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BACOPA MONNIERI (BRAHMI) – WHAT IS THE EVIDENCE IN RELATION TO COGNITION, MEMORY AND MOOD? A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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ABSTRACT

Ethnopharmacological Relevance: Previous research suggests that *Bacopa monnieri* has potential to improve cognition, particularly speed of attention.[1] The present article aims to update previous work and re-evaluates the evidence on *Bacopa monnieri* and cognitive function. It also considers the wider effects of *Bacopa monnieri* on memory and mood. **Materials and Methods:** PubMed, the Cochrane Library and ClinicalTrials.gov were searched to identify relevant RCTs using specified search terms. Reference lists of identified articles were also reviewed. Trials identified were objectively assessed for methodological quality using the Cochrane risk of bias tool and Jadad scale. Trials administering *Bacopa monnieri* in combinative with other active ingredients were excluded. **Results:** Thirteen studies met the inclusion criteria comprising of 685 subjects. Overall 11 studies had a low risk of bias and were regarded as good quality. Meta-analysis using data from 160 subjects showed improved State-Trait Anxiety for which there was no evidence of heterogeneity between studies (I^2=0%, p=0.58) and which was significantly reduced in the experimental group by -2.94 (95% CI: -3.97 to -1.92), p<0.0001. No significant findings were observed for the delayed recall Auditory Verbal Learning Task, Digital Span Forwards or Digital Span Backwards tests. **Conclusion:** This updated review suggests that *Bacopa monnieri* including the standardised CDRI 08 extract could help to reduce feelings of anxiety. These are promising findings and build on previous work observing cognitive benefits. Ongoing trials using aligned definitions of cognitive, memory and mood domains and evaluating the adjunctive or 'head to head' effects of *Bacopa monnieri* against conventional medications are also needed.

KEYTERMS: Bacopa monnieri, nootropic effects, cognition, attention, memory, mood, anxiety.

INTRODUCTION

Cognition is a focal point of interest in modern age with most research examining how cognitive abilities can be preserved, or how they decline with age.[2] As the global population expands and ages coinciding changes in brain health can impact substantially on society.[3] By 2050 the number of people living with dementia globally is expected to triple - from 47 to 132 million with estimated costs rising to $3 trillion.[4] This emphasises the need for innovative screening tools and interventions beginning earlier on in midlife.[4] "Optimally ageing" or optimal cognitive ageing is an important concept with modern relevance. Some older individuals have little decline in cognitive ability compared with younger adults thus meeting this description. Unfortunately, age-related diseases appear to be impacting on optimal cognitive ageing. For example, the incidence and prevalence of type 2 diabetes mellitus is rising worldwide and is now recognised as a factor contributing to cognitive decline, mainly by neurodegeneration.[5,6] There are many different domains of cognition which include: attention, emotion, executive control, language, memory and sensory functions.[1] Reserve can also be categorised into two distinct types: 1) Brain reserve – this relates to differences in brain structure which, in turn, can affect cognition (brain function) and 2) Cognitive reserve (CR) – this refers to how individuals perform tasks and explains why some people may be more resilient to brain changes than others.[7] There are an array of cognitive domains but CR appears to be most closely related to attention, memory (verbal and working), executive function (mental processing and skills) and orientation.[8]

Due to the state of poor cognitive health complementary and alternative (TCAM) systems are growing in interest amongst patients and medics alike with these largely contributing to the foundation of 'person-centred' medicine.[9] In 2014 a meta-analysis of nine trials ≥12 weeks showed that *Bacopa monnieri* extract had potential to improve cognition, particularly speed of attention.[1] A systematic review of five trials has also shown that *Bacopa monnieri* could improve elements of

cognition and attention-deficit domains in younger cohorts too - children and teenagers.[10]

The present review conducts an updated analysis – evaluating how *Bacopa monnieri* use could affect cognition, memory and mood. The review is not restricted by age and includes younger and older populations.

Brahmi

There is growing interest in Ayuvedic medicine - the science (ved) of life (ayu), due to its origin to Veda - the oldest documented wisdom of human civilization written in 3500 BCE providing extensive knowledge of various diseases and their therapeutic approaches.[11] Some even believe these may possess equal efficacy and even superior safety to modern medicines, though ongoing "equivalence trials" are needed[12] Botanicals which are renowned for their antioxidant and anti-inflammatory effects are now showing particular promise in relation to delaying and offsetting neurodegenerative conditions.[13]

Bacopa monnieri in Indian and Hindi is referred to as *Brahmi* and in Vietnamese: Rau Dang, *Herpestis monnieri* or water hyssop and the 'herb of grace'.[14,15] *Brahmi* itself was named after Lord Brahma, the mythological creator of the world and originator of the science of Ayurveda who is frequently mentioned in the religious, social, and medical papers of India.[15] *Bacopa monnieri* is a perennial plant native to the wet lands of India, typically found in the northeast and southern regions.[15] It has long been used in Ayurvedic medicine as a nootropic (to enhance memory and cognitive function).[16] Subsequently, in the Indian system of medicine it is considered to be a "*Medhya Rasayana*" – herb that sharpens the mind and the intellect.[17]

