Cognitive effects of two nutraceuticals Ginseng and Bacopa benchmarked against modafinil: a review and comparison of effect sizes

Neale C[1], Camfield D[1], Reay J[2], Stough C[1], Scholey A[1*]

[1] Centre for Human Psychopharmacology, Swinburne University, Melbourne, VIC 3122 Australia

[2] School of Life Sciences, Northumbria University, Newcastle upon Tyne, NE1 8ST UK

*Author for correspondence

Centre for Human Psychopharmacology

Swinburne University of Technology

Melbourne

VIC 3122

Australia

Tel: +61 (3)92148932

Fax: +61 (3)92145525

Email: andrew@scholeylab.com

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Summary

Aims Over recent years there has been increasing research into both pharmaceutical and nutraceutical cognition enhancers. Here we aimed to calculate the effect sizes of positive cognitive effect of the pharmaceutical modafinil in order to benchmark the effect of two widely used nutraceuticals Ginseng and Bacopa (which have consistent acute and chronic cognitive effects respectively).

Methods A search strategy was implemented to capture clinical studies into the neurocognitive effects of modafinil, Ginseng and Bacopa. Studies undertaken on healthy human subjects using a double-blind, placebo-controlled design were included. For each study where appropriate data were included, effect sizes (Cohen's *d*) were calculated for measures showing significant positive and negative effects of treatment over placebo.

Results The highest effect sizes for cognitive outcomes were 0.77 for modafinil (visuospatial memory accuracy), 0.86 for Ginseng (simple reaction time) and 0.95 for Bacopa (delayed word recall).

Conclusions These data confirm that neurocognitive enhancement from well characterised nutraceuticals can produce cognition enhancing effects of similar magnitude to those from pharmaceutical interventions. Future research should compare these effects directly in clinical trials.

Objectives

Over recent years there has been increasing interest in the area of cognitive enhancement. This field has traditionally focused on the effects of so-called nootropics in those with fragile cognition (e.g. those with age-related cognitive decline, mild cognitive impairment or dementia). However in recent years the field of cognition enhancement has also embraced studies into cognition enhancement in young, cognitively intact individuals (1). In the context of pharmaceutical cognition enhancers, methylphenidate and modafinil (Provigil) have taken centre stage (2). Modafinil had been taken as a cognitive enhancer by around 10% of respondents to an online survey of the readership of the journal Nature (3), though, it is worth noting that this study may have a high response bias from individuals using cognitive enhancers.

As well as pharmaceutical approaches to cognitive enhancement, there is growing interest in the possibility that certain nutraceuticals may enhance cognitive performance. Herbal extracts may contain multiple active components which, in concert, may influence numerous neuronal, metabolic and hormonal systems involved in behavioural processes (4). Additionally the interactions between these actives may be synergistic, resulting in complex dose and time dependent effects. These factors are challenging for psychopharmacology, making certain positive effects fragile even where there is strict batch-to-batch consistency across studies, and rendering negative findings sometimes difficult to interpret. Nevertheless there is growing evidence that certain standardised natural products have reproducible neurocognitive effects in humans, possibly because of their inherent polyphamacological properties. Examples of the most promising nutraceuticals in this context include species of *Salvia* (sage) (5-8), *Panax ginseng* (9-12) and *Bacopa monniera* (13-17). For the purposes of this short review we chose to concentrate on Ginseng and Bacopa; the former has been shown to robustly enhance cognitive performance after acute dosing (18), whilst Bacopa has been shown to have nootropic effects with chronic dosing (16).

We are not aware of any study to date which has directly compared the cognition enhancing effects of a nutraceuticals and a pharmaceutical in a head-to-head trial in healthy volunteers. The purpose of this review is to examine the literature describing clinical trials of the neurocognitive effects of modafinil, *Panax ginseng* and *Bacopa monniera* in order to compare their effect sizes across different cognitive domains.

