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Does *Bacopa monnieri* Improve Memory Performance in Older Persons? Results of a Randomized, Placebo-Controlled, Double-Blind Trial

Annette Morgan, MSc, and John Stevens, PhD

Abstract

Objective: The objective of this study was to investigate the effectiveness of *Bacopa monnieri* Linn. for improvement of memory performance in healthy older persons.
Study design: This was a randomized, double-blind, placebo-controlled trial.
Setting and participants: The trial took place in Lismore, NSW, Australia between February and July 2005. Ninety-eight (98) healthy participants over 55 years of age were recruited from the general population.
Interventions: Participants were randomized to receive an extract of *Bacopa monnieri* called BacoMind™ (Natural Remedies Pvt. Ltd.), 300 mg/day, or an identical placebo. Following screening, neuropsychologic and subjective memory assessments were performed at baseline and at 12 weeks.
Outcome measures: Audioverbal and visual memory performance were measured by the Rey Auditory Verbal Learning Test (AVLT), the Rey-Osterrieth Complex Figure Test (CFT), and the Reitan Trail Making Test (TMT). Subjective memory performance was measured by the Memory Complaint Questionnaire (MAC-Q).
Results: One hundred and thirty-six (136) subjects volunteered; 103 met entry criteria, 98 commenced, and 81 completed the trial. *Bacopa* significantly improved verbal learning, memory acquisition, and delayed recall as measured by the AVLT: trial a4 ($p = 0.000$), trial a5 ($p = 0.016$); trial a6 ($p = 0.000$); trial a7 (delayed recall) ($p = 0.001$); total learning ($p = 0.011$); and retroactive interference ($p = 0.048$). CFT, MAC-Q, and TMT scores improved but group differences were not significant. Bacopa versus placebo caused gastrointestinal tract (GIT) side-effects.
Conclusions: *Bacopa* significantly improved memory acquisition and retention in healthy older Australians. This concurs with previous findings and traditional use. *Bacopa* caused GIT side-effects of increased stool frequency, abdominal cramps, and nausea.

Introduction

Bacopa monnieri Linn. (*Bacopa*) is an aquatic plant that has been used for many centuries in the traditional Ayurvedic medical system of India to enhance memory and intellectual function and promote longevity. While the mechanism of action of *Bacopa* has not been elucidated, preclinical studies have demonstrated cholinergic,[1,2] antioxidant,[3–8] and adaptogenic effects[9,10] in the central nervous system. Cholinergic effects in animal models include recovery of acetylcholine (ACh) levels, choline acetyltransferase activity, and cholinergic muscarinic receptor binding following colchicine-induced depletion of ACh in frontal cortex and hippocampus,[1] as well as dose-dependent inhibition of acetylcholinesterase activity *in vitro*.[2] *Bacopa* has been shown to facilitate adaptation responses in stressor exposed rat brain,[9] and to normalize plasma corticosterone and brain monoamine levels in acute and chronic stress models.[10] Steroidal saponins called Bacosides have been identified as the major active constituents of *Bacopa.*[11]

Animal studies have shown that *Bacopa* facilitates learning and memory,[12–14] while the following five randomized, double-blind, placebo-controlled trials provide evidence for its efficacy in improving cognitive performance in humans. In a study of 54 subjects over 65 years of age and without clinical dementia, Calabrese et al.[15] found improvements in various parameters of cognition and affect, including delayed-recall memory task, Stroop task reaction times, as well as depression and anxiety measures in participants on *Bacopa* (300 mg/day; 12 weeks). Stough and colleagues[16] reported

School of Health and Human Sciences, Southern Cross University, Lismore, New South Wales, Australia.