The extract of *Brahmi*; *Bacopa monnieri* (EBM) contains an array of active ingredients including the triterpenoid saponins, bacoside A and B, flavonoids, alkaloids, glycosides, phytochemicals, sapogenin, brahmic acid, brahamoside, brahminoside and isobrahmic acid.[18] Amongst these bacoside A is regarded as the main neuroprotective constituent comprised of: bacoside A3, bacopaside II, bacopaside X and bacopasaponin C with these helping to establish a healthy antioxidant environment in brain tissues.[19] A number of mechanisms have been proposed regarding the ways in which *Bacopa monnieri* may affect cognition, memory and mood. These are summarised in **Table 1.**

METHODS

Data Sources and Search Strategies

The following database searches were undertaken: PubMed, Cochrane Library and www.clinicaltrial.gov. The Medical Subheading (MeSH) and keywords used were: "*Bacopa monnieri"* along with "cognition", *"cognitive reserve", "cognitive performance", "memory" and "mood"*. Within the mood search *"depression"* and *anxiety"* were included. The reference lists of retrieved articles were also searched.

Selection of Studies

Included studies all investigated the effects of *Brahmi* on cognitive reserve, memory and mood. Studies were included if participants had memory complaints but were free from major cognitive deficits. The following criteria was applied: 1) Studies were randomized placebo-controlled trials, 2) Studies investigated the effects of *Brahmi* using validated tools to assess cognition, memory and mood, 3) Studies used an intervention comprised of extract of *Bacopa Monnieri.*

Exclusion criteria included: *In vitro* studies, animal studies, non-clinical trials, studies where the outcomes listed were not the main point of interest and studies where only an abstract available. Trials that administered *Brahmi* in combinative with other active ingredients were also excluded.

Data Extraction: Data was extracted from full-text articles using standard approaches. All publications were written in English-language. The extracted data included the study setting, design, number, age and characteristics of subjects, experimental intervention, placebo intervention, dosage information, main outcome, effect sizes and main conclusion. Duplicate papers were eliminated from the search algorithm.

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] Publications were excluded if PRISMA benchmarks were not included in the trial publication but instead covered elsewhere. The abstracts and papers were evaluated for relevance.

The main methodologies used to assess cognitive, memory and mood domains were extracted from each trial so that these could be compared and contrasted (**Table 2**). A total of 21 main domains were identified, although it should be recognised that others were also used. It was observed that the delayed recall Auditory Verbal Learning Task (AVLT), Digital Span Forwards or Digital Span Backwards and State-Trait Anxiety tests were used most consistently across studies. Given this, data from these was extrapolated and formed the main meta-analysis. The meta-analysis was run in Stata Version 14 (StataCorp, Texas) using the metan command.

Data Quality and Validity Assessment

The methodological quality of studies was deciphered using the Cochrane tool to determine risk and level of bias[21] (**Table 3**). This tool has been adequately validated and consists of seven main categories: 1) Random sequence generation, 2) Allocation concealment, 3) Selective outcome reporting, 4) Patient and Practitioner Blinding, 5) Assessor Blinding, 6) Incomplete Data Outcome and 7) Other potential bias.

Following on from this each category was thoroughly evaluated and graded as H – high risk or bias (ROB), U – uncertain ROB or L – low ROB.

Alongside this the Jadad scale and criteria was used to develop quality scores for each RCT[22], also shown in **Tables 3 and 4**. Quality scores were graded between 1 and 5 with higher scores being indicative of higher quality.

RESULTS

PubMed, Cochrane Library and www.clinicaltrial.gov. The PubMed search identified 42 RCT papers after an adjustment for replica papers. Of these, 23 papers were discarded after reviewing the abstracts and article content as they did not meet the inclusion criteria. This left 13 RCT articles for general review. The algorithm of qualifying publications is shown in **Figure 1**. Of these, eight studies were conducted in Australasia, four in Asia and one in the United States.

Cognition

As shown in **Table 5** eight studies focused on aspects of cognition.[23-30] Findings are somewhat mixed depending on the length of the study, age and health of the baseline population. For example, amongst an intellectual sample of 60 medical students 300mg of standardised *Bacopa Monnieri* extract taken daily over 6-weeks significantly improved cognitive function tests, including immediate recall.[23] Similarly, in a longer trial 90 days of *Bacopa monnieri* CRDI 08 extract supplementation (2x150mg) amongst healthy adults (mean age 43 years) significantly improved working memory and spatial memory accuracy.[27] Other work of a similar duration using a similar CRDI 08 extract of *Bacopa* also noted significant improvements in the speed of visual information processing and learning rate in adults aged 20 to 50 years.[30] Shorter pharmacological windows have also been found to have benefits. Downey and colleagues (2013) observed that 320mg *Bacopa Monnieri* CRDI 08 extract improved cognition on the same day of ingestion, indicating potential value in assessing sensitive 'temporal' measures of brain activity.[24]