Methods

Search strategy

The electronic databases SCOPUS, PubMed and PsychInfo were accessed in early 2012 (April). Key word searches were conducted by combining "Ginseng", "Bacopa" or "Modafinil" with "cognition", "memory", "neuropsychological", "neurocognitive" and "executive function". Articles that did not relate to human cognitive trials were excluded as were articles that were not in English. Accepted articles were those that had completed double-blind, randomised, placebo-controlled empirical investigations on healthy human subjects using cognitive function as a primary outcome. Additionally studies were included only if they described an intervention with at least one arm assessing one of Ginseng, Bacopa or modafinil. In the case of Ginseng and Bacopa, only studies using 'pure' extracts were accepted, i.e. there were no other supplements present within the target nutraceutical arm. Furthermore, all extracts must have been used in isolation and not contaminated by co-use of other supplements as adjunct interventions.

Papers identified as meeting eligibility criteria were analysed for emerging common cognitive domains between the intervention types. Applying these criteria resulted in 8 relevant studies for modafinil, 7 for Bacopa, and 9 for Ginseng.

Effect Size Analysis

Effect sizes were calculated on statistically significant data in order to assess the magnitude of effects. Effect sizes were calculated using Cohen's *d* (19). The strength of clinical effects were defined as small: d=0.2, medium: d=0.5, and large: d=0.8 effect sizes as defined by Cohen (19). Chronic trials utilizing a repeated measures design were analyzed at endpoint and not mid-points. Effect sizes are presented in Tables 1, 2 and 3. It should be noted that all treatment-associated benefits (e.g. increased accuracy, shorter reaction times) are presented as positive effect sizes and impairments (e.g. more errors, slower reaction times) as negative effect sizes respectively.

Results

Modafinil

Modafinil ($C_{15}H_{15}NO_2S$ (20)) is a pharmaceutical drug used as a licensed treatment for excessive day time sleepiness associated with narcolepsy or shift-work (2). The mechanisms responsible for its effects remain largely unknown. It appears to exert a wide range of effects including via modulating catecholamine activity (21). The human pharmacokinetic profile is known, with peak effects between 2-4 hours after oral ingestion, and a half-life of 12-15 hours (22).

As noted in a review by Repantis et al (2), as well as its use in the context of sleep disorders, there has been an increase in academics and office workers using modafinil as a cognitive enhancer. Research into the cognitive enhancing effects of modafinil generally falls into one of two types; studies in sleep deprived and non-sleep deprived human subjects. These have typically compared doses of 100 mg and/or 200 mg doses against placebo. As modafinil is used as a treatment for excessive daytime sleepiness, there is a large body of research assessing cognitive effects in sleep-deprived participant groups. However, the results from these studies are not comparable with the participant groups used to assess the cognitive effects of Bacopa or Ginseng so are not included here.

In non-sleep deprived adults, modafinil is associated with improvements in accuracy of pattern recognition and the stop signal task following 100 mg and 200 mg (23), with several studies showing improvements in digit span with the 100 mg dose alone (23, 24). Furthermore, modafinil improved accuracy of an executive planning task (Stocking of Cambridge) (25). Faster reaction times have also been shown across a range of tasks, notably the stroop colour naming task of selective attention (23, 24, 26, 27). There are also numerous tasks that are unaffected by modafinil, regardless of dose, including trailmaking (28), mathematical processing (26), spatial working memory (24), logical memory (27), associative learning (29) and verbal fluency (30).

Effect sizes restricted to those domains significantly affected by modafinil are presented in Table 1 (note that all benefits are presented as positive effect sizes).

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Panax ginseng

Ginseng refers to extracts from the Araliaceae family of plants. It is estimated that, in the US, Ginseng is the second most used psychoactive herbal product (31). The active components are believed to be the ginsenosides, of which over 30 have been isolated, though many exist in trace amounts (32). The chemical structure of these aglycone saponins can be used to classify the ginsenosides into three groups: the protopanaxadiol group (e.g. Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1); the protopanaxatriol group (e.g. Re, Rf, Rg1, Rg2, Rh1); and the oleanolic acid group (e.g. Ro) (33).

Over the last decade or so a number of studies have revealed that single doses of *Panax ginseng* (also known as Asian ginseng) can modulate aspects of cognitive function (9); brain activity as measured by electroencephalography (34) and peripheral blood glucose levels (11, 35), in healthy young volunteers. Most of these studies have used a standardised extract (G115) which contains an invariant 4% ginsenosides.

