



A systematic review of the Ayurvedic medicinal herb *Bacopa monnieri* in child and adolescent populations



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ABSTRACT

Objectives: Clinicians utilise critical research to advance their knowledge when prescribing standard and alternative therapies for developmental disorders. Recent research has reported that the traditional Ayurvedic medicine *Bacopa monnieri* may improve cognitive outcomes in adult populations; however, few studies have investigated its benefits in younger cohorts. The aim of the current review is to systematically assess and critically summarize clinical trial outcomes and safety of Bacopa and its effects on the cognition and behaviour in children and adolescents.

Method: PubMed, Scopus, Cochrane Library, Google and CINAHL were searched up to August 2015 for trials investigating *Bacopa monnieri* in child and adolescent populations. There were no restrictions in study design. Cognitive and behavioural outcomes were grouped into validated constructs and effect sizes were calculated for all significant data to allow for direct comparisons.

Results: Five studies met inclusion criteria for this review. The results demonstrated significant consistent improvements in the language behaviour cognitive domain and in a number of the memory sub-domains. Significant improvements were also seen in hyperactivity and attention-deficit domains. Overall outcome data demonstrated small to medium effect sizes (mean $d = 0.42$). Safety and tolerability data was well reported for 80% of studies with only 2.3% of all participants reporting mild side-effects.

Conclusion: This review highlights the safe use of *Bacopa monnieri* in child and adolescent populations for improving elements of cognition as well as behaviour and attention-deficit domains. However, there is a significant need for replicated study designs and stringent statistical analysis to validate these outcomes.

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1. Introduction

Clinicians utilise empirical research to enhance their knowledge of viable treatment options when prescribing standard and alternative therapies for children with developmental disorders. Yet parents of children with these disorders can choose to make use of the wide variety of alternative options if they feel advised pharmaceutical options are unsuited to their child.^{1,2} Despite the aura of safety associated with the natural medicinal world, the unrestrained use of supplements poses health concerns for practitioners and raises doubt and uncertainty in the minds of the consumer. As an example, the Dietary Supplement Health and Education Act (DSHEA) in the United States allows supplements to reach consumers before the Food and Drug Administration (FDA) have approved them or verified their safety.³ With this in mind, there is a need for increased scrutiny in the field of natural medicine to ensure the benefits and risks of every vitamin, plant extract, and natural compound have been adequately assessed in stringently controlled clinical trials.

Complementary and alternative medicines (CAM) have been widely used throughout history. After 3000 years of practice, the Ayurveda medicinal system is one of the oldest health care systems in the world, promoting a holistic view of health and prescribing individualized treatments.⁴ One common CAM treatment deriving from the Ayurveda medicinal system is *Bacopa monnieri*, or “*Brahmi*”, from the plant family *Scrophulariaceae*. It is a perennial creeping herb that thrives in damp soils and marshes throughout the subcontinent and is classified as a nootropic (i.e. a cognitive enhancer).⁵ Early in-vivo studies investigating the effects of *Bacopa* demonstrated significant improvements in the areas of learning, memory and memory retention.^{6–8} More recently, the memory and learning enhancing effects of *Bacopa* have been demonstrated in healthy adult populations.^{5,9–12}

The isolated active constituents of *Bacopa* are denoted *bacoside A* and *bacoside B*,^{13–15} and have demonstrated safety and tolerability in human adult volunteers.¹⁶ Hypothesized mechanisms of action on the central nervous system (CNS) are the modulation of cholinergic densities,¹⁷ acetylcholine levels,¹⁸ and β -amyloid scavenging properties.¹⁹ This has directed research to investigate the possible benefits of *Bacopa* on age-related cognitive decline and as a possible treatment for Alzheimer’s dementia.²⁰

In clinical settings, *Bacopa* polyherbal formulations has demonstrated improvements in attention, cognition, intelligence, and behaviour in children diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD), potentiating the use of *Bacopa* as an alternative treatment for the disorder.^{21–24} Research has demonstrated that chronic intervention with *Bacopa* has yielded consistent efficacy in terms of cognitive benefits,^{5,12,20,25–28} as well as having anxiolytic capabilities.^{29–32} Observations from acute studies have shown mixed results with some indicating positive cognitive and mood outcomes at the standard adult dose (320 mg per day)^{9,33} whereas others reported no effects of treatment on cognitive performance.¹⁰ Given the mixed results of acute studies, majority of research has focused on chronic administration with an average administration period of 12-weeks.¹⁵ Despite encouraging results in healthy adults,^{5,9,11,12,15,20} very little research has focused on the efficacy of *Bacopa* within child and adolescent populations.