Bacopa (300 mg/day; 12 weeks) improved speed of information processing, learning rate and memory consolidation, and reduced state anxiety in healthy adults ($n = 46$), while Roodenrys and colleagues[17] demonstrated a significant effect of *Bacopa* (300 mg/day; 12 weeks) on retention of new information in healthy adults ($n = 76$). Raghav et al.[18] reported improved mental control, logical memory, and paired associate learning as measured on subsets of the Wechsler Memory Scale in participants aged 55 years and over with age-associated memory impairment ($n = 40$) in a 16-week trial (12 weeks on active treatment; 250 mg/day) with improvements maintained at 4 weeks post-treatment. Negi and colleagues[19] showed that *Bacopa* (100 mg/day; 12 weeks) effected improvements in a range of cognitive assessments in children with attention deficit hyperactivity disorder ($n = 36$). Conversely, in a randomized, double-blind, placebo-controlled trial of 85 adults (aged 19–68 years) that tested cognitive effects of a combined tablet of 300 mg *Bacopa* with 120 mg *Gingko biloba*, no significant effects were found in outcomes measured at 2 weeks and 4 weeks of treatment duration.[20] No cognitive-enhancing effects were found after acute administration of *Bacopa* (300 mg) versus placebo when outcomes were measured 2 hours postadministration ($n = 38$).[21] These last two studies suggest that longer-term administration of *Bacopa* is required to elicit cognitive benefits.

The safety and tolerability of BacoMind,™ the standardized extract of *Bacopa* used in the present study, was tested in a randomized, phase 1 clinical trial in which 23 healthy volunteers ingested 300 mg escalating to 450 mg daily for 30 days in total. Clinical and laboratory investigations evidenced no detrimental effects, with a total of 3 volunteers reporting mild gastrointestinal tract (GIT) side-effects.[22] Toxicology studies of BacoMind™ in Sprague-Dawley rats reported a median lethal dose of 2500 mg/kg as a single oral dose, with repeated oral dose up to 500 mg/kg over 14 days being well tolerated, and subchronic toxicology over 90 days in doses up to 500 mg/kg revealed no adverse findings in a range of clinical and laboratory evaluations.[23]

The current study was employed to replicate and extend on previous findings by assessing the efficacy and safety of *Bacopa* in the aged population specifically, as it is in this population that memory impairment becomes apparent.

Methods

Participants

Men and women 55-years of age and above were self-selected from the general population of the Northern Rivers region in New South Wales, Australia. The study was publicized via radio, television, and print media and also electronically via the staff intranet at Southern Cross University, Lismore.

People were included if they were aged 55 years or over, healthy, had absence of dementia as determined by a score of 24 or greater on the Mini-Mental State Examination (MMSE),[24] and absence of depression as determined by a score of 12 or less on the Hamilton Rating Scale for Depression (HAM-D).[25] People were excluded if they had diagnosed psychiatric or neurological disorder, history of brain inflammation, infection, or previous head injury, cerebral ischemia as determined by a score of 4 or greater on the modified Hachinski Ischaemia Scale (HIS),[26] disease of cardiovascular, renal, endocrine, liver, kidney, or respiratory systems, systemic disease or malignancy, psychoactive medication use, herbal medication use, recreational drug use, or consumed more than four standard alcoholic drinks per day. Compliance with the experimental regimen was assessed by counting tablets at the end of the trial, with more than 20% tablets remaining deemed to constitute noncompliance.

The study was conducted between February and July 2005 at Southern Cross University in Lismore, NSW. Prior to commencement of the trial, participants signed written informed consent forms and ethics approval was obtained from the Southern Cross University Human Research Ethics Committee, which adheres to ethical standards set by the Helsinki Declaration of 1975.

Design

The study was a 12-week randomized, double-blind, placebo-controlled clinical trial comparing the effects of a commercially available tableted extract of *Bacopa monnieri* called BacoMind™ to an identical placebo in memory performance improvement in healthy older persons.

