

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

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The Ayurvedic medicine *Bacopa monniera* (Brahmi) has been shown to exert cognitive enhancing effects in animals. The current study examined the acute effects of an extract of *Bacopa monniera* on cognitive function in normal healthy human subjects. The study was a double-blind, placebo-controlled independent group design in which subjects were randomly allocated to one of two treatment conditions, *Bacopa monniera* (300 mg) (n = 18) or placebo (n = 20). Neuropsychological testing was conducted before and 2 h after drug administration. No significant changes were found on any of the tests. The findings suggest that *Bacopa monniera*, at least for the dose administered, has no acute effects on cognitive functioning in normal healthy subjects. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — *Bacopa monniera*; brahmi; acute; cognition

INTRODUCTION

Bacopa monniera Linn. (Brahmi: Scrophulariaceae) is a traditional Ayurvedic medicine with reported memory-enhancing, anti-inflammatory, analgesic, antipyretic, sedative and anti-epileptic properties (Kirtikar and Basu, 1935; Tripathi *et al.*, 1996). Phytochemical studies have shown that *Bacopa monniera* contains many active constituents including alkaloids, brahmine, herpestine and saponins. The saponins include, bacosides A, A3 and B, bacopasaponin A to F, D-mannitol, betulinic acid, β -sitosteron, and stigmasterols (Chatterji *et al.*, 1963; 1965; Basu *et al.*, 1967; Rastogi *et al.*, 1994; Garai *et al.*, 1996a, 1996b; Mahato *et al.*, 2000). However, the major constituents identified are the steroidal saponins bacoside A and B (Chatterji *et al.*, 1965).

While *Bacopa monniera* has been reported to have many actions, its memory-enhancing effect has attracted most attention. Pharmacological studies in

animals have supported earlier claims that *Bacopa monniera* has memory-enhancing effects. Behavioral animal studies have shown that administration of *Bacopa monniera* improved motor learning (Prakash and Sirsi, 1962). Similarly it was shown to improve acquisition, retention and delayed extinction of newly acquired behavior in a brightness discrimination reaction task (Singh and Dhawan, 1982, 1997) and the conditioned avoidance response task (Singh and Dhawan, 1997). The memory-enhancing effects may be exerted by the active constituent saponins, as bacoside A and B have been shown to have a facilitatory effect on mental retention in avoidance response in rats (Singh *et al.*, 1988). Similarly, a more recent study (Bhattacharya *et al.*, in press) showed that a bacoside-rich extract reversed the cognitive deficits induced by intracerebroventricularly administered colchicine (a neurotoxin) and that induced by injecting ibotenic acid into the nucleus basalis magnocellularis.

Recent pharmacological studies suggest that the memory-enhancing effects of *Bacopa monniera* may be mediated by modulation of the cholinergic system and/or its antioxidant effects. *Bacopa monniera* has been reported to prevent the depletion of blood acetylcholine in an aged human population (Agrawal, 1993) and more recently has been shown to reverse

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the depletion of acetylcholine, the reduction in choline acetylase activity and the decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus induced by colchicines (Bhattacharya *et al.*, in press). In addition, it has been shown to exert potent antioxidant properties (Tripathi *et al.*, 1996). The mechanism of action of its antioxidant effects has been shown to be via metal chelation at the initiation level and also as a chain breaker (Tripathi *et al.*, 1996). The mechanism resembles that of both EDTA and vitamin E, two potent antioxidants. More recently Bhattacharya *et al.* (2000a) showed that a standardized extract of *Bacopa monniera* induced a dose-related increase in superoxide dismutase, catalase and glutathione peroxidase levels in rat prefrontal cortex, striatum and hippocampus, further supporting its mechanism of action as an antioxidant.

While pre-clinical studies suggest that *Bacopa monniera* may have cognitive-enhancing effects, no scientific studies conducted in humans have been published. Given that *Bacopa monniera* extracts have been shown to modulate the cholinergic system (Agrawal, 1993; Bhattacharya *et al.*, in press), and the well-established role of this system in cognition (Drachman and Leavitt, 1974), the aim of the current study was to examine the acute effects of an extract of *Bacopa monniera* on cognitive function in healthy normal subjects.

