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Examining the Nootropic Effects of a special extract of *Bacopa monniera* on Human Cognitive Functioning: 90 day Double-Blind Placebo-Controlled Randomized Trial

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While Ayurvedic medicine has touted the cognitive enhancing effects of *Bacopa monniera* for centuries, there is a need for double-blind placebo-controlled investigations. One hundred and seven healthy participants were recruited for this double-blind placebo-controlled independent group design investigation. Sixty-two participants completed the study with 80% treatment compliance. Neuropsychological testing using the Cognitive Drug Research cognitive assessment system was conducted at baseline and after 90 days of treatment with a special extract of *Bacopa monniera* (2 × 150 mg KeenMind) or placebo. The *Bacopa monniera* product significantly improved performance on the 'Working Memory' factor, more specifically spatial working memory accuracy. The number of false-positives recorded in the Rapid visual information processing task was also reduced for the *Bacopa monniera* group following the treatment period. The current study provides support for the two other published studies reporting cognitive enhancing effects in healthy humans after a 90 day administration of the *Bacopa monniera* extract. Further studies are required to ascertain the effective dosage range, the time required to attain therapeutic levels and the effects over a longer term of administration. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Bacopa monniera (Brahmi: Scrophulariaceae) is a traditional Ayurvedic medicine with reported memory enhancing, antiinflammatory, analgesic, antipyretic, sedative and antiepileptic properties (Ganguly and Malhtora, 1967a). Phytochemical studies have shown that *Bacopa monniera* contains many active constituents including alkaloids, saponins, D-mannitol, betulic acid, sitosteron and stigmasterols (Chatterji *et al.*, 1965). The major constituents identified are the steroidal saponins, bacosides A and B (Chatterji *et al.*, 1965), though more recently a number of other saponins have been isolated (Russo and Borelli, 2005).

While *Bacopa monniera* has been reported to have many actions, its memory enhancing effects have attracted most attention. Pharmacological studies have further supported earlier claims that *Bacopa monniera* has memory enhancing effects. Behavioural animal studies have shown that this extract improves motor learning (Prakash and Sirsi, 1962) and produces antidementic and anticholinesterase activity in mice (Das *et al.*, 2002). Similarly, it has been shown to improve acquisition, retention and delay extinction of newly acquired behaviour in a brightness discrimination reaction task (Singh and Dhawan, 1997). These memory enhancing effects have been attributed to the active constituent saponins (Bacosides A and B). These saponins have been found to facilitate mental retention in avoidance response in rats (Singh *et al.*, 1988) and to reverse the amnesic effects of neurotoxin, scopolamine, electroshock and immobilization stress (Bhattacharya *et al.*, 1999; Singh and Dhawan, 1997).

The exact mechanism of action of *Bacopa monniera* has not yet been determined. There is evidence that it may be mediated by modulation of the cholinergic system and/or antioxidant effects (Russo and Borelli, 2005). Recent pharmacological evidence suggests that the effects of *Bacopa monniera* on the cholinergic system include modulation of choline acetylase activity (Das *et al.*, 2002), acetylcholine release (Agrawal, 1993; Bhattacharya *et al.*, 1999) and muscarinic cholinergic receptor binding (Bhattacharya *et al.*, 1999). *Bacopa monniera* has also been shown to exert potent antioxidant effects (Tripathi *et al.*, 1996; Bhattacharya *et al.*, 2000). The mechanism of action of its antioxidant effects has been shown to be via metal chelation at the initiation level and also as a lipid peroxidation chain action breaker (Tripathi *et al.*, 1996). The mechanism resembles both that of EDTA and vitamin E, two potent antioxidants. Bhattacharya *et al.* (2000) found increases in the levels of the antioxidants: superoxide dismutase, catalase and glutathione peroxidase in the prefrontal cortex, striatum and hippocampus following chronic administration of *Bacopa monniera*. This finding

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suggests that *Bacopa monniera* may exert positive effects on cognitive processes attributed to these brain regions such as memory, executive function and information processing.

