all three occasions.

The battery of neuropsychological tests evaluated three main domains of memory functions in elderly persons:

Attention Tests

- Digit span forward and backward (Wechsler Adult Intelligence Scale; WAIS)
- Digit cancellation test
- Serial substraction test

Memory Verbal

- List learning (RAVLT) - Immediate and delayed recall
- Passages (WMS - I) - Immediate and delayed recall
- Paired associates-Similar and dissimilar pairs- Immediate and delayed recall
- Visual retention I (based on designs)
- Visual retention II (based on pictures)

Speed of Information Processing

- Digit Symbol (WAIS)

The objectives of the tests were to assess either the accuracy or the speed of performance as per the test guidelines and the performances were reported as scores.

Adverse Events Monitoring

Every case was closely monitored for adverse events in each follow up visit throughout the study period. Any adverse events either reported voluntarily by subjects or explored by the investigator were documented.

Statistics

All the values were expressed as mean±SEM. The results of each of the neuropsychological tests were analyzed using repeated measures of analysis of variance (RMANOVA) for both placebo and BacoMind® treated groups to compare the scores at 0, 12 and 24th weeks for each treatment group. In places wherein significance in time was observed, students paired t-test was used to analyse which time intervals differed significantly. The statistical significance was set at $p \leq 0.05$.

RESULTS

A total of 65 elderly individuals were recruited for the study and in that three subjects (one in placebo and two in BacoMind®) were not present for the second visit and hence no medication was dispensed. Out of 62 participants, 59 (37 males and 22 females) participated till the completion of the trial and 15 subjects were outliered. Finally 44 (21 in placebo and 23 in BacoMind®) participants were analysed for statistics (Table 1).

Neuropsychological Tests
Attention

The results of analysis showed a significant interaction effect between group and time (df = 2,84; F = 5.093; p = 0.008) in digit span backward task. A significant time effect (df = 2,84; F = 7.655; p = 0.001) was observed in digit cancellation time test between 0 and 12th week (p = 0.025) and 0 and 24th week (p = 0.001). Similarly digit cancellation error also showed significant time effect (df = 2,84; F = 7.640; p = 0.001) between 0 and 24th week (p = 0.000) and 12 and 24th week (p = 0.005) (Table 2).

Memory Verbal

A significant interaction effect between group and time (df = 2,84; F = 4.493; p = 0.014) was revealed in list learning delayed recall, paired associates dissimilar delayed recall test (df = 2,84; F = 3.182; p = 0.047) and in visual retention-I test (df = 2,84; F = 3.477; p = 0.035).

There was significant time effect observed in list learning delayed recall (df = 2,84; F = 3.954; p = 0.023) between 0 and 24th week (p = 0.005). A significant improvement (df = 2,84; F = 3.150; p = 0.048) between 0 and 12th week (p = 0.028) was seen in visual retention - I test (Table 2).

Clinical evaluation of general physical characteristics and systemic examination at different time intervals revealed no abnormalities. The vital parameters were reported within normal limits in both placebo and BacoMind® treated individuals. Haematological investigations done at 0 and 12th week in BacoMind® and placebo treated groups were within normal limits and no significant difference noted except for marginal increase in haemoglobin values ($p \leq 0.05$) and decrease in the lymphocytes values ($p \leq 0.05$) in BacoMind® treated group, but both were found to be within normal limits (Table 3). The placebo group showed slight increase in the monocytes ($p \leq 0.05$) but was found to be within normal range. Peripheral smear showed a normal picture of blood cells. The compliance of study medication was satisfactory throughout the study.

Table 1: Demographic information

Particulars	BacoMind®	Placebo
Participants	23	21
Age (mean±SD)	65.52±8.79	62.86±10.61
Sex (M/F)	14/09	15/06

Table 2: Effect of BacoMind® on battery of neuropsychological tests in elderly individuals