With regards to cognitive function, a number of controlled studies have identified both positive and negative behavioural effects. The most consistent finding, however, is one of improved secondary memory (i.e. declarative memory involving recollection) performance following extract G115 alone (10, 36, 37), and in combination with both *Ginkgo biloba* (37) and *Paullinia cupana* (guaraná) (36). In addition, *Panax ginseng* (G115) has been shown to enhance aspects of working memory (38), to improve mental arithmetic performance (in a task that loads heavily on working memory resources) (11, 12) and to speed attentional processes (39) in healthy volunteers. These benefits to reaction time occurred without a concomitant cost to accuracy, precluding the possibility of a treatment related shift in the speed/accuracy trade-off. One recent study has shown that acute administration of a standard extract of a different Ginseng species, *Panax quinquefolius* (American ginseng), which has a ginsenoside profile distinct from that of *Panax ginseng*, can also improve working memory performance (38).

Despite growing evidence supporting the efficacy of *Panax ginseng* (G115) in modulating cognitive processes following a single dose, only three empirical studies have directly investigated the cognitive and mood effects following more extended Ginseng ingestion periods (with only two of these studies using the standardised G115 extract). Two early studies revealed improved speed of performing a mental arithmetic task following 12 weeks administration of *Panax ginseng* (200 mg G115 per day) in young volunteers (40). The most recent, Reay et al (38, 41) found both positive and negative effects of 7 day dosing with G115

- whilst there were beneficial effects of the 400mg dose on various measures of the 3-back task there were also negative effects on reaction time limited to the 200 mg dose.

Effect sizes restricted to those domains significantly affected by Ginseng from selected publications are presented in Table 2.

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Bacopa monniera

Bacopa monniera (BM), known as Bacopa or Brahmi, is a herb from the Scrophulariaceae family of plants which has been used for centuries in Ayurvedic medicine. BM has been shown to contain a complex mixture of constituents including alkaloids, saponins and flavonoids. The key constituents of Bacopa are thought to be the triterpenoid saponins, bacosides A and B (42). These bacosides usually co-occur, differing only their optical rotation, with the presence of bacoside B believed to be an artefact generated during the isolation of bacoside A (43). Animal studies have shown BM to be an antioxidant (44), memory enhancer (45), antidepressant (46) and to reduce the levels of beta-amyloid in a mouse model of Alzheimer's disease (47).

Human studies reveal consistent cognitive enhancement as a result of BM administration across young, old and impaired adult populations (48). Unlike modafinil and Ginseng, Bacopa may not acutely improve cognitive functioning (although there are as yet unpublished reports of acute effects during more effortful cognitive processing). To date publications are restricted to effects which are evident only after chronic interventions (typically 12 weeks of a 300 mg daily dose), with no significant improvements occurring after a five week intervention (17) or acutely after two hours (49). The most robust effects of BM are on memory performance, including positive effects on learning and consolidation of target stimuli (17), delayed recall (13), total learning (14), visual retention of information (15) and working memory (16). There is also evidence that BM can improve speed of information processing in both the Inspection Time task and Rapid Visual Information Processing (16, 17). Using BM in an older population group (fifty five years and over) has shown improvements in executive functioning on the stroop task and the mental control subtest of the Wechsler Memory Scale (13, 14). There are also tasks which appear to be unaffected by BM administration including working memory speed (17), reaction time (13, 16, 17) and

divided attention (13). Effect sizes for significant findings restricted to those domains significantly affected by Bacopa are presented in Table 3.

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Effect Sizes

With regards to modafinil, our analysis revealed small effect sizes on reaction time and small to large effect sizes on response accuracy during visual-spatial working memory, as well as a dose-dependent increase in effect size for stroop reaction times (Table 1). There appeared to be no cognitive costs (i.e. cognitive impairments in other domains) associated with these effects, with effect sizes ranging from d = 0.083 to d = 0.774 (for accuracy of Visual Spatial Memory).

