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Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract

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ABSTRACT

Ethnopharmacological relevance: *Bacopa monnieri* has a long history in Ayurvedic medicine for neurological and behavioral defects. To assess its efficacy in improving cognitive function.
Materials and methods: MEDLINE, EMBASE, CINAHL, AMED, Cochrane Central of clinical trial, WHO registry, Thai Medical Index, Index Medicus Siriraj library and www.clinicaltrial.gov were searched from the inception date of each database to June 2013 using scientific and common synonyms of *Bacopa monnieri*, cognitive performance or memory. The reference lists of retrieved articles were also reviewed. Randomized, placebo controlled human intervention trials on chronic ≥ 12 weeks dosing of standardized extracts of *Bacopa monnieri* without any co-medication were included in this study. The methodological quality of studies was assessed using Cochrane's risk of bias assessment and Jadad's quality scales. The weighted mean difference and 95% confidence interval (95% CI) were performed using the random-effects model of the Dersimonian–Laird method.
Results: Nine studies met the inclusion criteria using 518 subjects. Overall quality of all included trials was low risk of bias and quality of reported information was high. Meta-analysis of 437 eligible subjects showed improved cognition by shortened Trail B test (-17.9 ms; 95% CI -24.6 to -11.2; $p < 0.001$) and decreased choice reaction time (10.6 ms; 95% CI -12.1 to -9.2; $p < 0.001$).
Conclusion: This meta-analysis suggests that *Bacopa monnieri* has the potential to improve cognition, particularly speed of attention but only a large well designed 'head-to-head' trial against an existing medication will provide definitive data on its efficacy on healthy or dementia patients using a standardized preparation.

1. Introduction

The global shift toward an aging population has brought with it an increase in prevalence of cognitive decline ranging from mild impairment to major dementias (e.g. vascular dementia, Alzheimer's disease) (Forman et al., 2004; Gauthier et al., 2006). Domains of cognition include motor functioning, attention, language, memory, executive control, vision, emotion, sensory functions and consciousness. Mild cognitive impairment is seen in 10–20% of individuals aged ≥ 65 years with the reported conversion rates to dementias ranging from 1% to 25% (Bischkopf et al., 2002; Manly et al., 2008). The World Health Organization estimated that the number of patients suffering from dementias will be approximately 44 million globally by 2030 (World Health Organization, 2006). The burdens of dementias are enormous with 11% of all years lived with this disability (Lin and Neumann, 2012; World Health Organization, 2006). Recent estimates for total cost per dementia patient in Europe for the year 2010 were €16,584 ($21,538), resulting in a total cost of €105,163 million ($136,575 million) in the region (Lin and Neumann, 2012). Corresponding excess cost of conversion or progression from mild cognitive impairment to dementias was estimated to be €4389 ($5700) (Wimo and Winblad, 2003).

Acetylcholinesterase inhibitors (AChEIs) continue to be the first-line nootropics for both Alzheimer's disease and vascular dementia. Although these medications have been shown to be effective for mild to moderate dementia patients, the overall outcomes are often unsatisfactory (May et al., 2009) because of various adverse drug effects and they do not modify the disease

Abbreviations: AVLT, auditory verbal learning test; ADHD, attention deficit hyperactivity disorder; MCI, mild cognitive impairment; MMSE, mini mental state examination

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progress in the long term. Thus, when patients discontinue the medication, their symptoms return.

Bacopa monnieri (L.) Wettst. (Synonyms: *Bacopa monniera* (L.) Pennell yes, *Herpestis monniera* L. Kunth; common names: Brahmi, bacopa, water hyssop) is a small herb with oblong leaves and light purple flowers and belongs to the family Scrophulariaceae (Rajani, 2008; Russo and Borrelli, 2005). This plant has been used for more than 3000 years as Indian Ayurvedic medicines for improving memory, increasing brain function, or promoting longevity (Abascal and Yarnell, 2011; Calabrese et al., 2008; Morgan and Stevens, 2010). This medicinal plant has protective effects against β-amyloid toxicity (Limpeanchob et al., 2008) and have beneficial effects on cognitive performance (Abascal and Yarnell, 2011; Calabrese et al., 2008; Morgan and Stevens, 2010; Uabundit et al., 2010).