Amongst a Indian population 450mg *Bacopa Monnieri* extract taken daily over 12 weeks by healthy urban adults did not yield any changes in cognitive measures although there was an improvement in anxiety scores.[25] Earlier Australian work by Nathan *et al.* (2001) also found that 300mg *Bacopa Monnieri* extract did not affect cognition when assessed 2 hours after ingestion.[29]

Amongst older adults findings appear to be more prominent. For example, when a sample of healthy elderly subjects (mean age 62 years) took 300 or 600mg *Bacopa monnieri* extract daily over 12 weeks plasma acetylcholinesterase levels were suppressed and working memory improved, indicating that this could be a potential mediator.[26] Calabrese *et al.* (2008) using a similar dosage (300mg/day) *Bacopa monnieri* extract also observed improved AVLT delayed word memory scores compared to the placebo in an older population aged 65 years+.[28]

The digit span tests are short tests often used to evaluates a person's cognitive status. The person is typically told to listen carefully and then hears a series of numbers and asked to repeat them back to you in the same order you say them (digital span forwards). When the person is asked to repeat the numbers backwards this is known as digital span backwards. As shown in **Figure 2a** for digital span forwards the heterogeneity test indicated that there were significant differences in the effect size between the studies (I^2=74%, p=0.002). Results were therefore combined using a random effects meta-analysis using the method of DerSimonian and Laird. The average treatment effect (Experimental-control) was -0.09 (95% CI: -0.39, 0.22), p=0.58 indicating no significant difference in digital span forwards between the groups.

For digital span backwards (**Figure 2b**) the heterogeneity test showed that there were significant differences in the effect size between the studies (I^2=84.3%, p<0.001). Results were therefore again combined using a random effects meta-analysis using the method of DerSimonian and Laird. This showed that the average treatment effect (Experimental-control) was -0.05 (95% CI: -0.55, 0.44), p=0.83 indicating no significant difference in digital span backwards between the groups.

Memory

Five studies focused on aspects of memory[26,31-34] Studied populations were found to be middle-aged or older. Morgan & Stevens observed that 300mg per day of *Bacopa monnieri* significantly improved memory acquisition after being taken daily after a meal for-12 weeks by adults aged 55 years and over who were free from dementia.[31]

Amongst those with mild cognitive impairments at baseline two studies noted improvements in markers of memory. Raghav *et al.* (2006) found that mental control and logical memory significantly improved in adults >55 years with memory loss in everyday activities who took a standardised 250mg *Bacopa monnieri* extract daily.[33] A 24-week Indian trial comprised of adults aged 50-75 years with memory complaints at baseline also found that 450mg *Bacopa monnieri* extract daily improved attention and verbal memory tests.[32]

An 18-week trial on healthy subjects with no reported head injuries found that the *Bacopa* extract CDRI 08 (weight-dependant dose) significantly improved the retention of new information amongst adults aged 40 to 65 years.[34] A shorter post-ingestion trial observed positive effects on letter search and Stroop tasks one and two hours post *Bacopa monnieri* CDRI 08 extract consumption at doses of both 320 and 640mg.[35]

The delayed recall AVLT is a test designed to evaluate different aspects of verbal memory in patients. In the present meta-analysis data from delayed recall AVLT was extracted as this was most consistently reported across studies. As shown in **Figure 2c** the meta-analytical heterogeneity test revealed that there were significant differences in the effect size between the studies (I^2=61.7%, p=0.03). Results were therefore combined using a random effects meta-analysis using the method of DerSimonian and Laird. The average treatment effect (Experimental-control) was 0.36 (95% CI: -0.45, 1.18), p=0.38 indicating no significant difference in AVLT between groups.

Mood: Four studies focused on aspects of mood within their study outcomes.[24,25,28,30] Most trials were conducted over a 12-week duration. An early trial by Stough *et al.* (2001) found that state anxiety was significantly reduced after 12-weeks of 300mg *Bacopa monnieri* CRDI 08 extract supplementation in adults aged 28-50 years.[30] In the same study 23% of the 46 healthy volunteers reported a decrease in stress.[30] In a well-designed trial comprised of healthy urban adults (35 to 60 years) 450mg *Bacopa monnieri* extract over 12-weeks was also associated with a lower anxiety state compared to the placebo group.[25] Calabrese *et al.* (2008) also reported that depression scores, anxiety scores and heart rate decreased over time amongst those taking 300mg *Bacopa monnieri* extract daily over 12-weeks whilst these outcomes increased in the placebo group.[28] Interestingly, in a post ingestion trial 640mg *Bacopa monnieri* CDRI 08 extract was associated with reduced cortisol levels indicating a potential physiological mechanism for stress reduction.[35]

As shown in **Figure 2d** when focusing on State Trait Anxiety there was no evidence of heterogeneity between studies (I^2=0%, p=0.58) when results were combined using a fixed effect meta-analysis. Overall state trait anxiety was significantly reduced in the experimental *Bacopa monnieri* group by -2.94 (95% CI: -3.97 to -1.92), p<0.0001.