Participants attended three clinical sessions. In the first session, demographic data, medical history, and vital signs were recorded, and urinalysis and screening assessments utilizing the HIS, MMSE, and HAM-D were performed. The next two sessions occurred at baseline and at week 12; at each of these visits outcome measures were assessed. At the baseline assessment, tablets were provided to last the 12-week period, with 10 extra tablets in case of loss or damage. Also given were an instruction sheet and record booklet in which participants recorded on a daily basis their medication ingestion as well as any symptoms experienced during the trial. Remaining tablets and record booklets were collected at the 12-week visit. Neuropsychologic tests were administered by one psychologist academic, and administration and scoring were supervised by one clinical neuropsychologist (to ensure internal consistency).

Participants were randomly allocated into two groups to receive either active treatment or placebo by using the method of randomly permuted blocks via the following Internet randomization Web site: http://randomization.com. Randomization was performed by a research academic not involved with the study. Randomization codes were stored electronically, and double-blinding was maintained until the data analysis stage of the research was completed.

Bacopa monnieri was administered in the form of a tablet from an extract called BacoMind™, which is derived from an alcoholic extract of the herb (herb to extract ratio, 20:1), standardized to contain total bacosides content of 40%–50%. BacoMind™ is standardized to nine active constituents: bacoside A_3, bacopaside I, bacopaside II, jujubogenin isomer of bacopasaponin C, bacopasaponin C, bacosine, luteolin, apigenin, and β–sitosterol-D-glucoside.[23] Each 300 mg of BacoMind™ in a tablet contains 6000 mg equivalent of the dried herb. The dosage instructed was 300 mg in one tablet daily, after a meal. Herbs of Gold (Australia) provided the Bacopa tablets using the BacoMind™ extract from Natural Remedies Pvt. Ltd. (Bangalore, India) and Tabco Pty. Ltd. (Australia) produced film-coated placebo tablets that were identical in

size, color, and shape to that of the *Bacopa* tablets. The dosage of Bacopa used was based on the manufacturers' recommendation and was the same as that used in previous clinical trials.[16,17]

Outcome measures

A series of three validated neuropsychologic tests and a memory complaint questionnaire were used to assess auditory–verbal memory, visuospatial memory, and subjective memory performance.

Rey Auditory Verbal Learning Test (AVLT)[27] is a word list learning test that assesses various aspects of memory including immediate recall, delayed recall, and retroactive and proactive interference. The same 15-word list (List A) is read to the participant for five repetitions (AVLT a1–5); after each repetition the subject recalls as many words as possible. During a sixth interference trial (AVLT b), 15 different words (List B) are presented, which are recalled, followed immediately by a sixth recall of the original list, (AVLT a6). A delayed recall of List A (AVLT a7) occurs after a 20-minute interval. The last part of the test consists of a recognition task (AVLT recognition) wherein a list of 50 words is read to the subject, who must identify the 15 words from List A embedded among 35 other words. Instructions given by Lezak[28] for AVLT administration and scoring were adhered to. A validated, alternate word list for the AVLT (Jones-Gotman, Szilkas, Majdan, p. 423)[29] was used at the end-of-trial assessment to avoid learning effects.

Rey-Osterrieth Complex Figure Test (CFT)[30,31] was used to assess visuospatial ability and visual memory. A complicated geometrical figure is presented to the subject, who is asked to copy it initially and then reproduce it from memory 3 minutes and then 30 minutes later. Scoring involves giving marks for both placement and accuracy of 18 different components of the drawing. Scoring instructions given by Lezak et al.[32] were adhered to.

Trail Making Test (TMT)[33] measures scanning and visuomotor tracking abilities, and involves cognitive processing (incorporating memory) as well as psychomotor speed.[34] In part A (Trails A), the subject must draw a line connecting circles containing consecutive numbers (from number 1 to number 25). In part B (Trails B), the subject again draws a line connecting circles, though now alternating between consecutive numbers and letters (i.e., from 1 to A to 2 to B and so on up until the number 13 and the letter L). The subject performs the task as quickly as he/she can. The scores obtained are the times taken (in seconds) to complete each task.