Complementary and alternative treatments including herbal medicines have increasingly been alternative choices of therapy (May et al., 2009) but evidence about their efficacy as medicines is often weak. A recent systematic review (Neale et al., 2013) showed that *Bacopa monnieri* enhanced memory free recall, thus might be used as a memory enhancer. Similar efficacies were obtained from publications on Panax ginseng and modafinil in healthy, mostly young adults. However, the review did not perform meta-analysis to quantitatively summarize the evidence including those papers showing no effects and did not include the Allied and Complementary Medicine (AMED) database. We have conducted such a formal meta-analysis which aims to examine the efficacy of *Bacopa monnieri* as a treatment for cognitive performance.

2. Methods

2.1. Data sources and search strategies

To identify studies that determined the effects of *Bacopa monnieri* on cognitive performance and/or anxiety, four reviewers electronically searched in MEDLINE, EMBASE, CINAHL, AMED, Cochrane Central of clinical trial, WHO registry, Thai Medical Index, Index Medicus Siriraj library and www.clinicaltrial.gov from the inception date of each database to June 2013. The subject headings were *Bacopa monnieri* or *Bacopa monniera* or *Herpestris monnieri* or *Herpestrismonniera* or *Monieraeuneifolia* or *Lysimachia monnieri* or Brahmi or coastal water hyssop or water hyssop or thyme leafed gratiola or thyme leaved graticula or thyme leafed graticula with cognitive performance or memory. To ensure thoroughness in our search, we reviewed the reference lists of retrieved articles and, where possible, searched for relevant unpublished works.

2.2. Study selection

Studies that investigated the cognitive effects of *Bacopa monnieri* on both healthy humans and subjects who showed memory impairment were selected by four reviewers using the following criteria: (1) studies were randomized placebo controlled clinical trial; (2) studies determined the effects of *Bacopa monnieri* on neuropsychological tests for cognitive performance; (3) studies reported outcomes after at least 12 weeks of administration; and (4) subjects received a standardized extract of *Bacopa monnieri* whose basoside composition was measured or discoverable. Those which used *Bacopa monnieri* in combination with other active compounds were excluded.

2.3. Data extraction and quality assessment

Data were extracted from each article by independent investigators using a standard abstraction form. The extracted data included the study setting, study design, duration of study, sample size, subject characteristics, methods of product extraction, standardization of product, dosage form, dosage and administration, and outcomes. The relevant cognitive outcomes were pre-specified as shown in Table 2. The methodological quality of studies was assessed using Jadad's quality scales on reporting (Jadad et al., 1996) and Cochrane's risk of bias tool for assessing the internal validity of the study (Deeks et al., 2008). Jadad's overall score of <3 or ≥ 3 indicates low or high quality of reporting, respectively. In addition, because drop-outs in studies involving complementary alternative medicine may have impacted the overall estimates, we assessed frequency (differential vs. non-differential dropouts) and causes of dropouts (i.e., missing completely at random, missing at random, and missing not at random) to identify attrition bias in each study (Bell et al., 2013; Dumville et al., 2006; Moher et al., 2010). All disagreements among investigators were solved by discussion and consensus.

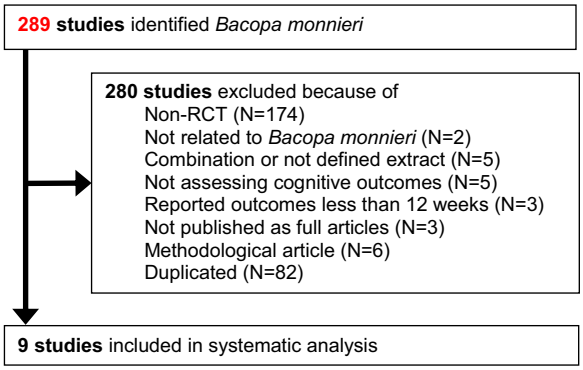

Fig. 1. Flow of included studies.

