

Effects of a Standardized *Bacopa monnieri* Extract on Cognitive Performance, Anxiety, and Depression in the Elderly: A Randomized, Double-Blind, Placebo-Controlled Trial

Carlo Calabrese, N.D., M.P.H.,¹ William L. Gregory, Ph.D.,¹ Michael Leo, Ph.D.,² Dale Kraemer, Ph.D.,³ Kerry Bone, F.N.I.M.H., F.N.H.A.A.,⁴ and Barry Oken, M.D.⁵

Abstract

Objectives: Study aims were to evaluate effects of *Bacopa monnieri* whole plant standardized dry extract on cognitive function and affect and its safety and tolerability in healthy elderly study participants.

Design: The study was a randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of 6 weeks and a treatment period of 12 weeks.

Setting/location: Volunteers were recruited from the community to a clinic in Portland, Oregon by public notification.

Subjects: Fifty-four (54) participants, 65 or older (mean 73.5 years), without clinical signs of dementia, were recruited and randomized to *Bacopa* or placebo. Forty-eight (48) completed the study with 24 in each group.

Interventions: Standardized *B. monnieri* extract 300 mg/day or a similar placebo tablet orally for 12 weeks.

Outcome measures: The primary outcome variable was the delayed recall score from the Rey Auditory Verbal Learning Test (AVLT). Other cognitive measures were the Stroop Task assessing the ability to ignore irrelevant information, the Divided Attention Task (DAT), and the Wechsler Adult Intelligence Scale (WAIS) letter-digit test of immediate working memory. Affective measures were the State-Trait Anxiety Inventory, Center for Epidemiologic Studies Depression scale (CESD)-10 depression scale, and the Profile of Mood States. Vital signs were also monitored.

Results: Controlling for baseline cognitive deficit using the Blessed Orientation–Memory–Concentration test, *Bacopa* participants had enhanced AVLT delayed word recall memory scores relative to placebo. Stroop results were similarly significant, with the *Bacopa* group improving and the placebo group unchanged. CESD-10 depression scores, combined state plus trait anxiety scores, and heart rate decreased over time for the *Bacopa* group but increased for the placebo group. No effects were found on the DAT, WAIS digit task, mood, or blood pressure. The dose was well tolerated with few adverse events (*Bacopa* $n = 9$, placebo $n = 10$), primarily stomach upset.

Conclusions: This study provides further evidence that *B. monnieri* has potential for safely enhancing cognitive performance in the aging.

Introduction

Aging is frequently associated with cognitive decline even in the otherwise healthy. The present increase in the aging demographic in many countries represents an emerging public health problem in terms of disability and

economic impact. Safe agents that enhance cognition in the elderly may mitigate the social and personal losses associated with cognitive decline.

Bacopa monnieri (L.) Pennel has been used for centuries in Ayurvedic medicine, either alone or in combination with other herbs, as a memory and learning enhancer, sedative,

¹Helfgott Research Institute, National College of Natural Medicine, Portland, OR.

²School of Nursing, Oregon Health & Science University, Portland, OR.

³School of Pharmacy, Oregon State University, Portland, OR.

⁴School of Health, University of New England, New South Wales, Australia.

⁵Department of Neurology, Oregon Health & Science University, Portland, OR.

and anti-epileptic.¹ It grows in wet tropical environments, and, under its common English name of water hyssop, is a popular aquarium plant. It has drawn the interest of phytotherapists and pharmacologists,²⁻⁴ and an Australian survey showed it to be one of the most popular aid for memory among 60–64-year-old consumers there.⁵

Animal studies of *B. monnieri* whole plant or alcohol extracts have reported cognition-enhancing effects including improved motor learning⁶ and acquisition, consolidation, and retention of memory in rats.⁷ Memory-enhancing effects have been attributed to saponins (bacosides, bacopasides, or bacopasaponins). Bacopasaponin constituents have been shown to facilitate mental retention in avoidance response in rats,⁸ and to reverse amnesic effects of neurotoxin, scopolamine, phenytoin, electroshock, and immobilization stress.⁹⁻¹¹ Hypothesized mechanisms of action include cholinergic upregulation,³ γ -aminobutyric acid-ergic modulation,¹² antioxidant effects,^{13,14} protein synthesis in the brain,⁷ 5-HT agonism,¹⁵ and modulation of brain stress hormones.¹⁶ *Bacopa* extracts have also ameliorated neurotoxic effects of nicotine¹⁷ and aluminum¹⁸ and reduced β -amyloid levels in the brain of a doubly transgenic mouse model of rapid amyloid deposition (PSAPP mice), suggesting mechanisms of action relevant to Alzheimer's disease.^{19,20}

Bacopa alcohol extract has shown memory-enhancing effects in three double-blind, randomized, placebo-controlled studies. A trial in 46 healthy volunteers 18–60 years old by Stough et al. evaluated their performance on a battery of cognitive tests after 5 weeks and after 12 weeks of 300 mg of *B. monnieri* extract daily.²¹ The investigators reported significant improvements in measures of the Rey Auditory Verbal Learning Test (AVLT)²² and in State Anxiety. Another 3-month study in 76 healthy adults, 40–65 years old, showed an effect of *Bacopa* on the retention of new information in delayed recall of word pairs.²³ A third trial in those over 55 with age-associated memory impairment, again with 3 months of treatment, showed more improvements at 12 weeks on subsets of the Wechsler Memory Scale with no loss of the cognitive gains 4 weeks after ending active treatment.²⁴ Conversely, in a single dose study of *Bacopa* extract in which neuropsychological testing was performed 2 hours after administration, no differences were found between groups.²⁵ A study by the same investigators with 4 weeks' treatment by a combination of *Ginkgo biloba* (maidenhair tree) 120 mg and *Bacopa* 300 mg in 85 healthy participants also did not show cognitive enhancement.²⁶ Stough's study showed effects at 12 weeks but not at 5 weeks, suggesting that cognitive effects with *Bacopa* may take months to appear. Two uncontrolled trials have reported memory- and learning-enhancing effects of *Bacopa* with long-term dosing in children²⁷ and in patients with anxiety neurosis.²⁸

