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RAPID COMMUNICATION

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The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects

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Abstract *Rationale:* Extracts of *Bacopa monniera* have been reported to exert cognitive enhancing effects in animals. However, the effects on human cognition are inconclusive. *Objective:* The current study examined the chronic effects of an extract of *B. monniera* (Keenmind) on cognitive function in healthy human subjects. *Methods:* The study was a double-blind placebo-controlled independent-group design in which subjects were randomly allocated to one of two treatment conditions, *B. monniera* (300 mg) or placebo. Neuropsychological testing was conducted pre-(baseline) and at 5 and 12 weeks post drug administration. *Results: B. monniera* significantly improved speed of visual information processing measured by the IT task, learning rate and memory consolidation measured by the AVLT ($P<0.05$), and state anxiety ($P<0.001$) compared to placebo, with maximal effects evident after 12 weeks. *Conclusions:* These findings suggest that *B. monniera* may improve higher order cognitive processes that are critically dependent on the input of information from our environment such as learning and memory.

Keywords *Bacopa monniera* · Brahmi · Nootropic · Cognitive function · Learning · Memory · Information processing · Anxiety

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Introduction

Bacopa monniera (Brahmi), a traditional Ayurvedic medicine has been used for centuries as a memory enhancing, anti-inflammatory, analgesic, antipyretic, sedative, and anti-epileptic agent. More recently, preclinical studies have reported cognitive enhancing effects with various extracts of *B. monniera*. Behavioral animal studies have shown that administration of *B. monniera* improved motor learning (Prakash and Sirsi 1962). Similarly *B. monniera* has been shown to improve acquisition, retention, and delayed extinction of newly acquired behavior in a brightness discrimination reaction task (Singh and Dhawan 1997). The memory enhancing effects have been attributed to the active constituent saponin, as bacosides A and B have been shown to exert facilitatory effects on mental retention in avoidance response in rats (Singh et al. 1988) and reverse amnesic effects of neurotoxin, scopolamine, electroshock, and immobilization stress (Bhattacharya et al. 2000a; Singh and Dhawan 1997).

Supporting the preclinical studies, two single-blind open clinical studies have reported memory and learning enhancing effects of chronic *B. monniera* in both children (Sharma et al. 1987) and patients with anxiety neurosis (Singh and Singh 1980). However these studies are limited by methodological weaknesses, including the lack of a double-blind design, suitable placebo control, the validity of neuropsychological tests, and the use of a patient group with anxiety.

While the exact mechanism of action of *B. monniera* is not known, there is evidence that the mechanism of action could be attributed to a combination of cholinergic modulation and antioxidant effects. Evidence shows that the effects of *B. monniera* on the cholinergic system include modulation of: (1) acetylcholine release (Agrawal 1993; Bhattacharya et al. 2000a), (2) choline acetylase activity, and (3) muscarinic cholinergic receptor binding (Bhattacharya et al. 2000a). In addition *B. monniera* has been shown to exert potent antioxidant effects (Bhattacharya et al. 2000b; Tripathi et al. 1996). The lat-

ter study showed increases in the levels of the antioxidants superoxide dismutase, catalase, and glutathione peroxidase in the prefrontal cortex, striatum, and hippocampus following chronic administration of *B. monniera*. This finding suggests that *B. monniera* may exert positive effects on cognitive processes such as memory, executive function, and information processing which are confined to these brain areas.

The aim of the current study was to use a double-blind placebo-controlled design and a battery of well-validated neuropsychological tests to examine the chronic effects of an extract of *B. monniera* on cognitive function in healthy human subjects.

Materials and methods

Participants

Forty-six healthy volunteers (11 males and 35 females) aged between 18 and 60 years (mean ± SD; 39.4±11.4) and weighing between 48 and 94 kg (mean ± SD; 66.5±10.8) were recruited for the study. Individuals were deemed suitable for the study if they had no pre-existing physical or psychiatric condition and were free of any medication. All participants gave written informed consent to participate in the study, which was approved by the Human Research Ethics Committee, Swinburne University of Technology.

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 *B. monniera* extract (Keenmind) group (n=23; 2×150 mg) or placebo group (n=23). The extract of *B. monniera* used is a standardized ethanolic extract made available by Central Drug Research Institute, Lucknow, India (CDRI) and licensed to Keenmind. This extract is trademarked Baccdrix (patent pending on extraction method). It is standardized for bacosides A and B (no less than 55% of combined bacosides). Each capsule contained 150 mg *B. monniera* extract (20:1) equivalent to 3 g dried herb. The active *B. monniera* and placebo capsules were identical in shape, color, smell, taste, and weight. The dose of *B. monniera* was based on the standard clinical dose recommended by the CDRI. Randomization was performed using a computer-generated randomization program that enables equal likelihood of being allocated to one of the two treatment conditions.