2.4. Data analysis

The differences of mean scores in each component of neuropsychological tests between treatment and control were outcome measures used for statistical pooling. The weighted mean difference and 95% confidence interval (95% CI) were performed using the random-effects model of the Dersimonian–Laird method (Dersimonian and Laird, 1986). A statistical heterogeneity was tested using the Cochran–Mantel–Haenszel method (Higgins and Thompson, 2002). $p<0.10$ was considered evidence of heterogeneity (Deeks et al., 2008; Higgins and Thompson, 2002). I^2-statistics was also performed to determine the degree of heterogeneity across studies. An I^2 of 25%, 50%, and 75% indicates low, medium, and high heterogeneity, respectively (Higgins and Thompson, 2002). Furthermore, clinical heterogeneity was also assessed according to subject, intervention, comparator, and main outcomes as described elsewhere (Thompson, 1994).

3. Results

3.1. Search results

A total of 289 articles were identified. Of these, 280 were excluded because they were non-randomized or uncontrolled clinical trials (174 articles), not related to *Bacopa monnieri* (two articles), combination products (five articles), not assessed in neuropsychological tests for cognitive performance (five articles), had not been published as full papers (three articles), reported outcomes less than 12 weeks (three articles), methodological papers (six articles) or duplicated (82 articles). In total, nine articles remained which met our criteria (Barbhaiya et al., 2008;

Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Raghav et al., 2006; Roodenrys et al., 2002; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001) (Fig. 1).

3.2. Study characteristics

Among the nine included studies (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Raghav et al., 2006; Roodenrys et al., 2002; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001), seven studies (Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Roodenrys et al., 2002; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001) were conducted in healthy volunteers and two studies (Barbhaiya et al., 2008; Raghav et al., 2006) were conducted in patients with memory impairment. For the dosage form of *Bacopa monnieri* extract, five studies used capsules (Roodenrys et al., 2002; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001), three studies used tablets (Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012), and one study did not report the method of *Bacopa monnieri* administration (Raghav et al., 2006). Four studies administered 300 mg/day of *Bacopa monnieri* extract as the intervention (Calabrese et al., 2008; Morgan and Stevens, 2010; Stough et al., 2008, 2001), two studies used 450 mg/day (Barbhaiya et al., 2008; Sathyanarayanan et al., 2013), one study used 250 mg/day (Raghav et al., 2006), one study used 300 or 450 mg/day depending on subject's body weight (Roodenrys et al., 2002), and one study used 300 and 600 mg/day as the intervention compared to placebo in 3-arm design (Peth-Nui et al., 2012) (Table 1). The outcomes of interest in each study are shown in Table 2.

3.3. Quality of included studies

Patients of all studies were randomly assigned to receive intervention or placebo. Even though all studies stated that they were randomized controlled trials, seven studies (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001) were conducted with appropriate sequence generation to ensure random allocations. Only four studies (Peth-Nui et al., 2012; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001) had appropriate allocation concealment which is an important approach for randomized controlled clinical trials. Six out of the nine studies (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Stough et al., 2008, 2001) had robust blinding procedures. Two included studies (Peth-Nui et al., 2012; Stough et al., 2001) reported no dropout of patients. One study (Sathyanarayanan et al., 2013) reported $<5\%$ dropout rate. The rest of them reported $>10\%$ dropout rates (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan and Stevens, 2010; Stough et al., 2008; Raghav et al., 2006; Roodenrys et al., 2002). Of these, only one study was considered to have a differential

Table 1
Baseline characteristics of included studies.