Chemical characterizations of the plant have been carried out by many investigators.²⁹⁻⁴⁰ There are no data currently available on the pharmacokinetics of *Bacopa* or its saponins. Phase I clinical studies confirmed the safety of bacosides in healthy male volunteers at both single and chronic dosing administered over a period of 4 weeks⁷ and 6 weeks with a dose of up to 450 mg of dried water extract.⁴¹ A water extract of *Bacopa* given orally up to a dose of 5 g/kg did not show toxicity in rats. The LD₅₀ of an alcoholic extract given

orally was 17 g/kg.⁴² In the trials cited, total adverse events (AE) were similar in placebo and treatment groups.

Materials and Methods

Design, participants, and screening

Our two-group randomized, placebo-controlled, double-blind trial was a 6-week placebo run-in and 12 weeks of treatment with either *Bacopa* or placebo. Sample size was determined from data in the study by Stough et al.²¹ Participants were recruited from volunteers 65 years or older; living independently; taking no medication other than aspirin, NSAIDs, vitamins, or stable doses of thyroid, HRT, anti-hypertensive, or anti-cholesterol drugs; no complaints of memory impairment compared to others their age and without signs of dementia by the Blessed Orientation-Memory-Concentration Test (BOMC);⁴³ and without known illness likely to produce clinically significant cognitive change in 4 months. Qualified participants had adequate corrected visual acuity and English language skills to successfully complete testing. They were recruited to a clinic at National College of Natural Medicine (NCNM) in Portland, Oregon by newspaper advertising and posters. Volunteers were asked to refrain from alcohol for 24 hours prior to visits and not to change lifestyle habits during the study. All provided informed consent before participation. The protocol was approved by two ethical review boards at NCNM and Oregon Health & Science University.

Intervention

The intervention was 12 weeks of a daily tablet comprising 300 mg of a proprietary dried *Bacopa monnieri* extract manufactured to the specifications of MediHerb Pty. Ltd. (Warwick, Queensland, Australia). This extract was manufactured from the dried aerial parts of *B. monnieri* from India. The herb was extracted with methanol:water (70:30) to produce a 50:1 dry extract with a minimum of 50% bacosides A and B, as determined by a spectrophotometric method. The extract was verified phytochemically by MediHerb against a botanically authenticated reference herb, and a sample of the extract has been retained by MediHerb. This extract was combined with pharmaceutical grade excipients, calcium hydrogen phosphate, cellulose, sodium starch glycolate, magnesium stearate, and hypromellose to produce an oval tablet that was given a final brown film coat. Each tablet contained the equivalent of approximately 15 g herb and 150 mg of bacosides A and B. Placebo tablets were manufactured using the same pharmaceutical excipients and replicated the active in appearance, odor, and texture. Packaging and randomization was performed by NCNM with medications dispensed by the study coordinator. Randomization was determined by a computer-generated series with the proper sequence applied to container labels and supplied to participants in the order enrolled. All study personnel were blinded to assignment until analysis.

Assessments

The primary outcome variable was the delayed recall score from the AVLT word memory task.²² A modified AVLT protocol was used in that a distraction word list was not used

in order to minimize fatigue. The test was administered at the beginning of the placebo run-in phase, at 6 weeks (baseline), 12 weeks (first follow-up), and at conclusion at 18 weeks (second follow-up) along with the Stroop Task⁴⁴ and the Divided Attention Task (DAT).⁴⁵

The Stroop effect occurs when reaction times (RT) to incongruous stimuli (e.g., a participant asked to name the word "green" when it is printed in red) is greater than reaction times to congruous stimuli (e.g., naming the word "red" when it is printed in red). In the DAT, participants saw a briefly presented symbol centered on a computer screen on which they made a discrimination (indicating either a car or truck) and specified the location (in which of eight sectors surrounding the center stimulus) of a different symbol. If the participant made 75% correct responses, the display speed of the stimulus was shortened incrementally. In this fashion, an algorithm finds the minimum display time required for the participant to get at least 75% trials correct. The DAT yields two measures: the minimum display time required to achieve 75% accuracy (referred to as the threshold) and the number of incorrect responses made when performing the task above the threshold (accuracy).

Administered on the same schedule were the Center for Epidemiologic Studies Depression scale (CESD-10),⁴⁶ the Profile of Mood States (POMS),⁴⁷ the State-Trait Anxiety Inventory (STAI),⁴⁸ and the letter-digit sequencing task from the Wechsler Adult Intelligence Scale III (WAIS),⁴⁹ a measure of immediate working memory. Blood pressure, heart rate, and temperature were also measured. The BOMC, the Wide Range Achievement test (WRAT),⁵⁰ and a demographic questionnaire (age, gender, race/ethnicity, and educational level) were administered prior to participation. Medication changes were monitored, as were pill counts of remaining *Bacopa* or placebo pills at each follow-up session. Each participant's guess as to which condition she or he was in was also assessed.