The aim of current review was to systematically summarize and critically assess the findings from clinical trials of *Bacopa* and its effects on the cognition, memory and behaviour of children and adolescents in clinical and non-clinical populations. Each trial involving *Bacopa* in single extract form was examined in terms of its dose, intervention time period and the population of children and adolescents on which its effects were assessed (clinical or non-clinical group). The primary outcome of the review was a summary of the current evidence for the efficacy of *Bacopa* on cog-

niton, behaviour, learning, and intelligence outcomes. Secondary outcomes investigated the safety and tolerability of *Bacopa* and its viability as an alternative treatment in clinical populations.

2. Method

Pubmed, Scopus, Cochrane Library, Google Scholar and CINAHL were searched up to August 2015 for trials with child and adolescent populations examining the cognitive, behavioural, and mood effects of various extracts of *Bacopa monnieri*. There were no restrictions in terms of study design. The following terms and truncations were searched: *cognit**, *executive function*, *neurocognit**, *memory*, *intelligence*, *behaviour*, and *attention*. These terms were searched against the following: *Bacopa monnieri*, *Bacopa monniera*, or *brahmi*. The reference lists of any relevant papers were also examined for trials with a similar design. Investigations into the efficacy of the extracts were detailed and any safety and tolerability information or data was collated. Websites promoting extracts containing *Bacopa monnieri* were explored in order to discover what research meeting inclusion criteria of this review had been listed as evidence for the efficacy of the product in the child and adolescent population including any published or unpublished materials. The following inclusion criteria were used:

Inclusion criteria:

1. Investigating a *Bacopa monnieri* extract alone (with no other ingredients).
2. Sample consisting of children or adolescents (aged 4–18).
3. Participant were not taking any other intervention during study period.
4. Sample size ≥ 20 (10 if a cross-over study).
5. Duration of intervention ≥ 1 month.
6. Have measurable outcomes on attention, cognition, behaviour, intelligence or mood.
7. Disclosed medical evaluations or safety reporting for any adverse events.
8. Full paper in English.

2.1. Effect size

For each study, Cohen’s *d* effect size calculations were performed on significant data and were reported in one of two ways. The first utilised the significant differences between treatment groups (ES) at study end (e.g. treatment vs. placebo). The second calculated a *treatment effect size* (TES) where only change scores were available (*Bacopa* baseline vs. *Bacopa* study end). Effect sizes were not calculated for non-significant results or where data was not appropriate to perform calculations (ES: N/A). To enable direct comparison of the studies, the total amount of *Bacopa* for each study, per participant, per day was calculated.

2.2. Behavioural data

Behavioural outcomes were grouped into constructs based on the ADHD framework, as described and validated by the *Diagnostic and Statistical Manual 5th edition* (DSM-5).³⁴ These behavioural domains comprise of symptoms that have been the subject of confirmatory factor analyses.³⁵ These symptoms include Hyperactivity – described as difficulty remaining seated, fidgeting with hands or feet, excessive running or climbing/always on the go; Inattention – described as losing things, difficulty organizing work, easily distracted, difficulty sustaining attention, difficulty following instructions, doesn’t listen and doesn’t finish tasks; Impulsivity – described as difficulty waiting and interrupts, engages in dangerous activities without considering consequences, blurts out answers,

acts before thinking³⁵; Peer relations – described as no friends, loses friends, does not make friends, doesn't get invited, feels inferior.³⁶ Symptoms of specific learning problems were described as difficulty with reading or writing, problems with math skills, difficulty remembering, problems paying attention, trouble following directions, poor coordination, difficulty with concepts related to time and problems staying organized.³⁷ Confirmatory factor analysis of the DSM-IV ADHD rating scales has previously indicated increased variance in teacher and parent rated behaviours.³⁸ In order to address this variance, any teacher and parent reports of behaviour were assessed separately.

2.3. Cognitive data

Any cognitive testing was assessed in terms of its true cognitive ability as described by Carroll.³⁹ These are outlined in Pase et al. (2012)¹⁵ and include reasoning – incorporating general, quantitative, syllogistic and verbal reasoning as well as induction; language behaviour – incorporating vocabulary, spelling ability, phonetic coding and verbal comprehension; memory – associative memory, free recall, visual memory and memory span; visual perception – incorporating figural relations, closure speed and perceptual speed; auditory perception – incorporating pitch discrimination; number facility – incorporating the ability to compute basic numerical operations; mental speed – processing speed and simple reaction time; and idea production – incorporating abilities in producing words, ideas and figural creations such as originality and word fluency.¹⁵

3. Results

Five studies were identified as investigating the benefits of Bacopa in child and adolescent populations using single extract interventions.^{40–44} See Fig. 1 for a flow chart of the included study trial search. Three studies were randomised controlled trials^{40–42} and two were open-label trials.^{43,44} None of the included studies matched treatment groups for age or sex. One included study was an unpublished report conducted by the Central Drug Research Institute (CDRI) of Lucknow, India of a standardised *Bacopa monnieri* extract (SBME).⁴² Study designs were similar in that they each investigated cognitive and behavioural outcomes, with the main variance in population samples which included healthy children,⁴⁰ ADHD children,^{41,42,44} and those children with a low intelligence quotient.⁴³ Age range was 4–18 years (mean age 8.57 ± 1.48). Bacopa doses ranged from 100 mg to 1050 mg per day. The overall average dropout rate was 13%. See Table 1 for detailed description of each study and effect sizes for each outcome measure.