Study (year)	Study setting	Subject	*N* (intervention: control)	Mean age (years)	Extraction	Standardization for dosage (Trade name)	*Bacopa monnieri* preparations		Duration of study (weeks)
							Dosage forms	Dose (mg/day)	
Barbhaiya et al. (2008)	India	Complaint of memory impairment	23:21	64.98 ± 9.37	NR	Each capsule contained 450 mg of standardized extract of *Bacopa monnieri* (BacoMind)	Capsules	450	24[a]
Calabrese et al. (2008)	USA	Healthy volunteers	24:24	73.5 ± NA	Methanol:water (70:30)	Each tablet contained the equivalent of approximately 15 g herb and 150 mg (> 50% of bacosides A and B (MediHerb)	Film-coated tablets	300	18
Morgan and Stevens (2010)	Australia	Healthy volunteers	36:45	65 ± 7.53	Ethanol	Each 300 mg in a tablet contains 6000 mg equivalent of the dried herb (BacoMind)	Tablets	300	12
Raghav et al. (2006)	India	Complaint of memory impairment	18:17	55–70 (range)	Ethanol	Standardized *Bacopa monniera* EtOH extract 125 mg 55% bacosides (NR)	NR	250	16[b]
Roodenrys et al. (2002)	Australia	Healthy volunteers	37:39	49 ± 7	NR	Capsule 300 mg, 450 mg equivalent to 6 g and 9 g dried rhizome, respectively (KeenMind)	Capsules	300[c]	18
Stough et al. (2001)	Australia	Healthy volunteers	23:23	39.4 ± 11.4	Ethanol	Each capsule contained 150 mg *Bacopa monniera* extract (20:1) equivalent to 3 g dried herb (KeenMind)	Capsules	300	12
Stough et al. (2008)	Australia	Healthy volunteers	33:29	18–60 (range)	50% Ethanol	Each capsule contained 150 mg *Bacopa monniera* extract (20:1) equivalent to 3 g dried herb (KeenMind)	Capsules	300	13
Peth-Nui et al. (2012)	Thailand	Healthy volunteers	40[d]:20	62.6 ± 6.5	Ethanol	Each tablet contained approximately 300 and 600 mg of the crude extract of *Bacopa monnieri*	Tablets	300, 600	16 [a]
Sathyanarayanan et al. (2013)	India	Healthy volunteers	33:33	42.1 ± 6.90	NR	> 50% of individually measured bacosides 2 × 225mg (BacoMind)	Capsules	450	12

NR: not reported.

[a] Subjects take *Bacopa monnieri* extract for 12 weeks, followed by withdrawal period until end of study at 16th week.
[b] Subjects take *Bacopa monnieri* extract for 12 weeks, followed by the placebo for another 4 weeks.
[c] 300 mg for persons under 90 kg, and 450 mg for persons over 90 kg.
[d] Each intervention (300 or 600 mg of *Bacopa monnieri*) had 20 subjects.

dropout rate and included a considerable proportion of 'missing not at random' type of dropouts (Morgan and Stevens, 2010) (Table 3). Therefore, this study was excluded from the meta-analysis as this was likely to be prone to attrition bias. All nine studies achieved high quality in their data reporting according to Jadad's score.

3.4. Effects of Bacopa monnieri

A total of 231 subjects were given a standardized *Bacopa monnieri* extract, while 206 subjects were assigned to the placebo groups. The meta-analyses of all outcomes are shown in Table 4. According to all meta-analyses in our study, the outcomes were classified either as (1) the effects of *Bacopa monnieri* on memory function, or (2) the effects of *Bacopa monnieri* on attention of the subjects.

3.5. Bacopa monnieri and memory function

To analyze the effect on memory function, an aggregate of 326 subjects from six studies was included in Barbhaiya et al. (2008), Calabrese et al. (2008), Morgan and Stevens (2010), Peth-Nui et al. (2012), Sathyanarayanan et al. (2013), and Stough et al. (2008, 2001). The association between *Bacopa monnieri* and improved memory function in most outcomes could not be identified, except the time taken to complete task (Trail B test). *Bacopa monnieri* decreased time taken to complete the task (Trail B test) by 17.9 ms (95% CI: −24.6 to −11.2 ms). However, the result was based on one study conducted by Stough et al. (2001).

3.6. Bacopa monnieri and attention

To analyze the effect on attention, seven studies were included that comprised a total of 303 subjects (Barbhaiya et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Raghav et al., 2006; Roodenrys et al., 2002; Sathyanarayanan et al., 2013; Stough et al., 2008, 2001). There was no detectable effect of *Bacopa monnieri* on choice reaction time when all the studies were grouped together irrespective of dose. However, subgroup analysis for studies administering 300 mg/day of *Bacopa monnieri* showed a decreased choice reaction time of 10.6 ms (95% CI: −12.1 to −9.2; I^2 =0.0%). Other analyses showed high heterogeneity (Table 4).