The additional cognitive measures were included to determine whether *Bacopa* affected cognitive functions more complex than short-term memory. Individual differences were assessed to control for potential covariates (e.g., intelligence, knowledge, education, mood) and to examine potential moderators of the relationship between *Bacopa* and memory (e.g., reduction in anxiety and/or depression).

Primary analysis

The resultant design analyzed was a 2 (between-subjects group: *Bacopa* versus placebo) by 3 (within-subjects time of assessment: baseline, first follow-up, second follow-up) mixed model. Given prior research results, it was predicted that the *Bacopa* participants would improve over time with the performance of the placebo participants remaining unchanged, or the *Bacopa* participants would remain unchanged and the placebo participants would decline in performance over time. Depending on whether the change was continuous or occurred between two time points only, this interaction would be the result of either a significant time of assessment linear trend or time of assessment quadratic trend in one group (*Bacopa* or placebo) but not the other. Thus, the primary analysis performed was an analysis of variance (ANOVA) single degree of freedom test of the lin-

ear time of assessment component within each group, and if neither was significant, the single degree of freedom quadratic time of assessment trend within each group was tested.

Results

Demographics

There were 117 respondents to recruitment outreach, of whom 45 were ineligible primarily on the basis of exclusionary concomitant medications; 18 refused participation and 54 qualifiers were enrolled. Three (3) dropped out in each group for reasons unrelated to the study, leaving 24 completers in each group. Sixty percent of participants were women, 94% were white, and 6% were Asian. The average age was 73.5 years. The mode educational level was a college graduate. No changes to psychoactive medications occurred during the study.

Covariate screening

To minimize co-linearity between covariates when analyzing the primary outcome measure, the baseline variables were analyzed to determine (1) whether they differed between the two groups, and (2) whether any were correlated with the delayed recall task. No differences between the groups existed for age, systolic or diastolic blood pressure, heart rate, temperature, BOMC scores, CESD scores, STAI scores (both trait and anxiety), or educational level (all $F_s < 1$), WRAT scores, and POMS scores (both $p > 0.22$), nor did they differ in gender or racial/ethnic composition (both $\chi^2 < 1$). The treatment group was slightly higher in WAIS digit scores ($p < 0.09$), though WAIS scores were not correlated significantly with the delayed recall measure ($r = 0.09$). The only measures that correlated significantly with the delayed recall measure were the WRAT ($r = -0.30, p < 0.04$) and the BOMC ($r = -0.39, p < 0.01$). These did not correlate significantly with one another, so both were included as covariates in analysis of delayed recall. Gender was also related to delayed recall scores ($r = .28, p < 0.05$), with women having better scores, so gender was included in the statistical model.

AVLT delayed recall

The delayed recall scores from the AVLT were analyzed using a 2 (between groups: placebo versus *Bacopa*) by 2 (between groups: gender) by 3 (within subjects assessment time: baseline versus first follow-up versus second follow-up) analysis of covariance (ANCOVA) with BOMC and WRAT scores as covariates. The multivariate approach to repeated measures ANOVA was employed, which provides an exact solution avoiding corrections to the degrees of freedom (e.g., the Huyndt-Feldt correction). The covariates were first centered (to avoid co-linearity with their respective interaction terms) and their interactions with the between group measures were tested while controlling for their linear effects. The BOMC by group, the BOMC by gender, the WRAT by group, and the WRAT by gender effects were not significant, all $F_s < 1$, indicating that the relationship between the covariates and outcome measures did not differ by group or gender. Thus, the assumption of parallel regression slopes necessary to perform covariate analysis was met.

BOMC was a significant covariate. High BOMC scores (indicating impaired cognition) were associated with poorer delayed recall. WRAT was not significant as a covariate, so it was dropped from the analysis. Women had significantly better delayed recall than men.

The linear component was tested within each group separately while controlling for BOMC and gender. The linear trend within the *Bacopa* group was significant but was not within the placebo group. The delayed recall scores of placebo group participants remained stable over the 12 weeks of treatment, but the scores of the *Bacopa* participants improved by over one word during the 12 weeks. Means, *F* values, alphas, and effect sizes for this and all other significant *p* values are displayed in Table 1.

AVLT immediate recall

The linear and quadratic components were tested in both groups while controlling for BOMC and gender. No effects were significant.

Stroop task reaction time

The difference between incongruous and congruous stimuli RT (reflecting the Stroop effect) was analyzed using the same linear and quadratic tests while controlling for BOMC and gender. Neither BOMC nor gender was significant. For

the placebo group, neither the linear nor quadratic component was significant. For the *Bacopa* group, both the linear component and the quadratic component were statistically significant. The means (Table 1) reveal that Stroop effect times were stable for the placebo group, but improved for the *Bacopa* group between baseline and the first follow-up, then remained relatively stable. Stroop task errors were too few to render a meaningful analysis.

Divided attention task

The linear and quadratic components were tested while controlling for BOMC and gender. There were no significant effects on either threshold or accuracy.

WAIS digit task

The linear and quadratic components were tested in both groups while controlling for BOMC and gender. The only significant effect was for BOMC.