METHODS

Thirty-eight healthy volunteers aged between 18 and 60 years (mean \pm SD = 37.4 \pm 11.3) and weighing between 48 kg and 94 kg (Mean \pm SD = 65.6 \pm 10.8) with no history of physical or psychiatric disorders, and free of any medication (including nicotine), were recruited for the study. The subjects comprised 11 males aged between 20 and 60 years (mean \pm SD = 37.3 \pm SD = 13.1) and weighing between 56 kg and 85 kg (mean \pm SD = 69.4 \pm 10.2) and 27 females aged between 18 and 53 years (mean \pm SD = 37.4 \pm 10.6) and weighing between 8 kg–94 kg (mean \pm SD = 63.9 \pm 10.1). Subjects were recruited from the general population through advertisements and by word of mouth. Subjects were deemed suitable for the study on the basis of a detailed physical examination and a semi-structured psychiatric interview by a physician. All subjects gave written informed consent to participate in the study, which was approved by the Human Research Ethics Committee, Swinburne University of Technology.

Study design

The study was a double-blind and placebo-controlled independent group design in which all subjects were randomly allocated to one of two treatment groups: the *Bacopa monniera* group (n = 18) and the placebo group (n = 20). Randomization was performed using a computer-generated randomization program that enables equal likelihood of being allocated to one of the two treatment conditions. The sample size was estimated based on previous pharmacological studies conducted in our laboratory using similar neuropsychological tests.

Procedures

On the day of testing, all subjects reported to the neuropsychology laboratory at the Swinburne University of Technology, having had a standard breakfast of two slices of bread or toast with jam and not having consumed alcohol or any drink with caffeine in the previous 24 h. Each subject underwent 30 minutes of baseline neuropsychological tests. Following baseline testing each subject was administered either 300 mg (2 \times 150 mg) *Bacopa monniera* extract (Keenmind Ltd, formerly the Central Drug Research Institute, Lucknow, India) or placebo. The extract of *Bacopa monniera* is prepared from the stems and leaves of a cultured variety of *Bacopa monniera* (collected in 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, color, smell, taste and weight. Subjects were reassessed on the same battery of neuropsychological tests 2 h post-drug administration. Between and within subjects the orders of test administrations (including alternative forms of tests) were counterbalanced using a latin square design. The time of testing was selected to coincide with the time of maximum pharmacodynamic effects, as observed in animals, of both the extract and the active constituents bacosides A and B (Singh *et al.*, 1988; Rao and Karanth, 1992). The dose of *Bacopa monniera* was based on the standard clinical dose recommended by the Central Drug Research Institute, Lucknow, India.

Neuropsychological tests

A combination of well-established auditory and visual neuropsychological tests were chosen: the

Rey Auditory Verbal Learning Test (AVLT)(Rey, 1964), Digit Span (DS) Memory Task and Digit Symbol Substitution Test (DSST)(Wechsler, 1981), Symbol Digit Modalities Test (SDMT), Speed of Comprehension Test (SCT), Trail Making Test (TMT), simple and choice reaction time and working memory, and inspection time (IT). These are now described.

Rey Auditory Verbal Learning Test (AVLT). Verbal recall of a list of 15 disyllabic concrete words is required for the AVLT. Several recall trials are involved. The test measures immediate memory span (Trial 1), verbal learning (Trials 1–5), short-term memory following an interference list (Trial 7) and long-term memory (Trial 8, 20–30 minutes after Trial 7). Long-term recognition (Trial 9) is also measured, but only in subjects who score less than 13 in Trial 8. Alternate forms of the AVLT were used in the present study for repeated testing. High comparability between alternate forms has been reported (Crawford *et al.*, 1989).

Digit Span (DS). Digit Span involves immediate verbal recall of numbers. It consists of two tasks: DS forwards and DS backwards. DS forwards requires the recall of a series of numbers in the same order that they are given. What DS forward measures is more closely related to the efficiency of attention (i.e. freedom from distractibility) than what is commonly thought of as memory. DS backwards requires recall of the numbers in the reverse order. Therefore it measures elements of working memory, as it requires recall and subsequent manipulation of incoming information (Lezak, 1995). Digit Span is a subtest of the WAIS-R, which has exhibited good test–retest reliability, with coefficients that range from 0.70–0.89 according to age group (Wechsler, 1981). Practice effects have been identified but are described as negligible (Lezak, 1995). The four alternate forms employed in the present study were derived from the WAIS-R (Wechsler, 1981), WISC-R (Wechsler, 1974), WISC-III (Wechsler, 1991) and the WMS-R (Wechsler, 1987).