3.7. Adverse effects of Bacopa monnieri

Eight included studies reported no serious adverse events in either *Bacopa monnieri* or placebo groups (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan and Stevens, 2010; Peth-Nui et al., 2012; Raghav et al., 2006; Roodenrys et al., 2002; Stough et al., 2008, 2001). Of these, two studies did not provide details of adverse events (Barbhaiya et al., 2008; Peth-Nui et al., 2012). The adverse events commonly reported in *Bacopa monnieri* group were gastrointestinal problems including increased stool frequency, nausea, abdominal cramps, and diarrhea. Other adverse events in

Table 2
Outcomes of interest for each trial.

Selected outcome measurement	Barbhaiya et al. (2008)	Calabrese et al. (2008)	Morgan and Stevens (2010)	Raghav et al. (2006)	Roodenrys et al. (2002)	Stough et al. (2001)	Stough et al. (2008)	Peth-Nui et al. (2012)	Sathyanarayanan et al. (2013)
AVLT immediate recall (words)	X		X						
AVLT delayed recall (words)	X	X	X						X
AVLT learning rate (words)			X			X			X
AVLT forgetting rate (words)			X			X			X
Trail A test (ms)			X			X			
Trail B test (ms)			X			X			
Digit span forward (digits)	X			X	X	X			
Digit span backward (digits)	X			X	X	X			
Simple reaction time (ms)						X	X	X	
Choice reaction time (ms)						X	X	X	
Choice reaction time (%accuracy)							X	X	
Word recognition (ms)							X	X	
Word recognition (%accuracy)							X	X	
Picture recognition (ms)							X	X	
Picture recognition (%accuracy)							X	X	
Spatial working memory (ms)							X	X	
Spatial working memory (%accuracy)							X	X	
Numeric working memory (ms)							X	X	
Numeric working memory (%accuracy)							X	X	
Digit vigilance (ms)							X	X	
Digit vigilance (%accuracy)							X	X	
Inspection time (ms)									X

Table 3
Quality of studies by risks of bias and Jadad's scale.

Study (year)	Risks of bias[a]						Jadad's scores	% Drop-out	
	Sequence generation	Allocation concealed	Blinded	Incomplete outcome data	Selective outcome reporting	Other sources of bias		*Bacopa monnieri*	Placebo
Barbhaiya et al. (2008)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	4	11.5	12.5
Calabrese et al. (2008)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	5	11.1	11.1
Morgan and Stevens (2010)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	5	26.5	8.6
Raghav et al. (2006)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Low risk	3	10.0	15.0
Roodenrys et al. (2002)	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Low risk	3	9.8	13.3
Stough et al. (2001)	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk	4	0	0
Stough et al. (2008)	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	4	41.1	39.6
Peth-Nui et al. (2012)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	5	0	0
Sathyanarayanan et al. (2013)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	4	8.3	8.3

[a] Risk of bias assessment is based on Higgins and Thompson (2002).

Bacopa monnieri group were reported such as flu-like symptoms, dry mouth, decrease in felt stress, and a reduction in number of dreams. One study reported an adverse event (i.e., back pain) from the placebo group only (Sathyanarayanan et al., 2013).

4. Discussion

Our systematic review and meta-analysis of randomized, controlled trials examined the beneficial effects of *Bacopa monnieri* extract on cognitive function. Our findings demonstrated that *Bacopa monnieri* extract has the potential to improve cognitive performance, particularly speed of attention by reducing choice reaction time. This finding is in agreement with that of Peth-Nui et al. (2012) in healthy volunteers which showed that choice reaction time was reduced ($p < 0.01$) after 12 weeks of *Bacopa monnieri* extract. Because attention was improved, the extract might be an appropriate treatment for young patients having attention deficit hyperactivity disorder (ADHD). Negi et al. (2000) have reported that 100 mg of *Bacopa monnieri* extract daily (50 mg twice a day) for 12 weeks increased cognitive performance in children with ADHD.