Depression

The BOMC correlation with CESD approached significance ($r = 0.27, p < 0.06$). Accordingly, it was used as a covariate in an ANCOVA on CESD scores. It did not achieve significance ($p > 0.25$). Gender approached significance ($p <$

TABLE 1. MEANS FOR COGNITIVE, AFFECTIVE, AND PHYSIOLOGIC MEASURES^a

Variables	Group	Baseline	+6 Weeks	+12 Weeks	F	df	p ^b	η^2
		M (SD)	M (SD)	M (SD)				
Cognitive								
AVLT Delayed Recall ^c (# of words)	Placebo	6.8 (3.6)	6.6 (3.9)	6.9 (4.2)	<1			
	<i>Bacopa</i>	6.4 (3.1)	6.6 (3.6)	7.6 (3.9)	5.4	1,21	0.03*	0.20
Stroop Task RT ^c (seconds)	Placebo	60.9 (12.2)	60.3 (13.5)	60.5 (13.8)	<1			
	<i>Bacopa</i>	60.1 (10.1)	56.3 (8.3)	57.2 (7.6)	9.4	1,21	0.003*	0.29
					10.6	1,21	0.006**	0.32
Affective								
CESD-10 ^c (depression)	Placebo	4.5 (3.5)	6.3 (4.0)	5.3 (4.2)	<1			
	<i>Bacopa</i>	6.5 (4.2)	6.3 (3.6)	5.6 (3.5)	4.0	1,43	0.05 ^d	0.08
STAI ^e (trait + state anxiety)	Placebo	27.7 (7.6)	30.4 (9.5)	28.6 (7.2)	<1			
	<i>Bacopa</i>	30.1 (8.4)	28.1 (8.4)	28.5 (7.8)	3.3	1,38	0.04* ^f	0.14
					3.3	1,38	0.05** ^f	0.12
Physiologic								
Heart rate (bpm)	Placebo	67.2 (8.1)	70.0 (9.1)	72.3 (8.4)	<1			
	<i>Bacopa</i>	68.8 (12.0)	67.4 (9.5)	67.9 (8.0)	7.3	1,44	0.01 ^d	0.09
MANOVA								
Composite measure ^g	Placebo	60.9 (6.9)	59.3 (6.2)	59.9 (5.5)	<1			
	<i>Bacopa</i>	59.6 (6.2)	61.3 (5.5)	61.0 (4.8)	4.9	2,33	0.01 ^d	0.23

^aOnly statistically significant variables are included. Nonsignificant measures included Rey Auditory Verbal Learning Test (AVLT) immediate reaction times, Stroop task errors, divided attention task scores, Wechsler Intelligence Scale for Children digit task, Profile of Mood States, and blood pressure.

^bA single asterisk (*) indicates that the adjacent *F*, *df*, *p*, and η^2 are for the linear component of time of assessment within a group. A double asterisk (**) indicates they are for the quadratic component.

^cMeans adjusted for significant gender effect and significant covariate (the Blessed Orientation Memory Concentration Test).

^dReported values are for an overall group by linear component of assessment time interaction.

^eMeans adjusted for significant covariate (initial screening trait + state anxiety).

^fOne-tailed.

^gSee footnote * in text.

CESD, Center for Epidemiologic Studies Depression scale; RT, reaction times; sd, standard deviation; M, mean; STAI, State-Trait Anxiety Inventory.

0.07). Women had higher depression scores than men. Neither the linear component nor the quadratic components within the placebo or *Bacopa* groups was conventionally significant. However, there was a time linear component by group interaction ($p < 0.05$). As can be seen in Table 1, depression scores for the placebo group are higher at the completion of the study than at the beginning, while the opposite is true for the *Bacopa* group.

Anxiety

BOMC was not correlated with STAI Trait or State scores. Because of the correlation between Trait and State anxiety, the two measures were combined into a single score. Gender was unrelated to anxiety (Spearman $p > 0.10$), so was not included in the model. A 2 (groups) by 3 (assessment time) mixed ANCOVA was performed on trait+state scores using initial screening trait+state anxiety scores as the covariate. First tested was the centered anxiety by group by time and the centered anxiety by group interactions. Neither was significant, indicating that it was appropriate to use anxiety scores in the ANCOVA. Anxiety scores proved a significant covariate ($p < 0.001$).

No effects were found for the linear or quadratic components within either group. There was an overall group by quadratic component of time interaction (Table 1). Inspection of the means reveals that *Bacopa* participants declined in anxiety from baseline to first follow-up and then remained relatively unchanged. In contrast, the placebo participants' anxiety scores were similar at baseline and second follow-up.

Mood

BOMC was not correlated with POMS scores. Thus, POMS scores were analyzed using a 2 by 2 by 3 mixed ANOVA. No effects were significant.

Physiologic measures

The linear and quadratic components were tested in both groups. No significant effects were observed on blood pressure or temperature. However, the linear component of time was significant within the placebo group. Heart rate increased in this group between baseline and the second follow-up. There were no other effects in the analysis on heart rate.

To control for the alphawise error inherent in performing multiple analyses, a doubly multivariate analysis of covariance (MANCOVA) was performed. The analysis was doubly multivariate in that there were multiple assessments of outcome measures (3), and multiple measures (5: delayed recall, Stroop RT, CESD-10, anxiety, and heart rate). A 2 (gender) by 2 (groups) by 3 (time of assessment) mixed MANCOVA employing both BOMC and screening anxiety as covariates was performed. Anxiety was a significant covariate ($p < 0.001$); BOMC was not. The group by time interaction was significant (by Pillai's Trace method) ($F(2,33) = 4.9$, $p < 0.01$), as was the group by linear component of time interaction ($p < 0.01$); the quadratic component approached

significance ($p < 0.06$). The composites* for each group represented in the 2 by 3 interaction reflected a pattern similar to those described above (Table 1). That is, the placebo group's score at the 6-week assessment was worse than at baseline, and remained worse at 12 weeks. The *Bacopa* group's score at the 6-week assessment was better than at baseline, and remained better at 12 weeks. These findings strengthen confidence in the overall pattern of results, suggesting that they are not due to statistical artifact.