The Memory Complaint Questionnaire[35] was designed to quantify subjective memory complaints of aging. Participants answer six questions comparing current everyday memory to that of earlier life. The total score is the sum of the six questions, scored on a 5-point Likert scale, with options ranging from "much better now" to "much worse now." The possible score range is 7–35, with scores over 25 indicating subjective memory impairment.

Statistical analysis

A power analysis, nominating an effect size of 0.4 with α at 0.05 and a power level of $\beta = 0.80$, determined a prospective sample size of 80 participants (40 in each group) for this study. Thus, it was planned to enroll 100 participants in the trial to allow for a 20% dropout rate.

All data were analyzed using the computer software package Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows.

For the primary efficacy analysis, neuropsychologic test scores and subjective memory complaints scores were analyzed using a general linear model, repeated-measures analysis of variance (ANOVA) utilizing group (*Bacopa* and placebo) and time (baseline and week 12) as between- and within-subject factors. Type 1 sum of squares was employed.

To test the successfulness of randomization, the potential difference between groups (*Bacopa* and placebo) on all variables at baseline was analyzed using independent-samples *t*-test for continuous variables and χ^2 test for categorical variables.

Side-effects as reported either verbally or in the participants' record booklets were analyzed using an independent-samples *t*-test for significant differences between groups.

Results

Of 136 people who volunteered for participation in the trial, 103 met the study selection criteria, 98 commenced the trial, and 81 provided evaluable data at the endpoint. A total of 17 (10 females and 7 males) withdrew after the baseline: 13 from the *Bacopa* group and 4 from the placebo group. Table 1 depicts the flow of participants through the phases of the trial.

Of those commencing the trial, 52 (53.1%) were female and 46 (46.9%) were male. The average age of participants was 65 years (range 55–86, standard deviation [SD] 7.53) and they had an average of 13 years of education (range 5–22, SD 4.01). Twenty-six (26) participants were single and 72 were married or *de facto*. The average MMSE score was 28.18 ± 1.56 and the average HAM-D score was 3.28 ± 2.89.

Table 1. Progression of Participants Through Trial

No. assessed for eligibility	136	
No. excluded	33	
Selection criteria not met	30	
Declined consent	1	
Other reasons	2	
No. randomized	103	
	Bacopa	Placebo
Randomization	51	52
Received intervention	49	49
Intervention not received	2	3
Work commitments	1	1
Death in family	1	0
Travel	0	1
Lost to follow-up	0	1
Followed up 12 weeks	36	45
Discontinued after baseline		
Side-effects	9	2
Lost to follow-up	2	0
Concurrent illness	1	1
Accidental injury	1	0
Elective surgery	0	1
Completed trial	36	45

No significant differences were found between groups at baseline for clinical characteristics, AVLT, TMT, or Memory Complaint Questionnaire (MAC-Q) scores ($p > 0.05$). However, significant baseline differences were found between the active and placebo groups' mean scores on the CFT delayed recall tasks at both 3 minutes (*Bacopa* 18.24 ± 6.43, placebo 14.65 ± 5.93; $p = 0.005$) and 30 minutes (*Bacopa* 18.26 ± 5.92; placebo 14.89 ± 6.42; $p = 0.008$). The *Bacopa* group performed significantly better than the placebo group on these tasks at baseline. This difference could not be explained. Table 2 summarizes the analysis of dependent variables at baseline.

Outcomes analysis

Initially, the normality of the distribution of scores for each of the continuous variables was tested, and it was found that the assumptions of normality were met. A general linear model was run to test for significant differences between the *Bacopa* and placebo groups on all dependent variables (memory complaint questionnaire and neuropsychologic test scores) from baseline to end-of-trial ($n = 86$). A repeated-measures ANOVA was used with time (baseline and endpoint scores) as the within-subjects factor, and treatment group (*Bacopa* and placebo) as the between-subjects factor. Type 1 sum of squares was employed.