The effect of *Bacopa monnieri* extract on memory remains inconclusive because a high heterogeneity was observed from these outcomes. Based on our meta-analysis, *Bacopa monnieri* did not improve the memory function in terms of picture recognition, numeric working memory, AVLT, word recognition, and spatial working memory. However, *Bacopa monnieri* might decrease time to complete task by about 18 ms. Nevertheless, it is noteworthy that there were other outcomes related to memory function not included in this meta-analysis. Overall, analysis across the included studies for the memory outcomes revealed that differences in the findings could be attributed to many factors, such as the characteristics of volunteers (healthy volunteers vs. volunteers with memory impairment) and the dose of *Bacopa monnieri* extract.

The outcome choice reaction time (ms) of the included studies (Stough et al., 2008, 2001) was consistent when subgroup analysis was done by dosage form of *Bacopa monnieri* preparations in which both studies used capsules. This demonstrates that the method of administration is one factor affecting heterogeneity of findings and should be considered in designing future trials when comparing the efficacy of *Bacopa monnieri* extract. The dose of *Bacopa monnieri* extract used in most of the included studies was 300 mg daily for 12 weeks after which *Bacopa monnieri* extract improved speed of attention and memory (particularly word memory). Acute single doses may (Downey et al., 2012) or may not (Nathan et al., 2001) show improved cognitive function compared to placebo depending on the nature of the test and the testing window. The dosage of 300 mg daily (about 50% bacosides) could be considered as a reference point for effective dosage and duration of *Bacopa monnieri* extract for future studies and/or for treatment of cognitive impairment in clinical settings.

These study outcomes (e.g., choice reaction time) derived from the included studies used healthy volunteers or volunteers with impaired memory. The findings from this review may not be applicable to those diagnosed as dementia patients but rather to those having mild cognitive impairment (MCI). This is supported by a study on patients with early Alzheimer's disease ($n=39$) given 600 mg of extract daily (300 mg twice a day) for 6 months (Goswami et al., 2011) using a clinical measurement tool 'Mini Mental State Examination (MMSE)'. It showed cognitive improvement in terms of time, places and persons as well as a better quality of life (reduced irritability and insomnia). However, this study was excluded from this review because it was open label, prospective, uncontrolled, non-randomized and highly prone to bias. Overall, test of publication bias could not be performed due to the small number of included trials. The results revealed in our meta-analysis might be influenced by the 'small study effect'.

Although the effect of *Bacopa monnieri* based on choice reaction time is rather small, the decrease in choice reaction time between *Bacopa monnieri* (10.6 ms) is likely to be slightly better than that of *Gingko biloba*, a herbal medicine widely used to improve cognition. The choice reaction time at 1, 2.5, 4, and 6 h(s) after administering *Gingko biloba* extract to young adults compared to baseline were −6.37, −7.29, 4.71, −5.16 ms, respectively (Kennedy et al., 2002). Like other herbal extracts, the small effect of *Bacopa monnieri* may be influenced by several factors involving methodological issues in herbal medicine. For example, the standard tests, particularly for those used in patients with MCI, have low sensitivity (Parra et al., 2012). The current treatments using licensed drugs such as anticholinesterases, including donepezil, generally have little effect on MCI (Tricco et al., 2013) while the improvements in more advanced disease are highly significant but their clinical impacts are more questionable (Birks and Harvey, 2006; Campbell et al., 2008). Given that, the effects of *Bacopa monnieri* reported here on MCI and non-impaired subjects, although small in absolute terms, suggest that *Bacopa monnieri* could be clinically useful. However,

Table 4
Meta-analyses of the effects of *Bacopa monnieri* on memory and attention.