With pre-clinical studies indicating that *Bacopa monniera* may have memory enhancing effects, there are limited scientific investigations conducted on the extract's cognitive enhancing and psychomotor effects in humans. Two single-blind studies have reported memory and learning enhancing effects of chronic *Bacopa monniera* administration in children (Sharma *et al.*, 1987) and patients with anxiety neurosis (Singh and Singh, 1980). Stough and colleagues (2001) conducted the first double-blind placebo-controlled trial investigating the memory enhancing effects of *Bacopa monniera* (KeenMind) in healthy participants aged between 18 and 60 years. Forty-six participants were randomly allocated to either a placebo or *Bacopa monniera* treatment group. A battery of well-validated neuropsychological tests was administered. After 90 days of *Bacopa monniera* (KeenMind) administration, a significant improvement was reported in information processing and memory consolidation, as well as a significant reduction in state anxiety. Roodenrys and colleagues (2002) replicated the memory enhancing effects of *Bacopa monniera* (KeenMind) in 76 participants aged between 40 and 65 years. They reported a significant decrease in the rate of forgetting newly acquired information after 90 days of treatment with *Bacopa monniera* (KeenMind) in a sample of older individuals than previously used earlier by Stough and colleagues (2001).

Although the results of these studies appear to support *Bacopa monniera* (KeenMind) as a natural nootropic agent, further research to confirm the effectiveness of the dose is essential before clinical applications may be considered (Russo and Borelli, 2005). To achieve this, the Cognitive Drug Research (CDR) computerized assessment battery was utilized. The CDR cognitive assessment battery has been used in hundreds of European and North American drug trials, and has been shown to be sensitive to acute and chronic cognitive improvements and impairments in a wide variety of substances (e.g. Wesnes *et al.*, 1997, 2000). A tailored version of the CDR battery was used that has been found to be sensitive to the effects of a variety of natural substances (see Kennedy *et al.*, 2004).

METHOD

Participants. One hundred and seven healthy volunteers, aged between 18 and 60 years, were randomly allocated to either the placebo group or the *Bacopa monniera* group. Participants were deemed suitable for the study if they had no history of the following: dementia or psychiatric disorders; neurological diseases; endocrine, gastrointestinal or bleeding disorders; no history of chronic illness or infection; not pregnant or lactating; not taking the following medications: anticoagulants, antidepressants, antipsychotics, anxiolytics, ACE inhibitors, anti-Parkinsons medication or other cognitive enhancing drugs; and a non-smoker. All participants gave written informed consent to participate in the study, which was approved by the Human Research Ethics Committee, Swinburne University of Technology.

Participants were excluded from the final statistical analysis if they did not consume 80% or greater of either the placebo or treatment over the 90 day trial (as calculated from the remaining treatment following the trial). Sixty-two participants completed the trial at 80% compliancy or higher. The placebo group comprised 12 males and 17 females with a mean age of 44.3 years (SD = 11.3). The *Bacopa monniera* group comprised 9 males and 24 females with a mean age of 41.6 years (SD = 13.4).

Study design and treatment conditions. A double-blind, placebo-controlled independent group design was employed. Participants were randomly allocated to one of two treatment conditions: KeenMind *Bacopa monniera* extract (Keen Health Pty Ltd) group (2 × 150 mg) or placebo group. This patented extract of *Bacopa monniera* is prepared from stems, leaves and roots of a cultured variety of *Bacopa monniera* (collected from West Bengal) and extracted with 50% ethanol. It is standardized for bacosides A and B (no less than 55% of combined bacosides). Each capsule contained 150 mg *Bacopa monniera* extract (20:1) equivalent to 3 g of dried herb. The active *Bacopa monniera* and placebo capsules were identical in shape, colour, smell, taste and weight. The *Bacopa monniera* was the standard clinical dose developed and patented by the Central Drug Research Institute, Lucknow, India (Dhawan and Singh, 1996) and the same used in the Stough and colleagues study (2001). Randomization was performed using a computer generated randomization program that enables equal probability of being allocated to one of the two treatment conditions.

Procedure. During baseline testing, participants completed a battery of cognitive tests from the Cognitive Drug Research (CDR) computerized assessment system (Wesnes *et al.*, 1999). This took 30 min to complete, with the primary outcome measures being five cognitive factors ('Secondary memory', 'Working memory', 'Speed of memory', 'Speed of attention', and 'Accuracy of attention') that can be derived from the complete CDR computerized assessment battery (Wesnes *et al.*, 2000). A rapid visual information-processing task (RVIP) (Wesnes and Warburton, 1984; Wesnes *et al.*, 1990) was also included. Subsequently, participants were given a 90 day supply of capsules (KeenMind *Bacopa monniera* extract or placebo). Participants were instructed to take two capsules a day for 90 days. Participants were re-tested after completing 90 days of treatment administration. Alternate forms of the test battery were used at each testing session and the test order was counter-balanced. Participants received weekly phone calls over the 90 day treatment period to monitor any treatment effects and to enhance compliance.