There was large variation in the effect sizes for Ginseng (table 2). The largest effect size, d = 1.396, was for amelioration of the self-rated mental fatigue during heavily loaded cognitive processing. Regarding cognitive processing the largest effect size was for simple reaction time (d = 0.860). Interestingly another measure, reaction time on the 3-back working memory task showed a large positive effect size (d = 0.806) following acute Ginseng administration also had the largest impairment d = -0.481 (41) following 8-day dosing. This raises the possibility of neuroadpaptations to the neural substrates influenced by acute Ginseng administration with longer-term dosing resulting in opposite effects to acute dosing.

Chronic BM interventions generally produced the most consistent and largest effect sizes. These ranged from small to medium effect sizes for measures of attention and information processing tasks such as RVIP, stroop and inspection time. Larger effect sizes were evident for auditory verbal learning tasks where the effect sizes ranged from d = 0.230 for delayed word pair memory to d = 0.950 for delayed word recall ($AVLT^4$) and d = 1.01 for protection from proactive interference during delayed memory ($AVLT^3$).

Conclusions

All three substances reviewed here exerted overwhelmingly positive effects on neurocognitive function across different cognitive domains. However, it must be made clear that this review has only looked at the statistically significant results and did not include the non-significant results from studies into the neurocognitive effects of these substances. Modafinil had the strongest effects on speed of information processing and executive

functioning. Ginseng exerts acute positive effects on secondary memory and more heavily cognitively loaded working memory tasks. Bacopa administration appears to predominantly enhance learning and memory, with effects restricted to chronic administration. The differential effects on cognitive domains presumably reflects different mechanisms of action of each substance. Modafinil has multiple effects on neurotransmitter systems including region-specific increases in adrenergic, histaminergic, glutaminergic activity and decreased GABAergic activity (50). The mechanisms for BM are unknown, but there is evidence that it has pro-cholinergic effects as suggested by the effects on inspection time and rapid visual information processing (17, 51) as well as anti-oxidant and anti-inflammatory properties. As might be expected from an extract with multiple components Ginseng has been reported to have multiple properties relevant to neurocognitive function. These include glucoregulation, modulation of cholinergic and dopaminergic activity as well as increasing nitric oxide synthesis (19). Whilst the purpose of this review was to compare nutraceuticals and pharmaceuticals, it is worth noting that the majority of the BM research presented here relates to chronic administration whilst the modafinil and Ginseng research is predominantly in the context of acute administration. However, the purpose of this review is to assess substances that enhance cognition.With regards to modafinil, the results here show the cognitive enhancing effects of the substance on non-sleep deprived subjects, rather than during the treatment of excessive tiredness in narcolepsy or after sleep deprivation. It is also worth noting that many research papers using non-sleep deprived individuals have not adequately reported the cognitive results so we were unable to compute effect sizes for these studies (although this factor is by no means limited to modafinil research). Regarding the effects of Ginseng and Bacopa, research into herbal medicines brings its own difficulties. For example human studies into BM have used different products across trials. Whilst the manufacturers of all BM products included in our review claim standardization, compositions of individual treatments have not been compared. However, all extracts used in studies to date are reported to have standardised bacoside content to levels between 50-55%. All Ginseng studies included in Table 2 used the standardised extract G115.

This review is limited by the number of studies currently available. As the number of double-blind, placebo-controlled, randomised trials is rising, it is likely that future reviews will be able to compare particular groups of individuals such as those with specific cognitive dysfunction or particular age-groups. At present, the number of available studies is too low to make such direct comparisons. Future research studies may wish to directly compare the

differences of these substances in the same cohort. We are also aware that some of the research into nutraceuticals is not widely available through popular search engines such as those used for this review.

In conclusion the nutraceuticals Ginseng and Bacopa produced effect sizes for cognitive enhancement which were comparable with those seen for modafinil, albeit in different cognitive domains. Future studies should directly compare the cognitive effects of these agents in direct, head-to-head clinical trials. Furthermore, presentation and statistical analysis of results in certain research papers have made calculating effect sizes difficult in some instances. This is an issue that will need to be addressed in future studies into both pharmaceutical or nutraceutical research aiming to establish any cognitive enhancing effects of said interventions.

Conflict of interest declaration

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, AS and CS have received funding from Soho Flordis International (SFI) in the previous 3 years; there are no other relationships or activities that could appear to have influenced the submitted work.