At the 0.05 probability level, *Bacopa* significantly improved memory function as measured by performance on the following AVLT tasks: trial a4, trial a5, trial a6 (postdistraction trial), trial a7 (delayed-recall trial), total learning (Σ trials a1–a5), and retroactive interference index. Table 3 summarizes these results. Improved scores were noted on the CFT, TMT, and the MAC-Q in both groups; however, there were no significant effects for *Bacopa* compared to placebo ($p > 0.05$) on these measures.

Side-effects

An independent-samples *t*-test was applied to test for significant differences in side-effects experienced between treatment groups. The following side-effects occurred significantly more often in the *Bacopa* group compared to placebo (at 95% confidence interval): increased stool frequency ($t = 4.106$, $p = 0.000$), nausea ($t = 2.744$, $p = 0.007$), and abdominal cramps ($t = 3.060$, $p = 0.003$). Table 4 lists the total number of side-effects reported by participants.

Discussion

This study investigated the effects of 12 weeks' administration of *Bacopa monnieri* (300 mg/day) on memory in people

Table 2. Dependent Variables at Baseline: Clinical Characteristics and Test Scores at Point of Randomization ($N = 98$), with Analysis of Group Differences

	Total sample	Bacopa *group*	*Placebo group*	p
Number of subjects	98	49	49	–
Gender (female/male)	52 (53%)/46 (47%)	24 (49%)/25 (51%)	28 (57%)/21 (43%)	0.54
Age (years)	65 ± 7.53	65.41 ± 6.87	65.39 ± 8.20	0.989
Range	55–86	55–77	55–86	–
Education (years)	13 ± 4.01	13.37 ± 3.97	12.82 ± 4.07	0.5
Range	5–22	5–20	6–22	–
Marital status (partner/single)	72 (73%)/26 (27%)	35 (71%)/14(29%)	37 (75%)/12 (25%)	0.81
MMSE	28.18 ± 1.56	28.05 ± 1.63	28.30 ± 1.50	0.423
Hamilton Depression Scale	3.28 ± 2.89	3.07 ± 2.73	3.48 ± 3.05	0.488
AVLT a1	5.91 ± 1.62	5.94 ± 1.63	5.88 ± 1.62	0.853
AVLT a2	7.63 ± 2.25	7.8 ± 2.48	7.47 ± 2.02	0.477
AVLT a3	8.68 ± 2.30	8.73 ± 2.29	8.63 ± 2.32	0.828
AVLT a4	9.36 ± 2.08	9.33 ± 2.13	9.39 ± 2.06	0.885
AVLT a5	10.17 ± 2.48	10.37 ± 2.44	9.98 ± 2.53	0.443
AVLT b (interference list)	4.28 ± 1.90	4.33 ± 2.01	4.22 ± 1.81	0.793
AVLT a6	7.85 ± 2.82	8 ± 2.83	7.69 ± 2.83	0.594
AVLT a7 (20-minute recall)	7.58 ± 2.79	7.86 ± 2.52	7.31 ± 3.05	0.332
AVLT recognition hit rate	12.45 ± 2.39	12.71 ± 2.09	12.18 ± 2.65	0.274
AVLT false positive rate	3.64 ± 3.20	3.43 ± 3.27	3.86 ± 3.15	0.511
AVLT true recognition rate	8.81 ± 3.84	9.29 ± 3.71	8.33 ± 3.94	0.218
AVLT total learning (Σ1–5)	41.67 ± 8.91	42.16 ± 9.42	41.18 ± 8.44	0.589
AVLT retroactive interference	2.33 ± 1.97	2.37 ± 1.99	2.29 ± 1.96	0.839
AVLT proactive interference	1.63 ± 1.98	1.61 ± 1.95	1.65 ± 2.03	0.92
AVLT forgetting rate	027 ± 1.62	0.14 ± 1.70	0.39 ± 1.53	0.458
CFT copy	34.24 ± 2.85	34.45 ± 2.21	34.03 ± 3.38	0.471
CFT 3 min	16.45 ± 6.41	18.24 ± 6.43	14.65 ± 5.93	0.005**
CFT 30 min	16.58 ± 6.37	18.26 ± 5.92	14.89 ± 6.42	0.008**
MAC-Q	26.07 ± 4.56	25.84 ± 3.78	26.31 ± 5.25	0.613
Trail Making Test A	36.05 ± 9.48	34.27 ± 7.95	37.84 ± 10.59	0.062
Trail Making Test B	87.07 ± 33.54	88.02 ± 31.61	86.12 ± 35.66	0.781