Tasks	Groups	0th week	12th week	24th week	Variables	df	F-value	p-value
Attention								
Digit span	P	4.86±0.28	5.05±0.29	5.24±0.21	Group	1,42	0.600	0.443
Forward	B	5.26±0.18	5.30±0.17	5.17±0.16	Time	2,84	0.571	0.567
					Group×Time	2,84	1.356	0.263
Digit span	P	3.33±0.23	3.00±0.24	3.48±0.25	Group	1,42	0.537	0.468
Backward	B	3.48±0.21	3.65±0.17	3.26±0.21	Time	2,84	0.171	0.843
					Group×Time	2,84	5.093	0.008
Digit cancellation test	P	167.00±11.48	156.10±14.92	147.33±13.39	Group	1,42	0.630	0.432
Time (sec)	B	179.48±8.94	166.35±9.24	161.09±11.05	Time	2,84	7.655	0.001
					Group×Time	2,84	0.065	0.937
Digit cancellation test	P	3.29±0.97	1.52±0.38	0.57±0.22	Group	1,42	0.122	0.729
Error	B	2.48±0.63	2.30±0.62	1.22±0.42	Time	2,84	7.640	0.001
					Group×Time	2,84	1.499	0.229
Serial subtraction	P	52.14±6.83	45.67±6.24	41.14±4.75	Group	1,42	8.832	0.005
Time (sec)	B	79.57±7.81	80.30±8.76	64.57±7.22	Time	2,84	12.035	0.000
					Group×Time	2,84	2.084	0.131
Serial subtraction	P	0.90±0.28	0.90±0.26	0.76±0.18	Group	1,42	3.312	0.076
Error	B	1.48±0.22	1.39±0.31	1.43±0.26	Time	2,84	0.196	0.823
					Group×Time	2,84	0.196	0.823
Memory verbal								
List learning	P	4.48±0.29	4.81±0.33	4.38±0.38	Group	1,42	0.389	0.536
Immediate	B	4.39±0.34	4.78±0.24	5.13±0.36	Time	2,84	1.078	0.345
Recall (IR)					Group×Time	2,84	1.483	0.233
List learning	P	2.24±0.34	2.14±0.40	2.19±0.28	Group	1,42	0.473	0.495
Delayed	B	1.78±0.37	2.43±0.34	3.17±0.31	Time	2,84	3.954	0.023
Recall (DR)					Group×Time	2,84	4.493	0.014
Paired associates	P	4.52±0.15	4.62±0.11	4.33±0.16	Group	1,42	0.203	0.655
Similar (IR)	B	4.65±0.10	4.48±0.12	4.52±0.12	Time	2,84	1.169	0.316
					Group×Time	2,84	1.284	0.282
Paired associates	P	8.67±0.56	9.81±0.81	9.67±0.92	Group	1,42	0.785	0.381
Dissimilar (IR)	B	8.52±0.59	9.22±0.73	8.39±0.72	Time	2,84	1.139	0.325
					Group×Time	2,84	0.437	0.648
Paired associates	P	4.14±0.21	4.38±0.18	4.52±0.15	Group	1,42	1.106	0.299
Similar (DR)	B	4.09±0.15	4.17±0.17	4.17±0.16	Time	2,84	1.829	0.167
					Group×Time	2,84	0.687	0.506
Paired associates	P	2.52±0.30	2.71±0.35	2.38±0.33	Group	1,42	0.556	0.460
Dissimilar (DR)	B	2.39±0.29	2.74±0.23	3.26±0.31	Time	2,84	1.525	0.224
					Group×Time	2,84	3.182	0.047
Passages	P	14.43±0.94	14.57±0.64	15.38±0.87	Group	1,42	0.802	0.375
Immediate	B	13.61±0.79	13.65±0.76	14.61±0.72	Time	2,84	2.068	0.133
Recall (IR)					Group×Time	2,84	0.01	0.99
Passages	P	14.00±1.01	14.05±0.69	15.00±1.00	Group	1,42	2.438	0.126
Delayed	B	12.04±0.90	12.43±0.81	13.35±0.95	Time	2,84	2.595	0.081
Recall (DR)					Group×Time	2,84	0.061	0.941
Visual	P	8.43±0.76	8.38±0.79	8.67±0.82	Group	1,42	0.003	0.955
Retention I	B	7.70±0.77	9.39±0.69	8.57±0.82	Time	2,84	3.15	0.048
					Group×Time	2,84	3.477	0.035
Visual	P	8.71±0.27	8.86±0.25	8.76±0.24	Group	1,42	0.028	0.868
Retention II	B	8.78±0.27	8.65±0.33	8.74±0.26	Time	2,84	0.001	0.999
					Group×Time	2,84	0.27	0.764
Speed of information processing								
Digit symbol	P	32.29±3.12	35.24±3.45	35.38±3.72	Group	1,42	3.88	0.055
	B	24.39±2.75	26.57±3.25	25.61±3.10	Time	2,84	4.897	0.01
					Group×Time	2,84	0.574	0.565

P-Placebo; B-BacoMind®; IR = Immediate Recall; DR = Delayed Recall

Table 3: Haematological parameters in elderly individuals

Parameters	BacoMind®		Placebo	
	0th week	12th week	0th week	12th week
Haemoglobin (g %)	11.81±0.30	12.39±0.24*	12.58±0.40	12.73±0.34
WBC (cells/cu mm)	8000.00±397.23	7263.64±406.90	8300.00±394.61	7957.14±259.26
Polymorphs (%)	62.36±1.72	65.00±1.56	60.71±1.84	60.48±2.03
Lymphocytes (%)	31.86±1.57	29.55±1.49*	33.24±1.87	32.76±1.76
Eosinophils (%)	3.55±0.30	3.09±0.25	3.81±0.53	3.86±0.38
Monocytes (%)	2.23±0.16	2.36±0.23	1.90±0.18	2.81±0.26*
Basophils (%)	0.00±0.00	0.00±0.00	0.33±0.23	0.00±0.00

Values are expressed in mean±SEM, BacoMind® n = 22; Placebo n = 21, except haemoglobin n = 20, *$p \leq 0.05$ significant 0th vs 12th week

Adverse Events

There were no serious adverse events reported throughout the study period. Also, there were no mild or moderate adverse effects reported by the participants or explored by the investigator during the clinical trial.