Digit Symbol Substitution Test (DSST). This test consists of nine predetermined symbols that are individually paired with the numbers one to nine. Subjects are required to substitute the appropriate symbols for a series of 100 numbers. The number of correctly substituted symbols in 90 seconds measures performance (Lezak, 1995). Motor persistence, sustained attention, response speed and visuomotor coordination

play important roles in a normal person's performance on the DSST (Schear and Sato, 1989). Perceptual organisation components also show up on this test (Kaufman *et al.*, 1991). Examination of the test–retest reliability of the DSST has produced relatively high correlation coefficients, ranging from 0.82–0.88 (Matarazzo and Herman, 1984; Youngjohn *et al.*, 1992).

Symbol Digit Modalities Test (SDMT). The SDMT is essentially a reversal of the DSST as it reverses the material such that numbers must be substituted for symbols. Hence, each number (from 1–9) corresponds with one of the nine symbols. There are 110 symbols and the subject is required to substitute as many numbers as possible in 90 seconds. This test primarily assesses complex scanning and visual tracking (Schum *et al.*, 1990). Manual speed and agility also contribute significantly to performance (Schear and Sato, 1989). Hinton-Bayre *et al.*, (1997) developed the alternate forms used in this study.

Speed of Comprehension Test (SCT). This test assesses the speed at which an individual can verify statements about the world (Baddeley *et al.*, 1992). The test consists of 100 simple statements that require a 'true' or 'false' response from the subject. The number of responses completed correctly in 2 min measures performance. Language comprehension, rapid decision-making, visual scanning and psychomotor speed are involved in the performance of the test. The SCT is a subtest of the Speed and Capacity of Language Processing Test (SCOLP). Baddeley *et al.* (1992) developed the alternate forms used in this study.

Trail Making Test (TMT). This test comprises two parts: part A (TMT A) and part B (TMT B). Part A requires the subject to draw a continuous line that connects 25 circled digits in sequence. Part B requires an alternation from number to letter (1-A-2-B-3-C etc). Errors during task completion require immediate correction and performance is measured by the speed at which the task is correctly completed. The Trail Making Test (TMT) measures visual-conceptual and visual-motor tracking (Giovagnoli *et al.*, 1996). Motor speed and agility make a strong contribution to performance (Schear and Sato, 1989). Reliability coefficients for the TMT have varied considerably, with most above 0.60, several in the 0.90 s and more in the 0.80 s (Spreen and Strauss, 1991). Experienced psychometric analysts administered the TMT to a sample of 39 participants (Fals-Stewart, 1992).

Table 1. Acute effects of Bacopa monniera (300 mg) on performance in a battery of neuropsychological tests (mean results \pm SD)