Outcomes	Analysis	No. of studies	*Outcome* differences		*Heterogeneity*[d]		*References*
			Mean (95% CI)	***p*-value**	I^2	***p*-value**	
Memory tests							
Picture recognition (ms)	All studies	**2**	**−85** (−308 to 137)	0.45	**70.7**	0.065	Peth-Nui et al. (2012), Stough et al. (2008)
Picture recognition (% accuracy)	All studies	**2**	**3.5** (−7.2 to 14.3)	0.52	**99.2**	0.522	Peth-Nui et al. (2012), Stough et al. (2008)
Numeric working memory (ms)	All studies	**2**	**−145** (−351 to 61)	0.17	**71.8**	0.167	Peth-Nui et al. (2012), Stough et al. (2008)
Numeric working memory (%accuracy)	All studies	**2**	**5.60** (−3.22 to 14.42)	0.21	**97.8**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)
AVLT immediate recall (words)	All studies	**1**	**0.06** (−0.10 to 0.12)	0.06	**N/A**	N/A	Barbhaiya et al. (2008)
AVLT delayed recall (words)	All studies	**3**	**0.49** (0.29 to 1.28)	0.22	**96.4**	<0.001	Barbhaiya et al. (2008), Calabrese et al. (2008), Sathyanarayanan et al. (2013)
AVLT learning rate (words)	All studies	**2**	**0.22** (1.17 to 1.13)	0.97	**98.7**	<0.001	Sathyanarayanan et al. (2013), Stough et al. (2001)
AVLT forgetting rate (words)	All studies	**2**	**−0.39** (−1.15 to 0.36)	0.31	**91.0**	<0.001	Sathyanarayanan et al. (2013), Stough et al. (2001)
Time to complete tasks (Trail B test) (ms)	All studies	**1**	**−17.9** (−24.6 to −11.2)	<0.001	**N/A**	N/A	Stough et al. (2001)
Word recognition (%accuracy)	All studies	**2**	**4.8** (−6.8 to 16.4)	0.42	**99.5**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)
Word recognition (ms)	All studies	**2**	**−76** (−206 to 53)	0.25	**90.7**	0.001	Peth-Nui et al. (2012), Stough et al. (2008)
Spatial working memory (%accuracy)	All studies	**2**	**10.5** (−4.0 to 25.0)	0.16	**97.6**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)
Spatial working memory (ms)	All studies	**2**	**−52** (−292 to 188)	0.67	**77.8**	0.034	Peth-Nui et al. (2012), Stough et al. (2008)
Attention tests							
Choice reaction time (ms)	All studies	**3**	**−30** (−80 to 20)	0.24	**98.3**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008, 2001)
	Subgroup (300 mg)[a]	**2**	**−10.6** (−12.1 to −9.2)	<0.001	**0.0**	0.341	Stough et al. (2008, 2001)
Choice reaction time (%accuracy)	All studies	**2**	**5.4** (−5.5 to 16.3)	0.33	**99.3**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)
Simple reaction time (ms)	All studies	**3**	**−35** (−115 to 45)	0.39	**98.5**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008, 2001)
	Subgroup[b]	**2**	**−5.5** (−26.4 to 15.4)	0.61	**24.4**	0.250	Stough et al. (2008, 2001)
Trail A test (ms)	All studies	**1**	**0.30** (−0.74 to 1.34)	0.57	**N/A**	N/A	Stough et al. (2001)
Digit span forward (digits)	All studies	**4**	**0.80**(−1.11 to 2.71)	0.41	**97.0**	<0.001	Barbhaiya et al. (2008), Raghav et al. (2006), Roodenrys et al. (2002), Stough et al. (2001)
Digit span backward (digits)	All studies	**4**	**−0.02** (−0.62 to 0.58)	0.96	**99.7**	<0.001	Barbhaiya et al. (2008), Raghav et al. (2006), Roodenrys et al. (2002), Stough et al. (2001)
	Subgroup[c]	**2**	**0.10** (−0.683 to 0.89)	0.80	**99.6**	<0.001	Barbhaiya et al. (2008), Raghav et al. (2006)
Digit vigilance (ms)	All studies	**2**	**−22** (−63 to 20)	0.30	**98.3**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)
Digit vigilance (%accuracy)	All studies	**2**	**12.1** (−12.5 to 36.7)	0.34	**99.7**	<0.001	Peth-Nui et al. (2012), Stough et al. (2008)

ALTV: auditory verbal learning test; ms: millisecond.