Risk of Bias: Overall 11 studies had a low risk of bias and were regarded as good quality i.e. a Jadad score of 3 or above 3.[25-35] Of the studies identified three were subject to potential gender bias having a higher ratio or males or females.[23,33,35] Most studies used appropriate methods of randomization such as computer generated random numbers and coin flipping but five studies did not provide sufficient details about such methods.[23,24,27,33,34] Equally one study did not clearly specify the method of blinding.[23]

Adverse events.

With regard to adverse events in one study comprised of 46 volunteers 23 percent reported feelings of a dry mouth after 12 -weeks of *Bacopa* supplementation.[30] Eighteen percent reported excessive thirst, nausea, palpitations and headache[30] though these symptoms were self-reported.

In one study more adverse effects were reported in the placebo group than the *Bacopa* group.[28] Amongst those in the *Bacopa* group flu-like symptoms and digestive problems were most reported.[28]

In other work gastrointestinal tract side-effects were observed including increased stool frequency, abdominal cramps and nausea amongst adults aged 55 years and over.[31] Other research has found the haematological profile to be similar between Bacopa and control groups.[32]

DISCUSSION

Previous meta-analytical work has found that *Bacopa monnieri* has potential to improve cognition, especially speed of attention.[1] Whilst evidence of such benefits was evident within studies cited in the present review no overall significant effects were observed for digital span forwards, digital span backwards and delayed recall Auditory Verbal Learning Task. It could be that *Bacopa monnieri* affects specific markers of cognitive function.[36] Bearing this in mind there is a need for studies to better align how markers of cognitive function are measured so data can be compared and contrasted more effectively. Previous work has estimated that a sample size of sample size of 30 subjects is warranted to generate estimate differences with sufficient accuracy.[28,30], so some studies could have benefited from larger sample sizes. As age advances the likelihood of cognitive deficits also rises thus the effects of interventions such as *Bacopa* appeared to become more prominent.[26,28]Equally, stronger findings particularly in relation to aspects of memory were found amongst those with mild deficits at baseline.[32,33]

With regard to form, it should be appreciated that the nature of the *Bacopa* was somewhat variable across interventions. Studies using the CDRI 08 extract have shown some benefits in relation to aspects of cognitive function, memory and mood. Potters Memory & Focus (also known as KeenMind®) is a high quality extract of Bacopa Monnieri containing 55% bacosides (based on spectrophotometry methods) and has been rigorously studied in the Central Drug Research Institute in India.[37] For example, six studies in the present review used this particular form of *Bacopa monnieri.*[24, 27, 29, 30, 34, 35] The dosages supplied tended to be 300/320mg up to 640mg with most studies suggesting that 300/320mg of *Bacopa monnieri* was adequate in improving markers of cognition, memory or mood where findings were observed.[24, 27, 30, 34, 35] The high quality extract of Bacopa (CDRI 08) appears to have several modes of action on the human brain and shows particular promise in improving cognition and memory, particularly amongst those with deficits at baseline.[32, 33, 37] As *Bacopa monnieri* has potential to enhance aspects of cognitive function and alertness it is becoming apparent that this could be relevant to sports performance.[38]

The present review observed a statistically significant reduction in State-Trait Anxiety amongst the *Bacopa* groups when data from the studies was combined. This is important given that anxiety disorders are now one of the most prevalent psychological problems worldwide.[39] Anxiety can begin in young age - it is not necessarily a complication of adulthood and has high social and economic costs imposed.[39] The International Classification of Diseases and Related Health Problems (ICD-11) now recognises that anxiety and fear-related disorders manifest across the lifespan and have brought together under a new grouping focusing on aspects of apprehension i.e. the stimulus or situation that triggers the fear or anxiety.[40] The guidelines also explain the relationship between panic disorder and agoraphobia (fear of public spaces) and a category is provided for panic attacks.[40] Given that the present review found that *Bacopa monnieri* could help to reduce State-Trait anxiety future research could also extend to panic disorders.

In relation to extended benefits Kumar *et al.* (2016) observed that blood serum calcium levels and HDL increased in the *Bacopa* group and serum cholesterol decreased although confounding factors needed to be better controlled for.[23] In terms of potential mechanisms *Bacopa monnieri* suppressed acetylcholinesterase in the cerebral cortex in one study - especially in the parietal cortex and hippocampus.[26] This could, in turn, increase its availability in other parts of the brain enhancing attention and memory operation.[26] While the present review did not include poly-herbal formulations other work has concluded that their use could improve cognitive and behavioural outcomes in children and adolescents.[41]

Regarding future research, hypothetically it is thought that *Bacopa monnieri* supplementation alongside cognitive training could work effectively in combination to further enhance and strengthen synaptic changes.[42] These effects could potential improve cognitive outcomes over and above that of the cited individual interventions although this is yet to be tested formally. It is also recommended that future RCTs incorporate neuroimaging particularly magnetic resonance spectroscopy into their methodologies to better understand changes in cognitive function.[43]

Table. 1: Proposed mechanisms of *Bacopa monnieri* on cognition, memory and mood.