Results are mean ± standard error unless otherwise specified. Chi-square test for gender and marital status. Independent *t*-test for age, education, and neuropsychologic tasks. p = two-tailed significance, for differences between groups. MMSE, Mini-Mental State Examination; AVLT, Rey Auditory Verbal Learning Test; CFT, Rey-Osterrieth Complex Figure Test; MAC-Q, Memory Complaint Questionnaire.
**$p < 0.01$.

Table 3. Results of Outcomes Analysis

	Bacopa *(n = 36)*		*Placebo (n = 45)*		*Significance* (df = *1; error* df = *79)*	
Task	*Baseline*	*12-weeks*	*Baseline*	*12-weeks*	F	p
AVLT a1	5.7(1.7)	5.6(1.6)	5.7(1.5)	5.2(1.6)	1.823	0.181
AVLT a2	7.5(2.4)	7.9(2.0)	7.5(2.0)	7.4(2.2)	0.894	0.347
AVLT a3	8.6(2.2)	9.3(2.2)	8.7(2.3)	8.5(2.4)	2.348	0.129
AVLT a4	9.2(2.1)	10.7(1.9)	9.3(2.1)	9.0(2.2)	13.204	**0.000**
AVLT a5	10.3(2.5)	11.1(2.2)	10.0(2.5)	9.4(2.4)	6.094	**0.016**
AVLT b (interference list)	4.3(2.0)	4.6(1.8)	4.3(1.8)	4.8(1.6)	0.143	0.706
AVLT a6	7.9(3.1)	9.8(2.0)	7.7(2.9)	7.2(2.0)	18.830	**0.000**
AVLT a7 (delayed recall)	7.9(2.7)	9.6(2.2)	7.8(3.1)	6.8(2.7)	12.021	**0.001**
AVLT recognition hit rate	12.6(2.2)	13.9(1.1)	12.4(2.5)	13.1(2.1)	1.242	0.269
AVLT false positives	3.5(3.5)	1.9(2.3)	4.0(3.2)	3.5(3.6)	2.555	0.114
AVLT true recognition	9.1(3.9)	11.9(2.6)	8.4(3.9)	9.6(4.1)	3.539	0.064
AVLT total learning (Σa1–a5)	41.4(9.2)	44.3(8.5)	41.2(8.4)	39.4(9.2)	6.761	**0.011**
AVLT retroactive interference	2.4(2.1)	1.2(1.6)	2.2(2.0)	2.2(1.6)	4.020	**0.048**
AVLT proactive interference	1.4(1.9)	1.0(1.9)	1.6(2.1)	0.5(1.5)	1.353	0.248
AVLT forgetting rate	0.0(1.8)	0.2(1.3)	0.4(1.6)	0.3(1.5)	0.365	0.547
CFT copy	34.4(2.3)	32.8(5.0)	33.9(3.5)	33.5(2.8)	0.649	0.423
CFT 3-min recall	18.1(5.8)	20.4(6.5)	14.1(5.7)	17.8(6.9)	1.101	0.297
CFT 30-min recall	18.4(5.3)	20.5(6.1)	14.5(6.4)	18.1(6.3)	1.887	0.173
MAC-Q	25.9(3.5)	22.4(5.3)	26.4(5.4)	24.7(4.6)	2.525	0.116
Trail Making Test A	33.6(7.6)	30.7(9.0)	37.9(10.7)	35.6(14.7)	0.038	0.847
Trail Making Test B	89.9(32.2)	71.8(27.5)	86.3(36.9)	75.5(22.3)	1.280	0.261

Results expressed as mean (and standard deviation). General linear model, repeated-measures analysis of variance employing time as within-subjects factor and group as between-subjects factor.