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Table 1. Summary of human trials into the cognitive effects of modafinil.

Author/Year	*n*	Dose	Sample	Trial Design	Outcome Measures	Results	Cohen's d Effect Size
Turner et al (2002)	60	100mg (N=20) or 200mg (N=20)	Placebo mean age 25.30years 100mg mean age 24.35 years 200mg mean age 25.10 years	Acute DB, PC, PG	Decision making (gambling), RVIP, Digit span, visual spatial working memory, pattern recognition, stop signal, stroop colour naming Self rated mood and wakefulness.	Significant improvements from drug on digit span, stroop colour naming, spatial planning, gambling deliberation and pattern recognition. Suggestion of reduction in impulsive responsiveness.	DS FAS 0.12 DS BAS 0.09 DS FS 0.12 DS BS 0.09 PRM 0.09 DMTS L 0.09 NTOL 0.11 DT 0.08 N.B. Effect sizes calculated as average mean and standard deviation of low and high dose combined in keeping with the analysis used by the authors
Randall et al (2003)	30	100mg or 200mg	Placebo mean age 20.7 years 100mg mean age 20.3 years 200mg mean age 20.7 years	Acute DB, PC, PG	Motor screening, RVIP, DMTS, IED, SOC, trail making, stroop, COWAT, clock drawing. VAS mood, sleep and wakefulness	No significant cognitive effects Significant improvements in self-reported mood and wakefulness	No cognitive effects
Muller et al (2004)	16	200mg	20-29 year olds Mean age 24.1 years	Acute DB, PC, CO	Visual spatial working memory, trail-making, state anxiety, numeric working memory	Significant decreases in error rates at longest delay (8000ms) in visual spatial task with Modafinil, as well as faster reaction times in 1000 and 4000ms delays. No speed-accuracy interaction	VSM E 8000ms 0.77 VSM RT 1000ms 0.21 VSM RT 4000ms 0.15
					Choice reaction time,		

Baranski et al (2004)	18	4mg/kg – average 300mg	18 – 40 Mean age 24.2 years	Acute DB, PC, CO	numeracy, DRN, visual comparison, logical reasoning Self rated mood and fatigue	Improvements in reaction time and vigilance as well as fatigue and motivation.	Effect Sizes unavailable – raw data not present in research paper
Randall et al (2004)	45	100mg or 200mg	50 – 67 years Placebo mean age 55.7 years 100mg mean age 58.8 years 200mg mean age 58.2 years	Acute DB, PC, PG	Motor screening, RVIP, DMTS, IED, SOC, trail making, stroop, COWAT, clock drawing. VAS mood, sleep and wakefulness	No improvements in executive functioning (trail making, SOC) Improvements in stroop response time, more pronounced with 200mg dose No improvements in self-reported mood and wakefulness	100mg Stroop RT 0.16 200mg Stroop RT 0.45
Stoops et al (2005)	6	100, 200, 400mg	22 – 28 years Mean age 24 years	Acute DB, PC, CO	Wakefulness and stress measures Mental arithmetic (x3 50 minute blocks)	Improved self-reported stress and wakefulness measures. Improved mental arithmetic performance	Effect Sizes unavailable – raw data not present in research paper
Winder-Rhodes et al (2010)	12	300mg	18 – 39 years Mean age 26.3 years	Acute DB, PC, CO	Digit span, RVIP, SOC, Pattern recognition, stop-signal	Placebo and Prazocin (used as another data point) decreased accuracy on SOC, whilst Modafinil did not exert this negative effect. However, the effects of Modafinil were not statistically significant.	No significant effects
Ghaharemi et al (2011)	19	200mg	Mean age 33.7 years	Acute DB, PC, CO	Part of a larger study using MD participants and fMRI Abstract picture associative learning	No effect on performance of the task in the healthy control group	Effect Sizes unavailable – raw data not present in research paper

DB= double-blind PC= Placebo-controlled, CO = Cross-Over, PG = Parallel Groups

COWAT = Controlled Oral Word Association Test, DMTS = Delayed Matching to Sample, DMTS L= Delayed Matching to Sample Latency, DRN = Detection of Repeated Numbers, DS BAS = Digit Span Backward Actual Span, DS BS = Digit Span Backward Score, DS FAS = Digit Span Forward Actual Span, DS FS = Digit Span Forward Score, DT = Deliberation Time (Gamble), IED = Intra/extra Dimensional Set Shift, MD = Methamphetamine-dependent, PRM = Pattern Recognition Memory RVIP = Rapid Visual Information Processing, S RT = Stroop Reaction Time, SOC = Stockings of Cambridge, VAS = Visual Analogue Scale, VSM = Visual Spatial Memory, VSM E= Visual Spatial Memory Error rates, VSM RT= Visual Spatial Memory Reaction Time.