Neuropsychological assessments. The following tests from the CDR cognitive assessment system were administered.

Word presentation. A list of 15 words was presented in the centre of the screen at the rate of one every 2 s for the participant to remember.

Picture presentation. A series of 20 photographic images of everyday objects and scenes were presented on the monitor at the rate of one every 3 s, with a stimulus duration of 1 s, for the participant to remember.

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Immediate word recognition. The 15 original words plus 15 distracter words were presented one at a time in a randomized order. For each word the participant indicated whether or not they recognized it as being from the 15 original words by pressing the YES or NO button. The measures were the percentage words correctly classified and the average reaction time (ms).

Simple reaction time. The participant was instructed to press the YES response button as quickly as possible every time the word YES was presented on the screen. Thirty stimuli were presented with a varying inter-stimulus interval of between 1 and 4 s. The measure was the average reaction time to the stimuli (ms).

Digit vigilance. A target digit was randomly selected and displayed to the right of the screen. A series of digits were presented in the centre of the screen at the rate of 2.5 digits per second. The participant was required to press the YES button as quickly as possible every time the digit in the series matched the target digit. The measures were the percentage of targets detected, the average reaction time (ms) and the number of false-positives (false alarms) made.

Choice reaction time. Either the word YES or the word NO was presented on the screen and the participant was instructed to press the corresponding button as quickly as possible. There were 30 trials with a varying inter-stimulus interval of between 1 and 4 s. The measures were the percentage of correct responses and the average reaction time to the stimuli (ms).

Spatial working memory. A picture of a house was presented on the screen with four of its nine windows lit. The participant was instructed to memorize the positions of the lit windows. For each of the subsequent presentations of the house the participant had to decide whether or not the one window which was lit was also lit in the original presentation. Participants recorded their response by pressing the YES or NO button as appropriate. The measures were the percentage of correctly identified stimuli and the average reaction time (ms).

Numeric working memory. A series of five digits was presented for the participant to hold in their memory. This was followed by a series of 30 probe digits for each of which the participant was required to decide whether the or not the digit was from the original series and indicate their choice by pressing either the YES or NO button. The measures were the percentage correctly identified stimuli and the average reaction time (ms).

Delayed word recognition. The original 15 words (presented in *Word presentation*) plus 15 distracter words were presented one at a time in a randomized order. For each word the participant indicated whether they recognized the word as being from the original list of words by pressing the YES or NO button as appropriate. The measures were the percentage of correctly identified words and the average reaction time (ms).

Delayed picture recognition. The original pictures plus 20 distracter pictures were presented one at a time in a randomized order. For each picture, participants indicated whether they recognized it as being from the original series by pressing the YES or NO button as appropriate and as quickly as possible. The mean reaction times were measured in ms, and the accuracies of responses to both original and novel (distracter) stimuli were also recorded.

Rapid visual information processing. A series of numbers are presented on the screen, one at a time, in quick succession for 7 min. Whenever three even numbers appear in a row with nothing in between (i.e. any three of 2, 4, 6, 8), or three odd numbers in a row with nothing in between (i.e. any three of 1, 3, 5, 7, 9) the participant presses the YES button. The measures were the percentage of targets detected, the average reaction time (ms) and the number of false-positives (false alarms) made.

Positive and negative symptom analyses. On a weekly basis, research nurses monitored the participants for subjective positive and negative symptoms associated with treatment. Negative symptoms reported included tiredness, fatigue, nausea, malaise, vomiting. Reported positive symptoms included feelings of increased energy, arousal and cognitive clarity.

RESULTS

Baseline scores

Prior to analyses of the cognitive factor outcome measures, all baseline scores were subjected to a one-way ANOVA to assess any group differences (placebo vs *Bacopa monniera* group) in cognitive performance (at the factor and individual task performance levels) and mood. No significant differences were observed.