Drop Outs

In the placebo treated group, one participant dropped out from the study following two weeks of treatment without stating any reasons and two individuals were withdrawn from the study one from each group due to medical reasons unrelated to therapy.

DISCUSSION

As the age advances, the likelihood of developing memory loss also increases. Impairment of memory causes concern to many people as they become older. While physicians and researchers worldwide are focusing much on the alzheimer's disease and other related dementias, elderly people are expressing greater concern about their common age-associated memory deficits. Several studies on drugs and other medical interventions that can treat cognitive impairment are currently in progress (Spiers *et al.*, 1996; Singh and Dhawan, 1997; Purdon *et al.*, 2007; Small, 2002; Tan *et al.*, 2004).

B. monnieri, an Indian herb has been used since time immemorial as a memory enhancer. Use of *B. monnieri* for memory improvement is well documented in preclinical and clinical studies. Extracts of *B. monnieri* were reported to improve attention, concentration and memory in study subjects (Singh and Dhawan, 1997; Bhattacharya *et al.*, 1999, 2000; Stough *et al.*, 2001; Roodenrys *et al.*, 2002; Kasture *et al.*, 2007; Pravina *et al.*, 2007).

The significant interaction effects between group and time observed in digit span backward test, list learning delayed recall test, paired associates dissimilar delayed recall test and in visual retention- I test revealed that BacoMind® improved performance in tests associated with attention and verbal memory in elderly participants. Detailed memory assessments, known as neuropsychological tests, will provide a better understanding about subtle memory deficits. Age associated memory impairment is characterised by self perception of memory loss and a standardised memory test score showing a decline in objective memory performance compared with younger adults (Small, 2002).

Backward digit span task provides invaluable information about verbal working memory as it requires recall and subsequent manipulation of incoming information (Conkiln *et al.*, 2000; Silver *et al.*, 2003). Substances that protect normal brain functioning under various ailments and are able to produce potential cognitive effects have shown improved scores in digit span backward test (Kemeny *et al.*, 2005). Treatment with BacoMind® for 12 weeks showed significant interaction effects in digit span backward test and these findings confirm the improved auditory registration of information and immediate attention skill in the participants as exhibited by the results of digit span subtest of Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Fann *et al.*, 2001).

Rapid forgetting, as measured by delayed-recall in different memory tasks has been proposed as an important neuropsychological marker for the early and differential diagnosis of dementia (Mattos *et al.*, 2003). Verbal list learning tests are useful in detecting memory impairment in people with cognitive deficiencies and memory enhancers are expected to produce better verbal list learning performance (Rich *et al.*, 2005). The results of the present study has shown significant effect in delayed recall in list learning test among elderly people after the treatment period of 12 weeks. The deleterious effects of aging on various cognitive abilities are widely recognized, as the elderly persons demonstrated significantly more rapid forgetting rates on the verbal paired associates subtest of the WAIS-R (Cullum *et al.*, 1990). The results of the current investigation indicated significant effects in paired associates-dissimilar delayed recall tasks in subjects administered with BacoMind®. Visual retention test examines a person's ability to reproduce visually presented designs (Silver *et al.*, 2003). Higher visual retention measures are indicative of improved retrieval of information (Fann *et al.*, 2001). The findings of the study support such an impact of the treatment on memory.

Usha *et al.* (2008) reported the cognitive enhancing effect of BacoMind® in children requiring individual education programme. A single daily oral dose of BacoMind® at 225 mg for four months showed significant improvement in working memory and short term verbal memory ($p \le 0.05$) in 70.83% of study population. Also, significant improvement ($p \le 0.05$) was noticed in logical memory, memory related to personal life and in visual as well as in auditory memory. In our present study, the placebo group did show improvements in certain parameters that could possibly be explained in terms of the uncontrollable nature of the placebo effect (Hróbjartsson, 1996) and generally recognized influential factors such as genuine appearance of the placebo material (the capsules), participant's expectations of the treatment to work with the regular follow up in the form of interviewing and examining by the clinicians for every fortnight as observed in this study. Placebo response rates in clinical trials vary considerably and are observed frequently. According to the published literature, the elements that contribute to the improvement in the placebo groups remain unclear (Walach *et al.*, 2005).

The clinical examination conducted for the purpose of safety of BacoMind® in study subjects did not show any abnormalities. The haematological profile found to be almost comparable to that of the control. There were no serious adverse events observed during the study period. These findings were found to be in concordance with the safety studies on *B. monnieri* reported by other researchers (Singh and Dhawan, 1997).

In conclusion, the study findings revealed that BacoMind® given at the dose of 450 mg once daily for 12 weeks to elderly individuals improved the cognitive functions such as attention and verbal memory and was also found to be well tolerated.

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