Table 2. Summary of human trials into the cognitive effects of *Panax ginseng.*

Author/Year	*n*	Dose	Sample	Trial Design	Outcome Measures	Results	Cohen's d Effect Size	
Kennedy et al (2001)	20	200, 400, 600mg (G115)	20-27 years Mean age 21.3 years	Acute DB, PC, CO	CDR Testing Battery, self-reported mood measures	400mg lead to improvements on quality of memory and secondary memory at all time point post dose. Significant negative effect on attention in the 200 and 600mg doses.	<u>200mg</u> IWR 4h DVFA 6h DVRT 4h DVRT 6h CRT 1h CRT 4h CRT 6h SMRT 1h SMRT 2.5h PR 1h PRRT 6H <u>400mg</u> IWR 1h IWR 2.5h IWR 4h IWR 6h SRT 6h DVA 1h DVA 4h DVFA 4h DWRT 2.5h WR 2.5h WR 6h PR 1h <u>600mg</u> IWR 1h IWR 2.5h IWR 4h SRT 4h SRT 6h DVA 2.5h	-0.17 0.60 0.50 0.40 0.36 0.15 0.22 0.17 0.05 -0.01 0.19 0.02 -0.15 -0.12 0.12 0.52 0.37 0.44 0.20 0.47 0.08 -0.10 -0.01 0.13 -0.01 0.03 0.86 0.64 -0.34

						DVFA 4h DVRT 4h DVRT 6h WR 2.5 h WR 6h	0.17 0.31 0.62 -0.06 -0.28
Kennedy et al (2002)	20	400mg (G115)	Mean age 21.1 years	Acute DB, PC, CO	CDR Testing Battery, S3, S7, Bond-Lader	Improvements in secondary memory (CDR score), speed of memory task performance and attentional accuracy. No effects of G115 on other measures in the CDR battery	IWR 4h IWR 6h DVFA 2.5h DVFA 4h CRTA 1h CRTA 2.5h SMRT 2.5h NMC 2.5h NMC 6h DWRA 2.5h DWRA 6h WR 2.5h WR 4h	0.54 0.77 0.37 0.41 0.16 0.23 0.39 -0.24 -0.30 -0.06 0.63 0.03 -0.08
Scholey et al (2002)	20	200, 400, 600mg (G115)	Mean age 19.9 years	Acute DB, PC, CO	S3, S7	No effects on S3 Fewer subtractions at all time points following 200mg dose on S7 400mg showed significant improvement in accuracy with reduced amount of errors.	Effect Sizes unavailable – raw data not present in research paper	
Kennedy et al (2004)	28	200mg (G115)	Mean age 21.4 years	Acute DB, PC, CO	CDR Testing Battery, S3, S7, sentence verification, logical reasoning, self-reported mood measures	Improvement on speed of attention and speed of memory (CDR scores)	DVRT 6h CRT 3h CRT 4h NWMRT 2.5h NWMRT 4h NWMRT 6h WRRT 1h WRRT 4h PRRT 4h	0.41 0.15 0.02 0.32 0.29 0.39 0.01 0.11 0.02