Pill count

An excess of pills was provided to participants to force a remainder without informing subjects of the exact number of pills provided. Compliance, as determined by remaining pills, was very high with an average of 3.9 (of 84) pills missed over the course of 12 weeks. There was no difference between groups. The number of pills taken between baseline and the first follow-up was not related to memory task score changes or affective score changes during that same interval or the entire study. Likewise, no relationship was found between the number of pills taken between the first and final follow-ups and changes in memory or affect scores during that period or the entire study. Total pills taken were not related to any memory or affect change measures.

Placebo run-in

The study design included a placebo run-in phase to minimize learning differences. A 2 (groups: *Bacopa* versus placebo) by 2 (time of assessment: screening versus baseline) mixed ANCOVA was performed on the delayed recall scores of the AVLT. The covariate of BOMC screening scores produced the only significant effect ($p < 0.01$). The BOMC scores were related to delayed recall scores and, overall, participants' scores did not change from screening to baseline. An identical ANCOVA was performed on immediate recall scores and, similarly, no effects were significant. Thus, there was no evidence of a placebo effect at this stage of the trial.

Masking

Most participants believed that they were in the treatment group. The frequency of this belief was greater than chance (32/48, binomial $p < 0.01$), but the conditions did not differ in the belief of receiving verum (placebo: 17/24; treatment: 15/24). Results of the delayed recall task were analyzed as a function of which group participants believed they were in, but there was no detectable effect of belief. No subject reported suspicions consistent with detecting the placebo run-in.

Adverse events (AE)

A total of 41 AE were reported. Twenty-three (23) were reported in the placebo group and 18 in the *Bacopa* group (binomial probability that these values differ significantly from a 50–50 random split is $p > 0.50$). Of the 41 total AE, 22 were considered "not related" and 19 "possibly related" (10 in the placebo group; 9 in the *Bacopa* group; binomial $p = 1.0$). Thus, there is no difference in AE between groups. Of the nine possibly related AE in the *Bacopa* group, "flu-like symptoms" and "digestive problems" were most often reported. Stough et al. reported side-effects of thirst, nausea,

*The composite measure created by the SPSS GLM procedure is the adjusted least squares mean of the sum of all of the outcome variables included in the multivariate analysis.

and muscle fatigue, which were not elevated in our *Bacopa* group.

Discussion

Using a rigorous design, the results demonstrate that *Bacopa* has positive benefits on multiple measures of cognitive performance and affect. *Bacopa* recipients improved in delayed recall memory and Stroop task reaction times over the course of the study while placebo recipients remained stable on both. *Bacopa* recipients displayed a decrease in depression and combined state plus trait anxiety scores with the placebo recipients increasing on both. Participants also had slightly lower heart rates after taking *Bacopa* while those taking the placebo displayed an increase in heart rate. No effects were shown on the immediate recall task, divided attention task, the WAIS digit span task, mood states, blood pressure, and body temperature.

The benefits of *B. monnieri* for both the delayed recall task and anxiety replicate the findings of Stough et al. and Roodenrys et al. in normal adults but in an elderly population, and reflect the findings of Raghav et al. in an elderly population with cognitive impairments.^{21,23,24} In all four studies, participants received *Bacopa* for 12 weeks. Nathan et al. failed to find benefits of *Bacopa* after 2 hours and 4 weeks.^{25,26}

These data extend the demonstrated benefits of *Bacopa* to another cognitive task, the Stroop test, and to depression scores and heart rate. Given the purported anxiolytic properties of *Bacopa*,²⁷ it is possible that the increased depression scores and increased heart rate in the placebo group may reflect frustration with the repeated visits in which the same tasks are performed, rather than an actual increase in depression. On the other hand, *Bacopa* has shown evidence of antidepressant activity in two mouse models.⁵¹ Insulation against such frustration may be a benefit of *Bacopa*, leading to better (or less impaired) task performance.

Conclusion

This study provides further evidence that standardized extracts of *B. monnieri* have potential for safely enhancing cognitive performance in aging, an indication that is closely comparable to the traditional uses of the herb. Whether this effect is due to a direct mechanism in which the active agents in *B. monnieri* act upon brain chemistry to influence memory processes or to greater tolerance for frustration, or due to decreasing the performance-degrading effects of arousal on complex tasks, or yet some other mechanism, remains to be explored.

Acknowledgments

This study was supported as pilot work by the Oregon Research Center for Complementary and Alternative Medicine Neurological Disorders with funds from the National Institutes of Health National Center for Complementary and Alternative Medicine. Additional funds were provided by the Northwest Health Foundation. MediHerb Pty. Ltd. provided the tablets at no cost.

Kerry Bone F.N.M.I.H., F.N.H.A.A., is the Chairman of the Board and Director of Research and Development of MediHerb Pty. Ltd. He was not involved with the conduct of the study nor analysis or interpretation of the results. The other authors have no conflicts to report.