Proposed mechanism	Based on	Source
BM acts via antioxidant mechanisms and appears to alter certain neurotransmitters (serotonin 5-HT, DA, ACh, GABA, 5-HT). 5-HT may alter neural plasticity involved in memory formation.	Review	[44]
BM may act via anti-oxidant neuroprotection, acetylcholinesterase inhibition and/or choline acetyltransferase activation, β-amyloid reduction, increased cerebral blood flow, and neurotransmitter modulation.	Review	[45]
BM down-regulated NO and TNF-α in stimulated RAW 246.7 macrophages and of IFN-γ in stimulated human blood cells. Findings suggest BM has anti-inflammatory effects which could affect brain inflammation driven by the innate immune system.	*In vitro*	[46]
BM inhibits the release of inflammatory cytokines from microglial cells and enzymes associated with inflammation in the brain thus appearing to limit inflammation in the CNS.	*In vitro* – cell cultures	[17]
BM increased long-term potentiation magnitude. Enhancement of this may strengthen hippocampal synapses, which play a role in learning and memory formation.	Animal study	[16]
BME CDRI-08 may aid the recovery of hypoxia led memory impairment involving Fmr-1 gene encoded protein called FMRP- a neuronal translational repressor that has been implicated in learning, memory, and cognition.	Animal study	[47]
BME CDRI-08 may regulate reelin (a glycoprotein) which may enhance NUMDAR interactions with synaptic protein and induce BDNF possibly improving object recognition memory.	Animal study	[48]
BME CDRI-08 led to down regulation of the microRNA 124-CREB pathway and increase in plasticity genes which may contribute to memory enhancement.	Animal study	[49]
BME CDRI-08 may act on the serotonergic system thus improving hippocampal-dependent tasks.	Animal study	[50]

Key: Ach, acetylcholine; BDNF, brain-derived neurotrophic factor; BM, *Bacopa monnieri*, BME, *Bacopa monnieri* extract; CNS, Central Nervous System; DA, dopamine; FRMP, Fragile X mental retardation protein; GABA, γ-aminobutyric acid; IFN, interferon; NIMDAR, N-methyl-D-aspartate receptor; NO, nitric oxide; TNF, Tumour Necrosis Factor; 5-HT, 5-hydroxytryptamine.

Table. 2: Main outcomes of interest for each trial.

	Kumar *et al.* (2016)[23]	**Benson *et al.* (2014)** [35]	**Downey *et al.* (2013)** [24]	**Sathyanarayanan *et al.* (2013)**[25]	**Pethi-Nui *et al.* (2012)** [26]	**Morgan & Stevens (2010)** [31]	**Barbhaiya *et al.* (2008)** [32]	**Calabrese *et al* (2008)** [28]	**Stough *et al.* (2008)** [27]	**Raghav *et al.* (2006)** [33]	**Roodenrys *et al.* (2002)**[34]	**Nathan *et al.* (2001)** [29]	**Stough *et al.* (2001)**[30]
AVLT immediate recall (words)						x	x						
AVLT delayed recall (words)				x		x	x	x				x	
AVLT learning rate (words)				x		x						x	x
Complex Figure Test						x							
Depression Scale						x		x					
Digit span forward (digits)	x						x			x	x	x	x
Digit span backward (digits)	x						x			x	x	x	x
Divided Attention Task								x					
Inspection Time Task				x									
Memory complaint questionnaire						x					x		
Mini-Mental State Examination						x							
Paired associate task	x						x			x	x		
Profile of mood states								x					
Reitan Trail Making Test						x							
RVIP			x	x					x				
State-Trait Anxiety		x*		x				x					x
Stroop Task		x		x				x					
Wechsler Adult Intelligence Scale							x	x					
Wechsler Memory Scale										x			
Working memory speed (ms)									x			x	x
Working memory capacity (ms)												x	x

Key: AVLT, Auditory Verbal Learning Task; RVIP, Rapid Visual Information Processing Test; *data presented as change scores.
Table updated and adapted from Kongkeaw *et al.* (2014).[1]

Table 3: Cochrane risk of bias and Jadad scores for the included RCTs.

Study	Random Sequence Generation	Allocation Concealment	Selective Outcome Reporting	Patient & Practitioner Blinding	Assessor Blinding	Incomplete Data Outcome	Further Bias	Jadad's scores
Kumar *et al.* (2016) India[23]	H	U	U	H	H	U	Gender	2
Benson *et al.* (2014) Australia[35]	L	U	U	L	L	U	Gender	4
Downey *et al.* (2013) Australia[24]	H	H	L	L	L	U	NA	2
Sathyanarayanan *et al.* (2013) India[25]	L	L	L	L	L	L	NA	5
Pethi-Nui *et al.* (2012) Thailand[26]	L	L	L	L	L	L	NA	4
Morgan & Stevens (2010) Australia[31]	L	L	L	L	U	L	NA	5
Barbhaiya *et al.* (2008) India[32]	L	L	L	L	U	L	NA	4
Stough *et al.* (2008) Australia[27]	H	H	L	L	L	U	NA	3
Calabrese *et al (2008) USA*[28]	L	L	L	L	L	L	N/A	5
Raghav *et al. (2006) Australia*[33]	U	U	L	U	U	L	Gender	3
Roodenrys *et al.* (2002) Australia[34]	U	U	U	U	U	L	NA	3
Nathan *et al.* (2001) Australia[29]	L	L	L	L	L	L	NA	4
Stough *et al.* (2001) Australia[30]	L	L	L	U	U	L	NA	4

Key: H, high risk of bias; L, low risk of bias; NA, not applicable; U, uncertain risk of bias.