[a] Subgroup defined by dose of *Bacopa monnieri*.
[b] Subgroup defined by dosage form of *Bacopa monnieri* (capsule).
[c] Subgroup defined by subject (with complaint of memory impairment).
[d] The Cochran–Mantel–Haenszel method.

more clear evidence is needed for justifying actual clinical significance of *Bacopa monnieri* on various cognitive outcomes.

Our study used a wide range of well-accepted international bibliographic databases in identifying relevant studies and quantified relevant outcomes using a meta-analytic approach. We considered it appropriate for quantitatively pooling the results in the following ways: (i) since there were some heterogeneities among different measures (e.g., choice reaction time, AVLT, Trail A, Trail B, digit span, etc.) across studies, we pooled only data from studies that used the same tools for evaluating the efficacy of *Bacopa monnieri* on cognitive function and attention; (ii) we applied the random-effect model of the Dersimonian–Laird method for pooling results which accounts for the between-study variance, which is recognized to have contributed to higher heterogeneity of the results compared to that of the fixed effect model. All in all, only the significant outcomes with no or low I^2 were used in formulating the conclusions about the efficacy of *Bacopa monnieri* , which broadly accord with a previous review of *Bacopa monnieri* (Pase et al., 2012). In addition, Thai medical databases were also included to maximize the likelihood of identification of all relevant clinical trials on *Bacopa monnieri* conducted in tropical areas. Overall, the quality of the included trials displayed a low risk of bias and the quality of reporting was high. This contributed to the robustness of the evidence for the effect of *Bacopa monnieri* extract. Our study adhered to standard methodology of systematic review and meta-analysis as indicated by the PRISMA statement (Moher et al., 2009).

The compounds extracted from *Bacopa monnieri* which are believed to increase cognitive performance and exhibit neuroprotective properties include steroidal saponins (bacoside A, i.e., bacosides A_2 andA_3; bacoside B, i.e., bacopasides N_1, N_2, IV andV, bacopasides I–VIII; bacopaside X; and bacopasaponins A–G) and triterpenoidal saponins (jujubogenin and pseudojujubogenin) (Calabrese et al., 2008; Limpeanchob et al., 2008; Morgan and Stevens, 2010; Rajani, 2008; Russo and Borrelli, 2005) although extracts contain many other potentially active compounds (Aguiar and Borowski, 2013). Comparisions have been helped by the use of standardized *Bacopa monnieri*-based nutraceutical extracts usually expressed as bacoside A content. Nevertheless, without being sure about the active ingredients, this is not a guarantee of consistency. Also, there is little data in the public domain on bioavailability, metabolism, and pharmacokinetics of these compounds in vivo. Thus, no clear mechanism for *Bacopa monnieri* action on cognition has emerged (Morgan and Stevens, 2010; Stough et al., 2001). However, many potential mechanisms of action have been identified and extensively reviewed (Aguiar and Borowski, 2013). These mechanisms include as follows: reducing β-amyloid levels and neuronal damage induced by β-amyloid; restoration of cholinergic

function; GABA modulation; promoting anti-oxidant defenses; augmentation of 5-HT levels; modulation of brain stress hormones; neuroprotection; reducing neuroinflammation (Rastogi et al., 2012); and increasing cerebral blood flow (Kamkaew et al., 2013). Such a complex spectrum of actions, in mostly animal studies, might reflect varying activity profiles of individual components contained in the *Bacopa monnieri* extracts. Likewise, increased attention and alertness may be a distinct pharmacological target from an action in dementia patients having dysfunctional cerebral blood flow or degenerating neuronal function. Thus, multiple targets may explain inconsistencies between studies and the variations between different extracts probably also account for inter-study discrepancies.

Future studies with *Bacopa monnieri* extract should focus on randomized controlled trials with a large cohort of diagnosed and well characterized patients with cognitive problems (e.g., dementia) using more sensitive tests, independent funding and comparing with an established and approved nootropic such as donepezil.

5. Conclusion

This meta-analysis suggests that *Bacopa monnieri* extract may be beneficial in improving cognitive function in the attention domain, especially speed of attention. Nevertheless, there is a clear and urgent need for large scale independent clinical trials on well characterized patient cohorts, using rigorously applied design criteria and well established end-points.

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