Baseline	Bacopa monniera (300 mg) (n = 18)	Placebo (n = 20)
AVLT list 1 (words)	7.6 \pm 1.8	8.1 \pm 2.7
AVLT list 2 (words)	10.6 \pm 1.7	10.4 \pm 2.7
AVLT list 3 (words)	12.2 \pm 1.6	11.8 \pm 2.3
AVLT list 4 (words)	13.1 \pm 1.6	12.2 \pm 1.8
AVLT list 5 (words)	13.7 \pm 1.3	12.6 \pm 2.5
AVLT list 6 (words)	6.7 \pm 2.5	7.3 \pm 2.8
AVLT list 7 (words)	12.5 \pm 1.8	11.7 \pm 2.5
AVLT list 8 (words)	12.5 \pm 1.8	11.6 \pm 3.0
Trail Making A (ms)	26.4 \pm 6.9	28.6 \pm 9.2
Trail Making B (ms)	75.0 \pm 28.0	62.7 \pm 19.6
Silly Sentences Test (sentences)	71.9 \pm 20.9	71.5 \pm 21.8
Digit Span Forwards (digits)	7.1 \pm 0.9	9.4 \pm 2.0
Digit Span Backwards (digits)	5.2 \pm 1.5	5.6 \pm 1.3
Digit Symbol (symbols)	59.0 \pm 11.5	65.5 \pm 8.7
Inspection Time (ms)	94.4 \pm 47.9	85.2 \pm 25.1
Simple Reaction Time (ms)	243.2 \pm 25.3	266.5 \pm 119.0
Choice Reaction Time (ms)	611.7 \pm 182.7	651.7 \pm 116.4
Working Memory Speed (ms)	1336.3 \pm 289.3	1471.0 \pm 353.4
Working Memory Capacity (ms)	1174.3 \pm 260.7	1146.8 \pm 227.9
2 h post-treatment		
AVLT list 1 (no of words)	6.8 \pm 2.3	6.9 \pm 1.5
AVLT list 2 (words)	10.3 \pm 1.7	9.7 \pm 1.9
AVLT list 3 (words)	11.7 \pm 2.1	11.2 \pm 2.7
AVLT list 4 (words)	12.5 \pm 1.8	11.5 \pm 2.8
AVLT list 5 (words)	13.3 \pm 1.4	12.1 \pm 2.6
AVLT list 6 (words)	7.5 \pm 2.1	7.7 \pm 3.2
AVLT list 7 (words)	12.5 \pm 1.4	10.2 \pm 3.5
AVLT list 8 (words)	12.0 \pm 2.5	9.3 \pm 3.8
Trail Making A (ms)	26.6 \pm 7.8	25.8 \pm 7.4
Trail Making B (ms)	65.6 \pm 24.5	53.9 \pm 16.1
Silly Sentences Test (sentences)	85.3 \pm 13.3	79.9 \pm 16.3
Digit Span Forwards (digits)	6.4 \pm 1.4	7.3 \pm 1.0
Digit Span Backwards (digits)	5.4 \pm 1.4	5.9 \pm 1.6
Digit Symbol (symbols)	67.8 \pm 13.2	67.2 \pm 10.2
Inspection Time (ms)	72.6 \pm 26.0	82.4 \pm 31.4
Simple Reaction Time (ms)	240.5 \pm 31.7	252.1 \pm 46.8
Choice Reaction Time (ms)	506.7 \pm 137.7	585.7 \pm 102.8
Working Memory Speed (ms)	1193.2 \pm 251.0	1319.1 \pm 370.6
Working Memory Capacity (ms)	1106.2 \pm 194.4	1006.9 \pm 150.4

AVLT=Rey Auditory Verbal Learning Test.

Inter-rater reliability on both parts (Fpart A=0.94; Fpart B=0.90) suggested that variance of scores is not introduced with different examiners (Fals-Stewart, 1992).

Reaction time. Simple and complex reaction time (RT) and working memory speed and accuracy were measured using a computerized neuropsychological program from the cognometer series of cognitive tasks published by Brain.com. Speed and error were measured for both tasks. The simple RT task involved pressing an arrow key when a stimulus appeared on the computer screen. The objective of the task was

to get speed (ms) as low (fast) as possible. The complex RT task was a complex multiple choice task that required participants to choose between eight possible responses. The objective of the task was to get speed (ms) as low (fast) as possible. The working memory task involved subjects holding information in memory for short periods of time and indicating whether subsequent stimuli were part of the previously presented array. The object was to be as accurate as possible.

Inspection time. Inspection time (IT) was measured by employing the Parameter Estimation by Sequential

Testing (PEST) procedure developed by Taylor and Creelman (1967). The program was installed on an IBM in compatible Pentium notebook computer. For this task the 80% accuracy level and number of errors were recorded. The IT task defined the time a subject required to make an observation or inspection of the sensory input on which a discrimination of relative magnitude is based. The objective of the task was to be as accurate in responding as possible rather than to get speed as low (fast) as possible.

Analysis

In order to determine whether the field exposure had a significant effect on neuropsychological performance in comparison with placebo, several repeated-measures analyses of variance (ANOVAs) were calculated. Each repeated-measures ANOVA calculated the change between 'pre-drug' or baseline administration and post-drug administration for each condition. Practice effects were adjusted for by studying the treatment-time interaction within subjects.