Table. 4: Jadad assessment scale used to assess RCT quality.

Publication	Randomisation	Method of randomisation described & appropriate	Blinding mentioned	Method of blinding described and appropriate	Withdrawal and dropout of subjects provided	Total score
Kumar *et al.* (2016) India[23]	1	0	0	0	1	**2**
Benson *et al.* (2014) Australia[35]	1	1	1	1	0	**4**
Downey et al. (2013) Australia[24]	0	0	1	1	0	**2**
Sathyanarayanan et al. (2013) India[25]	1	1	1	1	1	**5**
Pethi-Nui et al. (2012) Thailand[26]	1	1	1	1	0	**4**
Morgan & Stevens (2010) Australia[31]	1	1	1	1	1	**5**
Barbhaiya et al. (2008) India[32]	1	1	1	0	1	**4**
Stough et al. (2008) Australia[27]	1	0	1	1	0	**3**
Calabrese *et al* (2008) USA[28]	1	1	1	1	1	**5**
Raghav et al. (2006) Australia[33]	1	0	1	0	1	**3**
Roodenrys *et al.* (2002) Australia[34]	1	0	1	0	1	**3**
Nathan et al. (2001) Australia[29]	1	1	1	1	0	**4**
Stough et al. (2001) Australia[30]	1	1	1	1	0	**4**

Note: Total quality assessment score for which scores range between 1 and 5: with 1 being the lowest quality and 5 being the highest quality. 3=above average quality.*Included twice as markers of lipid metabolism and inflammation were recorded.

Table. 5: Summary of randomised placebo-controlled trials of Bacopa monnieri on cognitive reserve, memory and mood.

First author year, setting Ref.no	Study design	Study duration (weeks)	Age of Subjects	No. of Subjects		*Bacopa monnieri* preparation			Control Intervention	Main Outcomes	Conclusions
				Active intervention	Control	Standardization for dosage (Trade name)	Dosage form	Dose (mg/d)			
Kumar *et al.* (2016) India[23]	R PC DB (noncrossover, parallel)	6	19-22yrs Medical students	28	14	150mg standardised extract (Bacognize) twice daily	NR	300	Matching placebo	Cognitive function.	Statistically significant improvements were seen in cognitive function tests with use of BM in a population groups with already high cognitive function.
Benson *et al.* (2014) Australia[35]	PC DB crossover trial	1h and 2h post ingestion	18-44yrs	17	17	320mg or 640mg of BM (Keenmind CDRI 08). BM extract equivalent to 4g of dried herbs.	Capsules	320 or 640	Inert placebo	Stress Reactivity & Mood	BM consumption improved Letter Search and Stroop tasks 1hr and 2hr post ingestion. Positive effects on mood and reduced cortisol levels were also observed.
Downey et al. (2013) Australia[24]	PC DB crossover trial	Six reptititions – pre and post assessments.	18-56yrs	24	24	320mg or 640mg of BM (Keenmind CDRI 08). BM extract equivalent to 4g of dried herbs.	Capsules	320 or 640	Placebo identical in shape, smell, taste & weight	Sustained cognitive performance.	320mg BM improved performance on the CDB 1st, 2nd, 4th post-dosing tests.
Sathyanarayanan et al. (2013) India[25]	R PC DB trial	12	35-60yrs	33	33	Two capsules amounting to 450mg. One Brahmi capsule provided 225mg Bacomind.	Capsule	450	Same size & level of starch	Cognition and anti-anxiety.	There was a trend towards lower anxiety state in the BM group but this was not statistically significant.
Pethi-Nui et al. (2012)	R PC DB trial	12	Mean 62 yrs	40	20	300 or 600 mg dried BM extract	Tablet	300 or 600	Placebo tablet	Attention, cognitive	BM group showed improved working

Thailand[26]						(Bacomind). Mixture of bacoside A3, bacopaside II, bacopasaponin X, bacopasaponin C and bacopaside I.				processing, working memory & functions.	memory and suppressed AChE activity.
Morgan & Stevens (2010) Australia[31]	R PC DB trial	12	55yrs+	36	45	Extract equivalent to 6g dried herbs	Film-coated tablet	300 (after a meal)	Film-coated identical placebo	Memory performance.	BM significantly improved memory acquisition and retention in healthy elders.
Barbhaiya et al. (2008) India[32]	R PC DB trial	24	50-75 yrs	23	21	450mg BM after breakfast (BacoMind)	Capsule	450	Placebo capsule	Memory Improvement.	BM significantly improved cognitive functions such as attention and verbal memory.
Stough et al. (2008) Australia[27]	PC DB trial	12.8	18-60yrs	33	29	Each 2x capsules had 150mg BM (KeenMind CDRI 08). Extract equivalent to 3g dried herbs	Capsule	300	Placebo capsule	Cognitive functioning.	BM significantly improved working memory and spatial working memory.
Calabrese *et al* (2008) USA[28]	R PC DB trial	12	65yrs+	24	24	Around 15 g herb and 150 mg (>50% of bacosides A & B; Mediherb).	Tablet	300	Similar placebo tablet	Cognitive performance.	BM group had enhanced AVLT delayed word memory recall compared to the placebo.
Raghav et al. (2006) Australia [33]	R PC DB trial	16	55yrs+	20	20	Standardised BM extract 125mg x2 daily. 55% bacosides	NR	250	NR	Memory impairment	Significant improvements were noted for mental control, logical memory and paired associated learning.