Reay et al (2005)	30	200 and 400 mg separate doses	Mean age 22.6 years	Acute DB, PC, CO	Mental Fatigue (self-rated), RVIP, S3, S7. RVIP, S3, S7 are administered as a 10 minute 'cognitive demand battery' and is repeated at hourly intervals at baseline and up to 6 hours post dose.	More significant effects using the 200mg dose. Significant reduction of mental fatigue scores as well as increased performance in S7 in all except one time point (5hours). Significant positive effects shown in RVIP and S3. 400mg dose showed significant increase in mental fatigue at 3 hours post dose as well as modest improvements on RVIP and S3 error rates.	<u>200mg</u> MF 2h MF 3h MF 4h MF 5h MF 6h RVIP RT 5h RVIP 6h S3 4h S3 E 4h S3 E 5h S7 1h S7 2h S7 3h S7 4h S7 6h <u>400mg</u> MF 3h RVIP RT 6h RVIP 5h S3 6h S3 E 2h	 0.20 0.59 0.31 0.90 1.03 0.53 -0.11 0.27 0.17 0.39 0.34 0.36 0.45 0.35 0.39 0.61 0.29 -0.07 -0.09 0.17
Sünram-Lea et al (2005)	30	200mg	18 -25 years Mean age 20 years	Acute DB, PC, CO	CDR Testing Battery, self-report mood measures	Improvements on 'speed of attention' component of CDR battery from the choice reaction time task. No other measure was significant.	CRT	0.33
Reay et al (2006)	27	200mg	Mean age 21.89 years	Acute DB, PC, CO	Mental Fatigue (self-rated), RVIP, S3, and S7. RVIP, S3, S7 are administered as a 10 minute 'cognitive demand battery' and is repeated at hourly intervals at baseline	Mixed effects on mental fatigue Significant improvements on RVIP performance and reduced false alarms. Significant improvements on serial 3s at 4 and 6 hours, but significant	MF 5h MF 6h RVIP 4h RVIP FA 6h S3 3h S3 4h S3 6h S3E 6h	1.08 1.40 0.24 0.21 0.28 0.22 0.28 0.03

					and up to 6 hours post dose.	reduction in performance at 3 hours.		
Reay et al (2009)	30	200 and 400mg	Mean age 22.87 years	DB,PC,CO	Acute and sub-chronic (8 days) testing sessions. Multiple tests including corsi-blocks, 1/2/3/4 back and random number generation	Reduced reaction time on 3-back reaction time at 400mg, but increases in reaction time with 200mg Increased 3-back sensitivity index scores with 400mg, but decreased with 200mg Improved self-reported mood levels.	<u>Day 1</u> <u>200mg</u> 3BRT 4h <u>400mg</u> 3BRT 2.5h 3BSI 1h 3BSI 4h <u>Day 8</u> <u>200mg</u> 3BRT 1h 3BRT 2.5h 3BSI 4h <u>400mg</u> 3BSI 1h 3BSI 4h	 -0.25 0.81 0.40 0.30 -0.10 -0.48 -0.43 0.04 0.16

DB= double-blind PC= Placebo-controlled, CO = Cross-Over

3BRT = 3-back Reaction Time, 3BSI = 3-back Sensitivity Index CRT = Choice Reaction Time, CRTA = Choice Reaction Time Accuracy, DVA = Digit Vigilance Accuracy, DVFA = Digit Vigilance False Alarms, DVRT = Digit Vigilance Reaction Time, DWRA = Delayed Word Recall Percentage Accuracy, IWR = Immediate Word Recall (% accuracy), MF = Mental Fatigue, NMC = Numeric Working Memory Percentage Change, NWMRT = Numeric Working Memory Reaction Time, PRRT, Picture Recognition Reaction Time, RT= Reaction Time, RVIP = Rapid Visual Information Processing, RVIP FA = Rapid Visual Information Processing False Alarms, RVIP RT = Rapid Visual Information Processing Reaction Time,
S3 = Serial Threes correct, S3 E = Serial Threes errors, S7 = Serial Sevens correct, S7 E = Serial Sevens errors, SMRT = Spatial Memory Reaction Time, SMRT = Spatial Memory Reaction Time, PR = Picture Recognition, WR = Word Recognition, SRT = Simple Reaction Time, WRRT = Word Recognition Reaction Time.