References

- Jain SK. Ethnobotany and research on medicinal plants in India. *Ciba Found Symp* 1994;185:153–164; discussion 164–168.
- Kidd PM. A review of nutrients and botanicals in the integrative management of cognitive dysfunction. *Altern Med Rev* 1999;4:144–161.
- Russo A, Borrelli F. *Bacopa monniera*, a reputed nootropic plant: An overview. *Phytomedicine* 2005;12:305–317.
- Kumar V. Potential medicinal plants for CNS disorders: An overview. *Phytother Res* 2006;20:1023–1035.
- Jorm AF, Rodgers B, Christensen H. Use of medications to enhance memory in a large community sample of 60–64 year olds. *Int Psychogeriatr* 2004;16:209–217.
- Prakash JC, Sirsi M. Comparative study of the effects of Brahmi and chlorpromazine on motor learning in rats. *J Sci Ins Res* 1962;21:93–96.
- Singh HK, Dhawan BN. Neuropsychopharmacological effects of the ayurvedic nootropic *Bacopa monniera* Linn. (Brahmi). *Indian J Pharmacol* 1997;29:359–365.
- Singh HK, Rastogi RP, Sriman RC, Dhawan BN. Effect of bacoside A and B on avoidance response in rats. *Phytother Res* 1988;2:70–75.
- Bhattacharya SK, Kumar A, Ghosal S. Effect of *Bacopa monniera* on animal models of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. In: Mori A, Satoh T, eds. *Molecular Aspects of Asian Medicines*. Westbury, NY: PJD Publications, 2001.
- Kishore K, Singh M. Effect of bacosides, alcoholic extract of *Bacopa monniera* Linn. (brahmi), on experimental amnesia in mice. *Indian J Exp Biol* 2005;43:640–645.
- Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by *Bacopa monniera*, a reputed Indian nootropic plant. *J Ethnopharmacol* 2000;71:383–390.
- Dey PK, Datta C. Effect of psychotropic phytochemicals on cerebral amino acid level in mice. *Indian J Exp Biol* 1966;4:216–229.
- Tripathi YB, Chaurasia S, Tripathi E, et al. *Bacopa monniera* Linn. as an antioxidant: Mechanism of action. *Indian J Exp Biol* 1996;34:523–526.
- Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monniera* in rat frontal cortex, striatum and hippocampus. *Phytother Res* 2000;14:174–179.
- Hall B, Burnett A, Halley C, et al. Pharmacology of *Bacopa* at 5HT1a and 5HT2a receptors [poster]. 46th Annual Meeting Society of Pharmacognosy, Corvallis, OR, July 2005.
- Sheikh N, Ahmad A, Siripurapu KB, et al. Effect of *Bacopa monniera* on stress induced changes in plasma corticosterone and brain monoamines in rats. *J Ethnopharmacol* 2007;111:671–676.
- Vijayan V, Helen A. Protective activity of *Bacopa monniera* Linn. on nicotine-induced toxicity in mice. *Phytother Res* 2007;21:378–381.
- Jyoti A, Sharma D. Neuroprotective role of *Bacopa monniera* extract against aluminium-induced oxidative stress in the hippocampus of rat brain. *Neurotoxicology* 2006;27:451–457.
- Holcomb LA, Dhanasekaran M, Hitt AR, et al. *Bacopa monniera* extract reduces amyloid levels in PSAPP mice. *J Alzheimers Dis* 2006;9:243–251.
- Dhanasekaran M, Tharakan B, Holcomb LA, et al. Neuroprotective mechanisms of ayurvedic antidementia botanical *Bacopa monniera*. *Phytother Res* 2007;21:965–969.