Roodenrys *et al.* (2002) Australia[34]	R PC DB trial	18	40-65 yrs	37	39	300 mg for persons under 90 kg, and 450 mg for persons over 90 kg, equivalent to 6g and 9g dried rhizome (Keenmind CDRI 08)	Capsule	300 (under 90kg) 450 (over 90kg)	NR	Memory	Results showed a significant effect of BM on a test for the retention of new information.
Nathan et al. (2001) Australia[29]	R PC DB trial	2hr post ingestion	18-60yrs	18	20	2 x150mg BM extract standardized for bacosides A and B (Keenmind CDRI 08)	Capsules	300	Placebo capsule	Cognition function.	No effects on cognitive functioning observed.
Stough et al. (2001) Australia[30]	PC DB independent-group design	12	28-50yrs	23	23	Each capsule contained 160 mg BM (KeenMind CDRI 08). Extract equivalent to 4 g dried herb.	Capsules	320	Placebo capsule	Cognitive function.	BM significantly improved speed of visual information processing, learning rate & memory consolidation measured by `AVLT ($P<0.05$), & state anxiety ($P<0.001$) vs. placebo. Maximal effects evident after 12 weeks.

Key: AChE activity, acetylcholinesterase; AVLT, Rey Auditory Verbal Learning test; BM, *Bacopa monniera*; DB, double-blind; R, Randomised, PC, placebo-controlled; STAI, State-Trait Anxiety Inventory test; *Findings reported that were of most relevant and statistically significant.

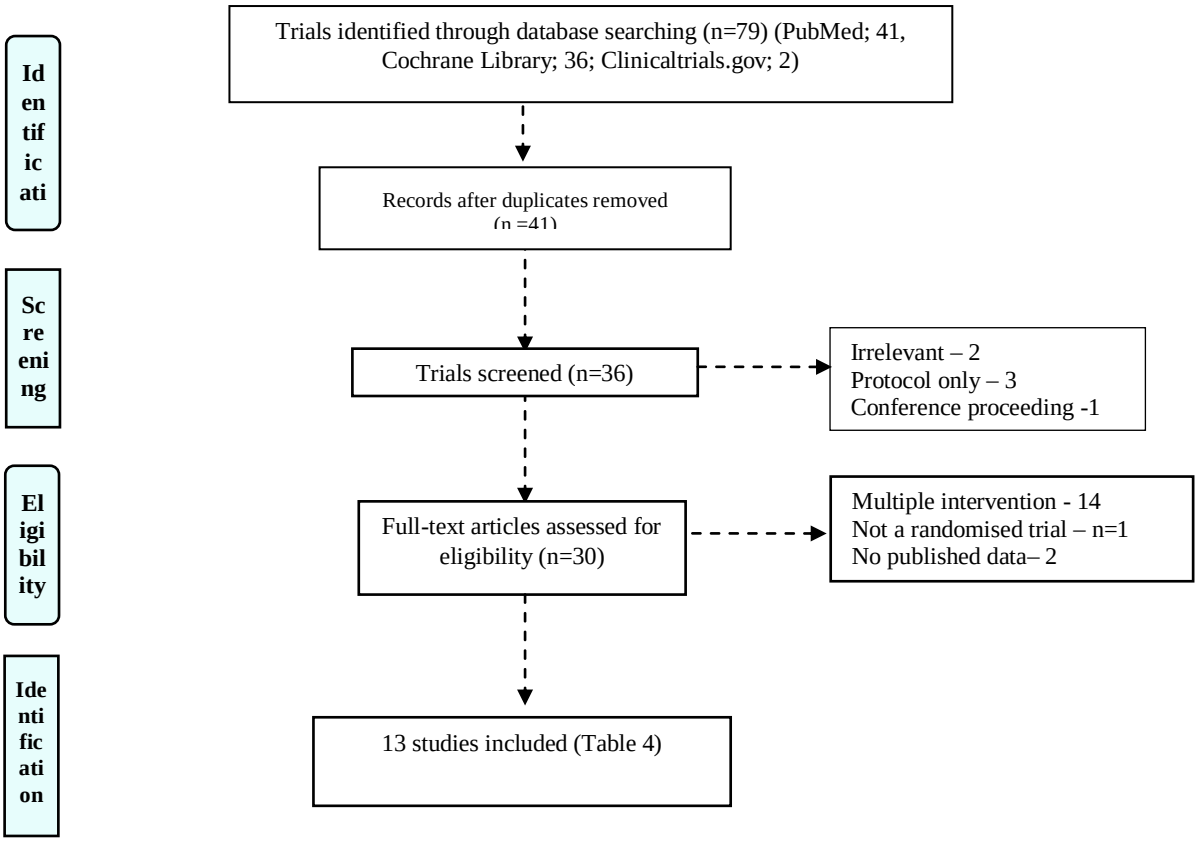

Figure. 1: Algorithm for database search results.