Table 3. Summary of human trials into the cognitive effects of *Bacopa monniera*

Author/Year	*n*	Dose	Sample	Trial Design	Outcome Measures	Results	Cohen's d Effect Size
Stough et al. (2001)	46 23(B) 23(P)	KM 300mg daily BC: min 55%	18-60 yrs	12-week DB, PC	IT, AVLT, RT, DS	Improved IT & three AVLT subtests (learning rate, proactive interference & forgetting rate) at 12 weeks compared to PL. RT & DS did not improve	IT: 0.25 AVLT[1]: 0.27 AVLT[2]: 0.52 AVLT[3]: 1.01
Nathan et al. (2001)	38 18 (B) 20 (P)	KM 300mg single dose BC: min 55%	18-60 years	0 and 2 hours DB, PC	AVLT; DS; DSST: SDMT: SCT; TMT; RT; IT	No improvements made on all measures.	N/S
Roodenrys et al. (2002)	76 37 (B) 39 (P)	KM 300mg (ppts < 90kg) 400mg (ppts >90kg) BC:55%	40 – 65 years	0 and 3 months DB, PC	Memory Questionnaire, Story recall, General Knowledge, WP, DS, VS, Coding	Improved recall of Delayed WP task. No improvements in DS, VS, Coding, General Knowledge, Memory Questionnaire or Story recall	DWP : 0.23
Stough et al. (2008)	62 33 (B) 29 (P)	KM 300mg daily BC: min 55%	18-60 years	0 and 90 days DB, PC	CDR Testing Battery	Improved two CDR subtests (RVIP & Working Memory); Remaining nine subtests showed no improvements	WM: 0.47 RVIP: 0.30
Calabrese et al. (2008)	44 24 (B) 24 (P)	MH 300mg daily BC: min 50%	65+ years	0 and 12 weeks DB, PC	Primary Outcome: AVLT Secondary Outcomes: Stroop, DAT, WAIS Letter Digit Test	Significant AVLT subtest (Delayed Word Recall) and Stroop improvements. No improvements on DAT, WAIS Letter Digit Test	AVLT[4]: 0.36 Stroop: 0.32
Barbhaiya et al. (2008)	44 23 (B) 21 (P)	BM 450mg daily BC: bacoside A_3 > 5% w/w	50 – 75 years MMSE 24+	0, 12 and 24 weeks DB, PC Treatment between 0 – 12 weeks	AVLT; WMS; WAIS; Cognitive testing battery administered after 12 weeks treatment and 24 week follow up.	Comparisons not between treatment groups but change from baseline in each group	No effect sizes available

Morgan & Stevens (2010)	81 36 (B) 45 (P)	BM 300mg daily BC: 40 – 50%	55+ years	0 and 12 weeks DB, PC	Multiple cognitive measures: AVLT, CFT, TMT, MAC-Q	Significant improvements on verbal learning, memory acquisition and delayed recall AVLT measures No significant differences on CFT, TMT or MAC-Q	$AVLT^4$: 0.95 $AVLT^5$: 0.53 $AVLT^6$: 0.57

Note: 0 in Trial Design column refers to baseline testing, i.e. prior to ingestion of first tablet

KM = KeenMind, CDRI = Central Drug Research Institute, Lucknow, India, MH = MediHerb, BM = BacoMind; DB= double-blind PC= Placebo-controlled.

AVLT= Auditory Verbal Learning Test, $AVLT^1$ = AVLT Learning Rate, $AVLT^2$= AVLT Forgetting rate, $AVLT^3$= AVLT Proactive Interference,

$AVLT^4$= AVLT Delayed Recall, $AVLT^5$= AVLT Total Learning, $AVLT^6$= AVLT Retroactive Interference, DS= Digit Span, VS= Visual Span,

DWP = Delayed Word Pairs, DSST= Memory Task and Digit Symbol Substitution Test, SDMT= Symbol Digit Modalities Test, SCT= Speed of Comprehension Test, RT= Reaction Time, IT = Inspection Time, RVIP = Rapid Visual Information Processing, WMS = Wechsler Memory Scale, WAIS = Wechsler Adult Intelligence Scale, CDR = Cognitive Drug Research, AAMI = Age Associated Memory Impairment, DAT = Divided Attention Task, WAIS = Wechsler Adult Intelligence Scale, BC = Bacoside Content, TMT = Reitan Trail Making Test, MMSE = Mini Mental State Examination, AE = Adverse Events, WM = Working Memory (CDR component).