In order to quantify the strength of a significant result, Cohen's *d* effect sizes were calculated for any study that reported treatment group scores (mean and standard deviation) at baseline and final visit. A variation of the Cohen's *d* effect size was carried out on those studies who reported significant *change scores* in Bacopa treated groups only (treatment effect size). Effect size calculations were conducted on two out of the five studies (range 0.13–0.81)^{41,42}; treatment effect size (TES) calculations were conducted on one study (range 0.66–1.43)⁴⁰; two studies reported data that was unable to be used for effect size calculations.^{43,44}

Table 2 outlines significant improvements in true cognitive abilities. Cognitive outcomes were assessed and categorized by two authors (JDK and LAD) and behavioural outcomes were assessed and categorized by a single author (JDK). Three studies examined and reported improvements in the language behaviour domain.^{41–43} Two of the three studies to include mental speed domains reported significant outcomes.^{42,43} Four studies investigated benefits of Bacopa on aspects of memory^{40–43}; three of these studies reported significant improvements in the mem-

ory span sub-domain^{40,42,43}; two studies reported significant outcomes in both visual memory^{42,43} and meaningful memory sub-domains^{39,40}; whereas there were single reports of improvements in free recall memory,⁴² associative memory⁴¹ and auditory memory.⁴³ One study examined and reported improvements in visual perception.⁴⁰ There were no reports of significant improvements in the reasoning cognitive domain. Table 2 also details the effects Bacopa has within behavioural domains; these measures were present in two studies investigating the benefits of Bacopa extracts in children with ADHD.^{42,44} Both studies presented data collected from parental sources only; no data was collected from the school-teacher perspective. Both studies found significant improvements in the hyperactivity and attention domains.^{42,44} Only one study found significant improvements in terms of impulsivity and learning problems domains⁴⁴; there were no improvements in peer relations.

Two studies captured data at multiple time-points, providing possible indications for early onset improvements.^{41,42} One of the current review authors (JDK) analysed the raw data from one study to determine the level of improvement, if any, at each time-point against placebo.⁴² This study employed a Mann-Whitney *U* test for treatment group comparisons at baseline and study end. At week 4 there were significant improvements in the language behaviour ($p < 0.05$), mental speed ($p < 0.05$), and associate memory ($p < 0.05$) cognitive domains. At week 8 there were significant improvements in language behaviour ($p < 0.01$), mental speed ($p < 0.01$), memory span ($p < 0.01$), and free recall memory ($p < 0.05$) against placebo.⁴² Only one group recorded behavioural outcomes at multiple time points and reported significant improvements in hyperactivity ($p < 0.05$ at four weeks; $p < 0.01$ at eight weeks), and inattention ($p < 0.01$ at four weeks) against placebo.⁴² There were no improvements in impulsivity at any stage of this study.

The same two groups included a placebo run-out phase in which all participants consumed only placebo for four weeks at the end of the study.^{41,42} Both studies reported sustained improvement ($p < 0.05$) in the language behaviour, free recall memory and visual recall cognitive domains.^{41,42} One of the studies demonstrated additional sustained improvements at four weeks post treatment in the number facility ($p < 0.01$), mental speed ($p < 0.01$), associative memory ($p < 0.01$), memory span ($p < 0.01$), and meaningful memory ($p < 0.01$) cognitive domains.⁴² These were complemented by the sustained improvements in attention ($p < 0.01$) and hyperactivity ($p < 0.01$) up to four weeks post Bacopa. All post-treatment improvement scores were verified by one of the review authors (JDK) using non-parametric Mann Whitney *U* test against change scores⁴² and a *t*-test calculator against reported means and standard deviations.⁴¹

Safety and tolerability data was well reported for 80% of studies with only 2.3% of all participants reporting side-effects involving stomach upset that subsided within days. In one study, medical check-ups were conducted as a basis for inclusion into the trial, however, no safety or tolerability data were reported.⁴⁰ Two studies utilised the Dosage Record Treatment Emergent Symptom scale (DOTES)⁴⁵ to monitor safety and tolerability.^{41,42} This symptom checklist monitors behavioural, neurological, autonomic, cardiovascular, and other symptoms such as weight (gain or loss), appetite and headaches. Neither study reported any adverse effects of the Bacopa treatment. The remaining two studies monitored for adverse effects during the intervention period and parents were asked to report any adverse reactions to investigators.^{43,44} Only one of these studies reported adverse symptoms of stomach upset and vomiting, which subsided after three days and participants were thereon able to continue in the trial.⁴³ Participant dropout rate was low overall (13%) with only one study having zero dropouts.⁴⁰ This study utilised powdered Bacopa in pineap-

Table 1Summary of reviewed *Bacopa monnieri* intervention studies in child and adolescent clinical and non-clinical populations (N = 5, 1987–2014).