Cognitive factor outcome measures

Task performance for all the CDR measures are presented in Table 1, for both baseline and post-treatment testing sessions. Repeated-measures ANOVA were conducted on the five cognitive factor outcome measures; mean baseline and post-treatment scores for each factor are presented in Table 2. Of the five repeated-measures ANOVAs conducted on the cognitive factor scores, only the 'Working Memory' factor reached significance: $F(1, 53) = 4.70$, $p = 0.035$, with the *Bacopa monniera* group performance significantly improving over the treatment period. With reference to the single tasks that make up this factor, performance on the Spatial Working Memory (accuracy) task also improved: $F(1, 54) = 3.98$, $p = 0.051$.

Rapid visual information processing (RVIP)

Performance on the RVIP task was also assessed via repeated-measures ANOVA, with the *Bacopa monniera* group performance improving after the 90 day treatment period, with a significant reduction in the amount of false alarms produced during this task: $F(1, 54) = 5.03$, $p = 0.029$.

Positive and negative symptoms

During weekly monitoring calls to each participant a large number (54) of positive and negative symptoms were collected and analysed (via independent samples *t*-test) to assess any differences between the *Bacopa*

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Table 1. Effect of treatment on individual CDR measures

Measure	Treatment group	*n*	Mean	SD Baseline	Mean	SD Post-treatment
Immediate word recall (% correct)	Placebo	29	42.07	12.83	46.09	13.03
	Bacopa	32	45.10	11.36	47.71	13.24
Simple reaction time (ms)	Placebo	29	269.65	52.63	270.37	41.49
	Bacopa	33	272.29	36.08	263.27	46.99
Digit vigilance – correct detections (%)	Placebo	29	98.16	2.85	99.16	1.72
	Bacopa	33	97.98	3.49	98.52	3.41
Digit vigilance – speed of detections (ms)	Placebo	29	385.43	34.23	385.04	26.29
	Bacopa	33	394.38	40.56	393.16	38.90
Digit vigilance – false alarms (#)	Placebo	29	1.07	1.58	0.31	0.54
	Bacopa	33	1.12	1.24	0.73	0.91
Choice reaction time – accuracy (%)	Placebo	29	96.76	2.23	97.03	2.04
	Bacopa	33	96.06	3.06	96.24	3.53
Choice reaction time (ms)	Placebo	29	436.51	53.87	430.44	52.74
	Bacopa	33	445.25	62.99	428.49	65.81
Spatial working memory (% correct)	**Placebo**	**28**	**95.67**	**6.91**	**97.97**	**2.53**
	Bacopa	**33**	**91.40**	**9.99**	**96.84**	**5.91**
Spatial working memory – speed (ms)	Placebo	29	1048.95	576.56	851.89	230.95
	Bacopa	33	1001.03	410.18	881.14	381.00
RVIP – accuracy (%)	Placebo	28	51.07	17.43	56.61	17.96
	Bacopa	32	43.75	17.79	53.51	19.29
RVIP – speed (ms)	Placebo	28	534.48	72.60	537.13	80.46
	Bacopa	32	567.94	77.99	550.50	78.38
RVIP – false alarms (#)	Placebo	28	7.61	8.88	8.82	14.25
	Bacopa	31	10.00	10.40	6.52	5.84
Numeric working memory (% correct)	Placebo	28	92.94	6.34	91.88	8.26
	Bacopa	33	93.70	6.15	93.80	5.22
Numeric working memory – speed (ms)	Placebo	29	863.37	230.59	860.52	305.45
	Bacopa	33	850.72	218.50	783.23	183.69
Delayed word recall (% correct)	Placebo	29	28.74	11.90	34.37	13.37
	Bacopa	31	31.61	14.40	34.58	14.46
Word recognition (% correct)	Placebo	29	81.72	11.43	84.14	8.48
	Bacopa	33	83.84	8.50	85.15	9.43
Word recognition – speed (ms)	Placebo	29	970.03	274.99	906.82	232.14
	Bacopa	33	915.05	247.27	837.95	185.23
Delayed picture recognition (% correct)	Placebo	29	84.40	7.75	86.90	9.18
	Bacopa	33	86.29	8.73	86.82	10.94
Picture recognition – speed (ms)	Placebo	29	1269.01	794.71	1105.76	325.08
	Bacopa	33	1128.08	343.57	1027.28	331.15

Significant Time × Group differences are indicated with bold type.