21. Stough C, Lloyd J, Clarke J, et al. The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects. *Psychopharmacology* 2001;156:481–484.
22. Rey A. The Clinical Examination in Psychology [in French]. Paris: Presses Universitaires de France, 1964.
23. Roodenrys S, Booth D, Bulzomi S, et al. Chronic effects of Brahmi (*Bacopa monniera*) on human memory. *Neuropsychopharmacology* 2002;27:279–281.
24. Raghav S, Singh H, Dalal PK, et al. Randomized controlled trial of standardized *Bacopa monniera* in age-associated memory impairment. *Indian J Psychiatry* 2006;48:238–242.
25. Nathan PJ, Clarke J, Lloyd J, et al. The acute effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy normal subjects. *Hum Psychopharmacol* 2001;16:345–351.
26. Nathan PJ, Tanner S, Lloyd J, et al. Effects of a combined extract of *Ginkgo biloba* and *Bacopa monniera* on cognitive function in healthy humans. *Hum Psychopharmacol* 2004;19:91–96.
27. Sharma R, Chaturvedi C, Tewari PV. Efficacy of *Bacopa* in revitalizing intellectual functions in children. *J Res Edu Indian Med* 1987;1:12.
28. Singh RH, Singh L. Studies on the anti-anxiety effect of the *medhya rasayana* drug Brahmi (*Bacopa monniera* Wettst.). *Res Ayur Siddha* 1980;1:133–148.
29. Ahmed B, Rahman A. Bacosterol, a new 13, 14 secosteroid and Bacosine, a new triterpene from *Bacopa monniera*. *Indian J Chem Sect B Organic Chem Med Chem* 2000;39:620–625.
30. Chakravarty AK, Sarkar T, Masuda K, et al. Bacopasides I and II: Two pseudojubogenin glycosides from *Bacopa monniera*. *Phytochemistry* 2001;58:553–556.
31. Chakravarty AK, Sarkar T, Nakane T, et al. New phenylethanoid glycosides from *Bacopa monniera*. *Chem Pharm Bull* 2002;50:1616–1618.
32. Chakravarty AK, Garai S, Masuda K, et al. Bacopasides III–V: Three new triterpenoid glycosides from *Bacopa monniera*. *Chem Pharm Bull* 2003;51:215–217.
33. Deepak M, Amit A. The need for establishing identities of “bacoside A and B” the putative major bioactive saponins of Indian medicinal plant *Bacopa monniera*. *Phytomedicine* 2004;11:264–266.
34. Deepak M, Sangli GK, Arun PC, Amit A. Quantitative determination of the major saponin mixture Bacoside A in *Bacopa monnieri* by HPLC. *Phytochem Analysis* 2005;16:24–29.
35. Garai S, Mahato SB, Ohtani K, Yamasaki K. Dammarane-type triterpenoid saponins from *Bacopa monniera*. *Phytochem* 1996a;42:815–820.
36. Garai S, Mahato SB, Ohtani K, Yamasaki K. Bacopasaponin D: A pseudojubogenin glycoside from *Bacopa monniera*. *Phytochem* 1996b;43:447–449.
37. Hou CC, Lin SJ, Cheng JT, Hsu FL. Bacopaside III, Bacopasaponin G, and Bacopasides A, B and C from *Bacopa monniera*. *J Natural Products* 2002;654:1759–1763.
38. Mahato SB, Garai S, Chakravarty AK. Bacopasaponins E and F: Two jubogenin bisdesmosides from *Bacopa monniera*. *Phytochemistry* 2000;53:711–714.
39. Rastogi S, Pal R, Kulshreshtha DK. Bacoside A(3): A triterpenoid saponin from *Bacopa monniera*. *Phytochemistry* 1994;36:133–137.
40. Rastogi S, Kulshreshtha DK. Bacopside A(2): A triterpenoid saponin from *Bacopa monniera*. *Indian J Chem Sect B Organic Chem Med Chem* 1999;38:353–356.
41. Pravina K, Ravindra KR, Goudar KS, et al. Safety evaluation of BacoMind in healthy volunteers: A phase I study. *Phytomedicine* 2007;14:301–308.
42. Martis G, Rao A. Neuropharmacological activity of *Herpestis monniera*. *Fitoterapia* 1992;63:399–404.
43. Blessed G, Tomlinson E, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797–811.
44. MacLeod CM. Half a century of research on the Stroop effect: An integrative approach. *Psycholog Bull* 1991;109:163–203.
45. Ball K, Owsley CJ. The useful field of view test: A new technique for evaluating age-related declines in visual function. *Am Optom Assoc* 1993;64:71–79.
46. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med* 1994;10:77–84.
47. McNair DM, Heuchert JWP, Shilony E. Research with the Profile of Mood States (POMS) 1964–2002: A comprehensive bibliography. Toronto: Multi-Health Systems, 2003.
48. Spielberger CD. Manual for the State-Trait Anxiety Inventory (STAI). Palo Alto, CA: Consulting Psychologists Press, 1983.
49. Tulsy DS, Ivnik RJ, Price LR, Wilkens C. Assessment of cognitive functioning with the WAIS–III and WMS–III: Development of a six-factor model. In: Tulsy DS, Chelane GJ, Ivnik RJ, et al., eds. *Clinical Interpretation of the WAIS–III and WMS–III*. San Diego: Academic Press, 2003:149–182.
50. Wilkinson GS, Robertson GJ. *The Wide Range Achievement Test 4*. Lutz, FL: Psychological Assessment Resources, Inc., 2004.
51. Zhou Y, Shen YH, Zhang C, et al. Triterpene saponins from *Bacopa monniera* and their antidepressant effects in two mice models. *J Nat Prod* 2007;70:652–655.

Address reprint requests to:
Carlo Calabrese, N.D., M.P.H.
Helfgott Research Institute
National College of Natural Medicine
049 SW Porter Street
Portland, OR 97201

E-mail: ccalabrese@ncnm.edu

This article has been cited by:

1. Amrita Mishra, Arun K. Mishra, Om Prakash Tiwari, Shivesh Jha. 2013. HPLC analysis and standardization of Brahmi vati – An Ayurvedic poly-herbal formulation. *Journal of Young Pharmacists* . [[CrossRef](#)]
2. Sarah Benson, Luke A. Downey, Con Stough, Mark Wetherell, Andrea Zangara, Andrew Scholey. 2013. An Acute, Double-Blind, Placebo-Controlled Cross-over Study of 320mg and 640mg Doses of Bacopa monnieri (CDRI 08) on Multitasking Stress Reactivity and Mood. *Phytotherapy Research* n/a-n/a. [[CrossRef](#)]
3. Jerome Sarris, Erica McIntyre, David A. Camfield. 2013. Plant-Based Medicines for Anxiety Disorders, Part 2: A Review of Clinical Studies with Supporting Preclinical Evidence. *CNS Drugs* . [[CrossRef](#)]
4. Vidya Sathyanarayanan, Tinku Thomas, Suzanne J. L. Einöther, Rajendra Dobriyal, M. K. Joshi, Srinivasan Krishnamachari. 2013. Brahmi for the better? New findings challenging cognition and anti-anxiety effects of Brahmi (Bacopa monniera) in healthy adults. *Psychopharmacology* **227**:2, 299-306. [[CrossRef](#)]
5. Prasanna Habbu, Smita Madagundi, Ramesh Kulkarni, Sagar Jadav, Rashmi Vanakudri, Venkatrao Kulkarni. 2013. Preparation and evaluation of Bacopa–phospholipid complex for anti-amnesic activity in rodents. *Drug Invention Today* **5**:1, 13-21. [[CrossRef](#)]
6. Con Stough, Vanessa Cropley, Matthew Pase, Andrew Scholey, James Kean Assessing the Utility of Bacopa monnieri to Treat the Neurobiological and Cognitive Processes Underpinning Cognitive Aging 241-250. [[CrossRef](#)]
7. Herbal approaches to system dysfunctions 183-350. [[CrossRef](#)]
8. Luke A. Downey, James Kean, Fiona Neme, Angela Lau, Alex Poll, Rebecca Gregory, Margaret Murray, Johanna Rourke, Brigit Patak, Matthew P. Pase, Andrea Zangara, Justine Lomas, Andrew Scholey, Con Stough. 2012. An Acute, Double-Blind, Placebo-Controlled Crossover Study of 320mg and 640mg Doses of a Special Extract of Bacopa monnieri (CDRI 08) on Sustained Cognitive Performance. *Phytotherapy Research* n/a-n/a. [[CrossRef](#)]
9. Carlo Calabrese, Amala Soumyanath Brahmi 205-226. [[CrossRef](#)]
10. Neetu Saini, Devinder Singh, Rajat Sandhir. 2012. Neuroprotective Effects of Bacopa monnieri in Experimental Model of Dementia. *Neurochemical Research* **37**:9, 1928-1937. [[CrossRef](#)]
11. Matthew P. Pase, James Kean, Jerome Sarris, Chris Neale, Andrew B. Scholey, Con Stough. 2012. The Cognitive-Enhancing Effects of Bacopa monnieri: A Systematic Review of Randomized, Controlled Human Clinical Trials. *The Journal of Alternative and Complementary Medicine* **18**:7, 647-652. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
12. Bhupinder S. Brar, Richa Chhibber, Vani Murthy H. Srinivasa, Bianca A. Dearing, Richard McGowan, Ralph V. Katz. 2012. Use of Ayurvedic Diagnostic Criteria in Ayurvedic Clinical Trials: A Literature Review Focused on Research Methods. *The Journal of Alternative and Complementary Medicine* **18**:1, 20-28. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
13. Paul G. Harch, Susan R. Andrews, Edward F. Fogarty, Daniel Amen, John C. Pezzullo, Juliette Lucarini, Claire Aubrey, Derek V. Taylor, Paul K. Staab, Keith W. Van Meter. 2012. A Phase I Study of Low-Pressure Hyperbaric Oxygen Therapy for Blast-Induced Post-Concussion Syndrome and Post-Traumatic Stress Disorder. *Journal of Neurotrauma* **29**:1, 168-185. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
14. Andrew Pengelly, James Snow, Simon Y. Mills, Andrew Scholey, Keith Wesnes, Leah Reeves Butler. 2012. Short-Term Study on the Effects of Rosemary on Cognitive Function in an Elderly Population. *Journal of Medicinal Food* **15**:1, 10-17. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
15. Tatimah Peth-Nui, Jintanaporn Wattanathorn, Supaporn Muchimapura, Terdthai Tong-Un, Nawanant Piyavhatkul, Poonsri Rangseekajee, Kornkanok Ingkaninan, Sakchai Vittaya-areekul. 2012. Effects of 12-Week Bacopa monnieri Consumption on Attention, Cognitive Processing, Working Memory, and Functions of Both Cholinergic and Monoaminergic Systems in Healthy Elderly Volunteers. *Evidence-Based Complementary and Alternative Medicine* **2012**, 1-10. [[CrossRef](#)]
16. Khalid Rauf, Fazal Subhan, Robert D. E. Sewell. 2011. A Bacoside Containing Bacopa monnieri Extract Reduces Both Morphine Hyperactivity Plus the Elevated Striatal Dopamine and Serotonin Turnover. *Phytotherapy Research* n/a-n/a. [[CrossRef](#)]
17. Hari Sharma, H.M. Chandola. 2011. Prameha in Ayurveda: Correlation with Obesity, Metabolic Syndrome, and Diabetes Mellitus. Part 2—Management of Prameha. *The Journal of Alternative and Complementary Medicine* **17**:7, 589-599. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
18. Khalid Rauf, Fazal Subhan, Muzaffar Abbas, Amir Badshah, Ihsan Ullah, Sami Ullah. 2011. Effect of Bacoposides on acquisition and expression of morphine tolerance. *Phytomedicine* **18**:10, 836-842. [[CrossRef](#)]
19. Robert Jesky, Chen Hailong. 2011. Are Herbal Compounds the Next Frontier for Alleviating Learning and Memory Impairments? An Integrative Look at Memory, Dementia and the Promising Therapeutics of Traditional Chinese Medicines. *Phytotherapy Research* n/a-n/a. [[CrossRef](#)]

20. Manish Kumar Saraf, Sudesh Prabhakar, Krishan Lal Khanduja, Akshay Anand. 2011. Bacopa monniera Attenuates Scopolamine-Induced Impairment of Spatial Memory in Mice. *Evidence-Based Complementary and Alternative Medicine* **2011**, 1-10. [[CrossRef](#)]
21. A. Scholey, C. Stough Neurocognitive effects of herbal extracts 272-298. [[CrossRef](#)]
22. Dementia and Alzheimer's disease 281-305. [[CrossRef](#)]
23. Annette Morgan, John Stevens. 2010. Does Bacopa monnieri Improve Memory Performance in Older Persons? Results of a Randomized, Placebo-Controlled, Double-Blind Trial. *The Journal of Alternative and Complementary Medicine* **16**:7, 753-759. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
24. Jun-Young Lee, Ka Young Kim, Ki Young Shin, Beom Young Won, Hee Yeon Jung, Yoo-Hun Suh. 2009. Effects of BT-11 on memory in healthy humans. *Neuroscience Letters* **454**:2, 111-114. [[CrossRef](#)]
25. 2009. Current awareness in geriatric psychiatry. *International Journal of Geriatric Psychiatry* **24**:2, i-viii. [[CrossRef](#)]