The analysis was carried out on each of the following cognitive measures: AVLT 1, AVLT learning rate, AVLT 7, AVLT 8, DS forwards, DS backwards, DSST, SDMT, SCT, TMT A, TMT B and TMT difference. The AVLT learning rate was calculated by subtracting the result of Trial 1 from Trial 5. TMT difference was calculated by subtracting TMT A from TMT B. This calculation is designed to remove the effects of visual scanning involved in TMT A and leave the residual effects of visual scanning and cognitive processing required for TMT B.

RESULTS

A series of one-way repeated-measures ANOVAs employing time (pre- and post-assessments of each test) by group (*Bacopa monniera* and placebo) interactions indicated that there were no significant changes in any of the neuropsychological tests at the 0.05 probability level (Table 1). Further analysis did not show any difference in baseline scores between males and females or any age-related drug effects in any of the neuropsychological tests.

DISCUSSION

The current study examined the acute effects of an extract of *Bacopa monniera* in healthy normal subjects. No significant changes were found following administration of *Bacopa monniera* in tests examining attention, working and short-term memory, verbal

learning, memory consolidation, executive processes, planning and problem solving, information processing speed, motor responsiveness and decision-making. The findings suggest that *Bacopa monniera*, administered acutely at a dose of 300 mg, does not exert any observable effects on cognitive function in healthy normal subjects. This finding is consistent with previous studies on other herbal nootropics, such as Ginkgo biloba, which have been found to have no acute effects on cognitive function at low doses (Subhan and Hindmarch 1984; Kennedy *et al.*, 2000). However, the latter study showed positive effects on cognitive function with higher doses of Ginkgo biloba (Kennedy *et al.*, 2000). Similarly, one cannot rule out the possibility that there may be acute dose-related effects of *Bacopa monniera* on various cognitive processes, given that dose-related acute neuropharmacological effects have been reported in animals (Rao and Karanth, 1992).

An important methodological consideration is the time of testing. In the present study, neuropsychological testing was conducted 2 h post-drug administration, based on previously published data on maximum pharmacodynamic effects in animals. While the time at which pharmacodynamic effects are observed in animals may not reflect that observed in humans, we are limited by the lack of any data on either the pharmacokinetic profile of the active constituents or any acute pharmacodynamic effects in humans. Thus the present study may have failed to capture the maximum acute pharmacodynamic effects of *Bacopa monniera* on cognitive function in humans. As the present study is only a preliminary observation, a larger dose-related study examining pharmacodynamic effects at multiple time points is warranted to examine the acute effects of *Bacopa monniera* on cognitive function. Furthermore, previous studies have shown acute dose-related effects with other herbal nootropics such as Ginkgo biloba (Kennedy *et al.*, 2000), indicating that similar effects may also be apparent with *Bacopa monniera*, especially given the fact that they share similarities in their pharmacological mechanism of action (Nathan, 2000; Bhattacharya *et al.*, in press, 2000a).

The current study examined the acute effects of *Bacopa monniera* in healthy normal subjects with a normal level of cognitive functioning. Acute effects may be observed in individuals with a lower baseline level of cognitive functioning. Such age-dependent effects have been reported with Ginkgo biloba (Rigney *et al.*, 1999), with greater effects observed in participants over the age of 55. Although our study did not have many subjects over 50 years of age, we

found no significant relationship between age and drug effects.

While the current study examined the effects of *Bacopa monniera* on the basis of evidence that it modulates the cholinergic system (Agrawal, 1993; Bhattacharya *et al.*, in press), the lack of acute effect is not surprising given that (1) most specific cholinergic modulators such as cholinesterase inhibitors have maximal effects on cognitive function when administered chronically (Becker, 1991), and (2) *Bacopa monniera*'s most potent effects are its antioxidants properties, which are evident only after chronic administration (Bhattacharya *et al.*, 2000a). Taken together, these findings suggest that *Bacopa monniera* may have positive effects on cognitive function when administered chronically.

In summary, the current findings suggest that *Bacopa monniera*, at least at the dose administered, has no acute effects on cognitive functioning in normal healthy subjects. However, one cannot rule out the possibility that there may be acute dose-related, age-dependent and/or chronic effects of *Bacopa monniera* on cognitive function in healthy, normal subjects.

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