Table 2. Baseline and post-treatment CDR factor scores

CDR factor	Treatment	Baseline M	Baseline SD	Post-treatment M	Post-treatment SD
Speed of attention	*Bacopa*	1111.92	118.38	1084.93	138.68
	Placebo	1091.58	123.28	1085.86	106.31
Speed of memory	*Bacopa*	3894.88	925.00	3529.59	878.03
	Placebo	3926.04	982.24	3725.00	950.08
Accuracy of attention	*Bacopa*	97.02	2.78	97.38	2.74
	Placebo	97.46	1.63	98.09	1.55
Secondary memory	*Bacopa*	246.64	33.74	254.66	39.36
	Placebo	236.93	34.75	251.49	34.53
Working memory	***Bacopa***	**185.11**	**13.16**	**190.64**	**9.39**
	Placebo	**188.71**	**9.50**	**189.85**	**9.08**

Significant Time × Group differences are indicated with bold type.

monniera and placebo groups. Across the 12 week treatment period the *Bacopa monniera* group reported significantly greater incidence of: increased energy levels; diarrhoea; and a reduction in the number of dreams. The placebo group reported greater incidence of: trouble with teeth and gums; and easy bruising. The incidence of the other 52 positive and negative symptoms did not significantly differ between the two groups, suggesting the two treatments were reasonably well tolerated by both groups.

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Participant withdrawals

Further evidence to the high degree of tolerance of *Bacopa monniera* (and placebo) was the similar pattern of participant withdrawals from the study. The *Bacopa monniera* and placebo groups had 22 and 23 withdrawals, respectively, with reasons for withdrawal being: adverse effect to treatment (three *Bacopa monniera* and two placebo); failure to return for testing (seven *Bacopa monniera* and six placebo); participant request (one *Bacopa monniera* and three placebo); protocol violation (ten *Bacopa monniera* and seven placebo); and unrelated medical event (two *Bacopa monniera* and one placebo).

DISCUSSION

The present study examined whether chronic (90 day) dosage of the Indian herb *Bacopa monniera* (KeenMind) improved performance in comparison with placebo in healthy participants. The results indicated that 'Working Memory' performance was improved in the treatment group, a specific improvement was noted on the accuracy scores of the Spatial Working Memory task. The number of information-processing false alarms was also significantly reduced. The CDR cognitive assessment tasks provide information on both accuracy and reaction time performance. The improved performance by the treatment group was characterized in an improvement in accuracy or 'quality' of their performance in the measures that produce the 'Working memory' factor.

Although there were several tasks that were not significantly improved by the *Bacopa monniera* treatment, many of the statistical analyses trended towards an improvement in cognitive functioning in areas of attention, working memory and psychomotor tasks. The variability associated with some of these tasks may have precluded the detection of statistically significant differences due to the *Bacopa monniera* treatment within the limitations of the present sample size. Additional studies employing significantly larger sample sizes may be able to detect an improvement in a larger number of variables due to *Bacopa monniera* treatment. Within the confines of the present experimental conditions, there is evidence that favours the conclusion that 90 day *Bacopa monniera* (KeenMind) treatment improves accuracy in more complex cognitive tasks.

The variables assessed in the present study involved speeded computerized tasks in which the participant records both a reaction time to a series of specific neuropsychological tasks and an assessment of the accuracy associated with that response. These tests may be contrasted to the paper and pencil tests employed in our previous study in which several tests did not require a speeded (reaction time) type of response. Therefore it is not surprising that there may be some differences between the two studies. The results of our previous study (Stough *et al.*, 2001) indicated that 90 day *Bacopa monniera* (KeenMind) treatment in healthy volunteers improved simple information processing speed indexed by the Inspection Time task (this was not measured in the present study) and memory consolidation, both measured by a non-speeded psychological tasks. The improvement in Inspection Time is consistent with the improvement in basic information processing observed in the present study. A significant departure of the finding of the present study from those of the earlier study (Stough *et al.*, 2001) was the lack of reduction in state anxiety.

There was also evidence that the *Bacopa monniera* (KeenMind) was very well tolerated with reporting of negative symptoms not differing greatly from those in the placebo condition. This pattern was again reflected in the similar numbers and reasons for withdrawal from the study for both treatment groups. The results of our two studies taken together indicate that there is mounting evidence for the utility of *Bacopa monniera* in improving cognitive functioning in healthy human participants. Apart from the Chinese herbal agent *Ginkgo biloba*, there is little evidence for a nootropic (i.e. cognitive enhancing) effect for any other known substance (natural or pharmaceutical based). Further studies are required to ascertain the effective dosage range, time required to attain therapeutic levels and effects over a longer term of administration.

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