Procedures

On the first testing session (baseline testing), all participants completed a 30-min standard battery of neuropsychological tests (see below). Following baseline testing, each participant was then given a bottle of capsules (*B. monniera* extract or placebo) for 12 weeks. Participants were instructed to take two capsules a day for 12 weeks. Participants were retested at 5 weeks and 12 weeks following commencement of treatment. Alternate forms of the test battery were used at each testing session and test order was counterbalanced. Participants received weekly phone calls over the 12-week treatment period to monitor any treatment effects and to enhance compliance. In addition to the trial regime (two capsules for 12 weeks), additional capsules ranging in number from 1–10 (randomly allocated) were also placed in the bottles so that compliance could be accurately examined. At the completion of the 12 weeks, participants were asked to bring in their bottles and the remaining capsules were counted. Participants were excluded if greater than 10% of the total number of capsules required were not consumed by the end of the 12 weeks.

Table 1 Neuropsychological test battery results at baseline and after 5 and 12 weeks of treatment with *Bacopa monniera* or placebo. *AVLT* Auditory verbal learning test

	Bacopa monniera (300 mg/day) (n=23)	Placebo (n=23)
Baseline		
AVLT – learning rate	5.9±2.1	4.6±2.3
AVLT – forgetting rate	1.2±1.2	0.9±1.7
AVLT – proactive interference	–0.9±2.7	–0.6±2.8
AVLT – retroactive interference	–1.1±1.5	–0.9±1.4
Trail making A (ms)	26.4±6.9	28.6±9.2
Trail making B (ms)	75.0±28.0	62.7±19.6
Speed of comprehension test (sentences)	71.9±20.9	71.5±21.8
Digit span forwards (digits)	7.1±0.9	9.4±2.0
Digit span backwards (digits)	5.2±1.5	5.6±1.3
Digit symbol (symbols)	59.0±11.5	65.5±8.7
Inspection time (ms)	94.4±47.9	85.2±25.1
Simple reaction time (ms)	243.2±25.3	266.5±119.0
Choice reaction time (ms)	611.7±182.7	651.7±116.4
Working memory speed (ms)	1336.3±289.3	1471.0±353.4
Working memory capacity (ms)	1174.3±260.7	1146.8±227.9
State anxiety	11.7±2.4	11.9±2.6
Five weeks post-treatment		
AVLT – learning rate	4.7±1.5	5.1±2.1
AVLT – forgetting rate	0.6±1.2	2.2±2.5
AVLT – proactive interference	–1.7±2.2	–1.4±1.9
AVLT – retroactive interference	–0.7±1.3	–1.5±2.3
Trail making A (ms)	23.7±5.3	28.4±7.5
Trail making B (ms)	50.1±12.6	57.4±21.6
Speed of comprehension test (sentences)	81.3±17.7	79.5±20.1
Digit span forwards (digits)	7.4±0.9	72±0.9
Digit span backwards (digits)	5.8±1.7	5.6±1.5
Digit symbol (symbols)	69.0±11.2	67.3±13.0
Inspection time (ms)	73.5±20.5	74.6±24.4
Simple reaction time (ms)	242.4±28.4	237.0±28.8
Choice reaction time (ms)	584.4±111.7	605.4±118.8
Working memory speed (ms)	1204.7±418.0	1335.4±366.8
Working memory capacity (ms)	1136.4±289.9	1093.8±257.5
State anxiety	11.2±2.2	12.9±2.1
Twelve weeks post-treatment		
AVLT – learning rate	5.7±2.2*	5.0±2.4
AVLT – forgetting rate	1.0±1.9*	1.5±1.8
AVLT – proactive interference	0.1±2.0*	–1.2±2.5
AVLT – retroactive interference	–1.1±1.4	–1.7±1.9
Trail making A (ms)	23.0±6.3	24.9±7.5
Trail making B (ms)	50.2±16.5	55.8±20.8
Speed of comprehension test (sentences)	87.4±24.5	85.7±20.8
Digit span forwards (digits)	6.8±1.2	7.3±0.9
Digit span backwards (digits)	5.2±1.5	6.0±1.5
Digit symbol (symbols)	69.3±11.3	69.1±12.3
Inspection time (ms)	64.5±16.7*	75.9±26.3
Simple reaction time (ms)	240.3±25.5	242.5±29.1
Choice reaction time (ms)	564.6±145.1	603.0±138.6
Working memory speed (ms)	1215.9±264.7	1183.3±307.2
Working memory capacity (ms)	1127.2±240.5	1039.1±247.1
State anxiety	9.6±1.7**	12.8±2.4

*P<0.05 indicates significant differences compared to placebo
**P<0.001 indicates significant differences compared to placebo

Table 2 Adverse effects of *B. monniera* and placebo reported over the 12-week treatment period