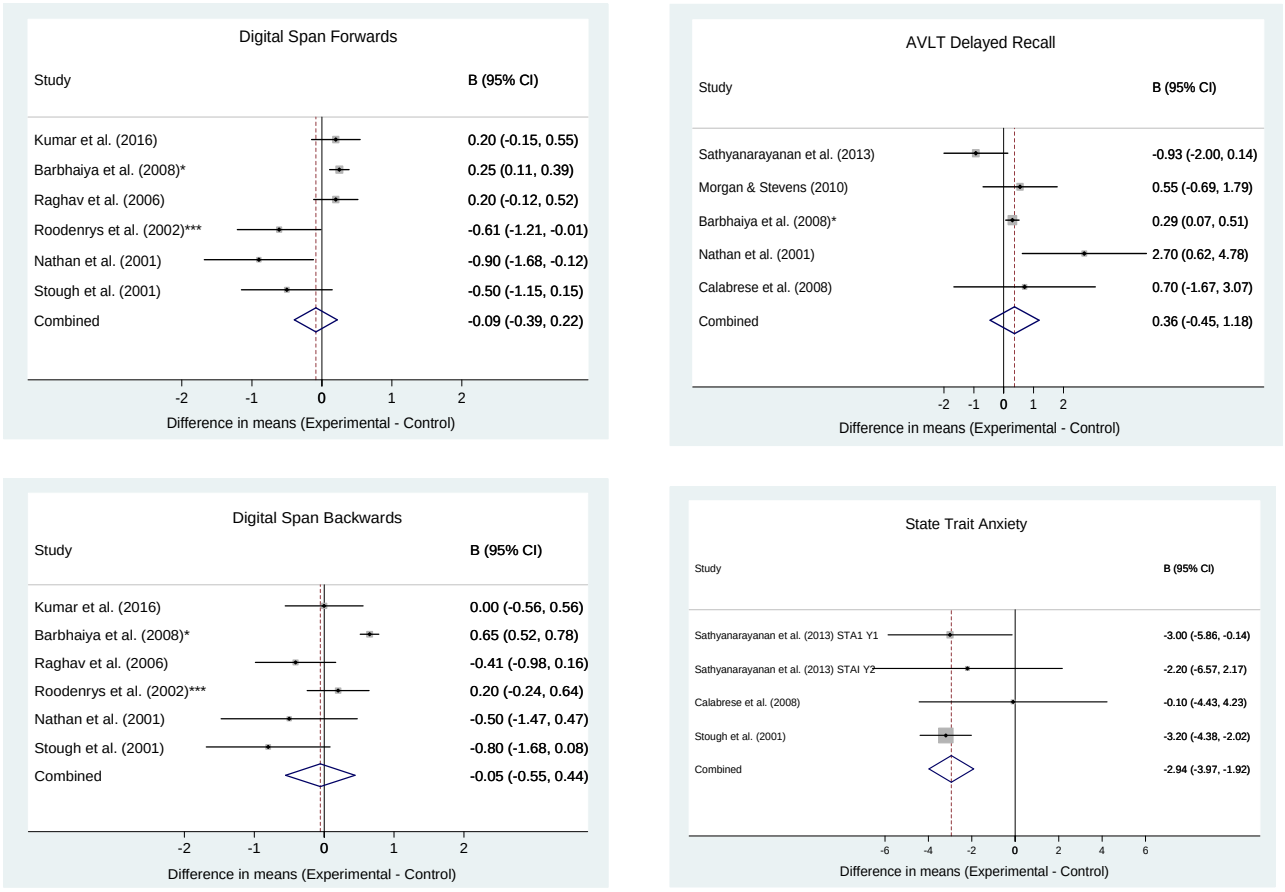

Figure 2: Forest plots of the meta-analysis results for digital span forwards (a), digital span backwards (b), delayed recall AVLT (c) and State-Trait Anxiety (d).

CONCLUSIONS

The present review suggests that *Bacopa monnieri*, including the high quality CDRI 08 extract appears to have a beneficial role in reducing anxiety – a growing public health problem. Significant findings were not observed for delayed recall Auditory Verbal Learning Task, Digital Span Forwards or Digital Span Backwards tests. It is possible that potential benefits may relate to other cognitive domains. Considering this greater consistency is needed in the way that studies report cognitive, memory and mood domains and neuroimaging should also be used where possible. Next, ongoing trials are needed looking at the adjunctive and 'head-to-head' effects when used with conventional medications.

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Disclosure

The views expressed are those of the author alone and Potter's Herbals personnel had no role in writing the review.

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