F = Fisher value for significance of group contrasts; *df* = degrees of freedom for the two treatment groups; error *df* = degrees of freedom for error; Significance = one-tailed significance; AVLT = Rey Auditory Verbal Learning Test; AVLTa1–a7 = repetitions of word list A (possible range 0–15), AVLT b = interference word list B (possible range 0–15); AVLT rec = recognition list hit rate (possible range 0–15); AVLT recognition false positives (possible range 0–35); AVLT true recognition rate = recognition list hit rate minus false positives, (possible range −35 to +15); AVLT total learning a1-a5 = total learning score (sum of trials a1 to a5, range 0–75), AVLT retroactive interference score (trial a5 minus trial a6, possible range −15 to +15, lower scores = better performance); AVLT proactive interference score (trial a1 minus trial b, possible range −15 to +15, lower scores = better performance); AVLT forgetting rate (trial a6 minus trial a7, possible range −15 to +15, lower scores = better performance); CFT = Rey-Osterrieth Complex Figure Test (possible range 0–36 on all tasks); MAC-Q = Memory Complaint Questionnaire (possible range 7–35, lower scores = better performance); Trail Making Test A and B scores = time taken to complete task in seconds (lower scores = better performance).

Bolding indicates *p*-values of significance > 0.005.

over 55 years of age. Primary outcome measures were well validated neuropsychologic tests to objectively measure audioverbal and visual memory, and a memory complaint questionnaire to measure subjective memory complaints. The results demonstrated that *Bacopa* versus placebo significantly improved memory acquisition and retention in older Australians as measured by performance on the AVLT. This concurs with findings from previous human and animal studies, as well as providing support for traditional Ayurvedic claims and uses.

Improvement in memory acquisition was demonstrated by an increasing amount of words recalled over the five learning trials that were retained at the delayed-recall trial, a7.[36] Performance on the delayed-recall trial also demonstrates improved memory retention. Furthermore, retention of the learned material was less affected by the introduction of an interference word list (B), as evidenced by significantly improved retroactive interference scores in the *Bacopa* group.

The finding of improved memory retention concurs with the findings of Roodenrys et al.,[17] who also found a significant effect of Bacopa on retention of new information. Unlike Roodenrys et al., who suggest that *Bacopa* improves retention by decreasing the forgetting rate rather than by improving the learning rate, the current study demonstrated an improved learning rate and no effect on the forgetting rate.

This study also concurs with findings of improved delayed-recall scores on the AVLT reported by Calabrese and colleagues.[15] Stough and colleagues[16] previously reported

Table 4. Total Number of Side-Effects Reported

	Number of participants reporting side-effect	
Side-effects reported	*Bacopa group* (n = *49*)[a]	*Placebo group* (n = *49*)[a]
Increased stool frequency	15	1
GIT cramps	8	0
Nausea	9	1
Reflux	0	2
Flatulence	1	0
Bloating	1	2
Decreased appetite	1	0
Constipation	0	1
Headache	1	1
Hypertension	0	1
Insomnia	1	0
Vivid dreams	2	0
Increased sense of well-being	2	2

[a]Includes study withdrawals.
GIT, gastrointestinal tract.

improvements on various measures from the AVLT, in that *Bacopa* significantly improved the learning rate (acquisition) and memory consolidation (assessed by decreased proactive interference and decreased forgetting rate). The current study concurs with the finding by Stough et al. of improved learning and consolidation; however, it differs in that improvement in memory consolidation was not associated with improvements in proactive interference or forgetting rate for which no effects were found. Rather, the current study suggests that the observed enhancement of memory consolidation may be related to reduced retroactive interference ($p = 0.048$).