Adverse effect	*Bacopa monniera* (300 mg/day)	Placebo
Drowsiness	5%	4%
Allergies	14%	16%
Cold/flu symptoms	9%	28%
Skin rash	5%	12%
Skin itching	5%	12%
Headache	18%	28%
Tinnitus	9%	16%
Vertigo	9%	8%
Strange taste in mouth	14%	16%
Dry mouth	23%	16%
Palpitations	18%	8%
Abdominal pain	9%	8%
Appetite increase	18%	20%
Appetite reduction	0%	4%
Excessive thirst	18%	8%
Nausea	18%	4%
Indigestion	9%	4%
Constipation	9%	8%
Increased regularity of bowel movements	9%	4%
Increased frequency of urine	14%	8%
Muscular fatigue	14%	4%
Muscular pain	5%	8%
Cramps	5%	8%
Increase in felt stress	9%	12%
Decrease in felt stress	23%	28%
Improved mood	5%	8%
Worsened mood	5%	8%

Neuropsychological tests

A battery of well-validated neuropsychological tests were employed to assess a wide range of cognitive variables including attention, short-term memory, verbal learning, memory consolidation, executive processes, planning and problem solving, information processing speed, motor responsiveness, and decision making. This battery comprised Cognometer tests of working memory, Digit Symbol Substitution Test (Weshsler 1981), Speed of Comprehension Test (Baddley et al. 1992), Digit Span (Wechsler 1981), Trail Making Test (Giovagnoli et al. 1981), Rey Auditory Verbal Learning Test (AVLT; Rey 1964), and Inspection Time (IT; Taylor and Creelman 1967). Changes in state anxiety were examined using the State-Trait Anxiety Inventory (Speilberger 1979).

Adverse effects monitoring

A large number of adverse effects were monitored over the 12-week period. Only the reported adverse effects (more than one adverse effect could be reported by participants) were documented.

Results

A series of one-way repeated measures analysis of variance (ANOVA) employing time (pre- and post assessments of each test) by group (*B. monniera* and placebo) interactions indicated that *B. monniera* significantly improved speed of visual information processing measured by the IT task (F=4.5; P=0.018) and learning rate (F=3.49; P=0.042), and memory consolidation [decrease proactive interference (F=3.467; P=0.042) and decrease forgetting rate (F=3.84; P=0.03)] measured by the AVLT compared to placebo with maximal effects evident after 12 weeks (Table 1). *B. monniera* also produced a significant decrease in state anxiety compared to placebo (F=9.37; P=0.001). Percentage of adverse effects was similar for both treatment conditions (Table 2), except for a greater percentage in the *B. monniera* group reporting nausea, dry mouth, and fatigue.

Discussion

The current findings indicate that the Keenmind *B. monniera* given chronically for 12 weeks improves speed of early information processing (measured by IT), verbal learning rate and memory consolidation (measured by AVLT) in humans. IT is regarded as a measure of the integrity of the early stages of information processing and may act as a rate-limiting factor for cognition (Stough et al. 2001a). These findings support previous preclinical animal studies (Bhattacharya et al. 2000a; Prakash and Sirsi 1962; Singh and Dhawan 1997) and clinical studies in children (Sharma et al. 1987) and patients with anxiety neurosis (Singh and Singh 1980) that have shown learning and memory enhancing effects of *B. monniera* extracts. It is possible that the effects of *B. monniera* on cognitive function may be related to its modulatory effects on the cholinergic system and/or its potent antioxidant effects. The modulation of IT by *B. monniera* further supports a possible modulatory effect on the cholinergic system, as IT has been shown to be predominantly modulated by the cholinergic system (Stough et al. 2001a). The current findings also support our previous study with another herbal cognitive enhancer, *Ginkgo biloba* (Stough et al. 2001b), which shares similarities with *B. monniera* with respect to mechanism of action (Nathan 2000).

An interesting observation with *B. monniera* was evidence for an anxiolytic effect, with significant differences between treatment groups on the state measure of anxiety. This finding supports the study of Singh and Singh (1980) who also found significant anxiolytic effects with an extract of *B. monniera* in patients with anxiety neurosis and preclinical animal studies showing tranquilizing effects of *B. monniera* in rats and dogs (Prakash and Sirsi 1962). While the cholinergic and antioxidant effects may not explain the anxiolytic action of *B. monniera*, it is possible that this may be due to modulation of the serotonergic system, as it has been shown that *B. monniera* modulates brain serotonin levels in animals (Ganguly and Malhotra 1967).

An interesting finding was that the effects of *B. monniera* were only significant after 12 weeks of treatment. This is consistent with the study of Sharma et al. (1987) who also observed positive effects on learning and memory following 12 weeks administration. Singh and Singh (1980) showed memory enhancing effects following

4 weeks, however this study was confounded by concomitant improvements in anxiety and the use of a higher dose of *B. monniera*.

In summary, the current study showed that the Keenmind *B. monniera* extract (300 mg) given chronically for 12 weeks improved early information processing, verbal learning, and memory consolidation in humans. The current finding suggests that *B. monniera* may improve higher order cognitive processes that are critically dependent on the input of information from our environment such as learning and memory. Future research using a wider battery of tests, different doses, and examining possible age-related effects is warranted to further examine the effects of *B. monniera* on human cognitive function.

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