There was no significant effect found on visuospatial memory performance or visuomotor skills as measured by the CFT and the TMT. Likewise, there was no effect found on subjective memory improvement as measured by the MAC-Q. In the CFT in both the 3-minute recall and 30-minute recall tasks, and in TMT parts A and B, both the placebo and *Bacopa* groups performed better at the 12-week end-of-trial session than at baseline, with no significant differences between the groups. Better performance for the whole sample on the CFT and TMT may reflect practice effects, as the same CFT figure and the same TMT task were used at both baseline and end-of-trial, due to the nonavailability of equivalent versions. This must be considered a limitation of the current study as practice effects may constitute a threat to internal validity, albeit the inclusion of a control group attenuated this threat.

A further limitation of the study was the inexplicable difference between the two treatment groups means scores at baseline on the CFT only. The group means were normally distributed and the difference was not accountable for by effects of gender, age, or education. The reason for the difference remains unaccounted for and could have indicated a difference in a variable not measured, for example, eyesight or motor skills, (as visual-motor but not audioverbal tasks showed group difference). Retrospectively, assessment of visual and auditory acuity would have been pertinent data to collect in the pretrial screening session.

The improved MAC-Q scores in both groups may reflect either an improved attitude to memory because of increased attentional monitoring of it due to study participation (Hawthorne effect), or a desire to give the researcher positive feedback (Rosenthal effect). These effects were controlled for in this study by double-blinding and the use of a control group.

Bacopa's use was associated with GIT side-effects, specifically increased bowel movements, nausea, and abdominal cramping. These side-effects have been reported, though less frequently, in other studies. For example, Roodenrys et al.[17] reported one dropout due to GIT side-effects, while Stough et al.[16] reported a significant occurrence of nausea (18% versus 4%), dry mouth (23% versus 16%), and fatigue (14% versus 4%). Calabrese and colleagues report that of nine possible Bacopa-related adverse events, digestive and "flu-like" symptoms were most frequent.[15]

The side-effects noted in the current study could all be explained by a cholinergic effect of *Bacopa*. Cholinergic stimulation in the GIT causes both parasympathomimetic effects—increased tone, peristalsis, and secretions of the stomach and intestines, and motor effects—nausea, vomiting, belching, abdominal cramps, and increased bowel movements. These observations lend support to the notion that the cognitive-enhancing effects of *Bacopa* may be, at least in part, mediated via enhanced cholinergic modulation in the central nervous system as suggested by animal studies.[1,2] It may be prudent to use caution in concurrent administration of *Bacopa* and acetylcholinesterase inhibitor medications, which are the current mainstay in dementia therapy.

The observed side-effects may also have been related to the saponins in Bacopa. Mills and Bone caution that herbs with high saponin content can irritate the gastric mucosa.[37] The high level of saponins (bacosides) in the study drug used—which was standardized to contain at least 40%—coupled with a high concentration of the herb per tablet (one 300-mg tablet is equivalent to 6 g of dried herb), may have resulted in GIT irritation. However, toxicology studies of the extract used in the current study—BacoMind,™—have not shown GIT reactions in rats,[23] and safety and tolerability studies of BacoMind™ in human volunteers reported only mild GIT reactions in 3 of 23 participants that subsided spontaneously. Possibly the higher incidence of GIT reactions in the current study was due to the older age of participants, lowering their capacity to tolerate *Bacopa*.

Conclusions

Bacopa monnieri is effective in enhancement of memory performance in healthy older people, with improvements in both memory acquisition and retention. *Bacopa* caused gastrointestinal side-effects of increased stool frequency, abdominal cramps, and nausea. These side-effects suggest either an upregulation of acetylcholine activity or saponin-mediated GIT irritation, or both. Exploration of *Bacopa*'s efficacy in neurodegenerative pathology is an area for possible future research.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Annette Morgan, MSc
School of Health and Human Sciences
Southern Cross University
P.O. Box 157
Lismore, New South Wales 2480
Australia

E-mail: annette.morgan@scu.edu.au