Bacopa Extracts									
Author	Intervention	n	Male (%)	Study Design	Population	Outcome Measures	Safety	Dropouts (%)	Results (ES)
Sharma et al. ⁴⁰	BS x 3 Tblsp p/d (BM: 1050 mg p/d) PL x 3 Tblsp p/d	40 20 (B) 20 (P)	N/A	3-months OL, PC	6–8 yrs Healthy	WISC Maze; Raven's Colored Progressive Matrices; Bender Gestalt Test for Children	Not declared	0	Significant treatment effects in children taking BM over PL on WISC Maze Overall (TES: 1.43), WISC Maze Reaction Time (TES: 0.66), WISC Maze Performance (TES: 0.80) and WISC Digit Span (TES: 1.13).
Negi et al. ⁴¹	MP x 1 Cap 2/d (BM: 100 mg p/d) PL x 1 Cap 2/d	36 19 (B) 17 (P)	84.2	3-months R, DB, PC	6–12 yrs ADHD Diagnosed	Memory Scale test	There were no side effects reported by participants ^a	22.5	Significant treatment effects in children taking BM over PL in terms of Logical Memory (ES: 0.81), Sentence Repetition (ES: 0.13) and Paired Associate Learning (ES: 0.50).
CDRI Lucknow ⁴²	SBME x 2 Caps p/d (BM: 100 mg p/d) PL x 2 Caps p/d	40 20 (B) 20 (P)	75	3-months R, DB, PC	6–12 yrs ADHD Diagnosed	Memory Scale test; McCaerney Rating Scale	There were no significant side effects reported by participants ^b	22.5	Significant treatment effects in children taking BM over PL on Sentence Repetition (ES: 0.45), Logical Memory (ES: 0.49), Digit Span (ES: 0.28), Word Recall – Meaningful (ES: 0.36) & Non-Meaningful (ES: 0.43), Delayed Response Learning (ES: 0.27), as well as Attention (ES: 0.35) and Hyperactivity (ES: 0.59).
Dave et al. ⁴³	BMi x 1 Cap p/d (BM: 225 mg p/d) No control group	28 28 (B)	46.4	4-months OL	4–18 yrs Q, 70–90	Memory Scale Test	Some side effects reported ^c	7.1	Authors reported responder's data (%) ^d . Improvements seen in Digit Span (70.83%), Repeating Words (70.83%), Visual Reproduction (58.33%), and Repeating Sentences (50.00%). ES: N/A
Dave et al. ⁴⁴	BMi x 1 Cap p/d (BM: 225 mg p/d) No control group	31 31 (B)	90.3	6-months OL	6–12 yrs ADHD Diagnosed	ADHD Symptom Subtest Scores	Reported safety and tolerability of SBME with no treatment-related adverse effects	12.9	Authors reported responder's data (%) ^d . Improvements seen in Restlessness (93%), Impulsivity (67%), Attention-deficit (85%), Self-Control (89%), Psychiatric problems (52%) and Learning Problems (78%). ES: N/A

BM – *Bacopa monnieri*; PL – placebo; BS – Bacopa syrup; MP – Memory Plus; SBME – standardised *Bacopa monnieri* extract; BMi – BacoMind; mg – milligrams; Tblsp – tablespoon; Cap – capsule; Caps – capsules; p/d – per day; 2/d – twice a day; 3/d – three times a day; 4/d – four times a day; (B) – Bacopa; (P) – placebo; N/A – not available; OL – open-labelled; R – randomised; DB – double-blind; PC – placebo-controlled; yrs – years; I.Q. – intelligence quotient; WISC – Wechsler's intelligence scale for children; ADHD – attention deficit hyperactivity disorder; ES – Cohen's d effect size (versus placebo); TES – treatment effect size (change from baseline).

^a Pre & post drug monitoring of clinical haematological and biochemical parameters did not suggest any drug related abnormality in either treatment group. Reported increases in appetite and concentration in MP group.

^b One child reported abdominal pain four weeks into the trial which then subsided and did not appear related to the extract. Reported increases in appetite and concentration in SBME group.

^c Three children reported vomiting and upset stomach. Following three days of non-treatment the symptoms subsided and the same participants were able to thereafter continue the trial with no further side effects.

^d Responders were those participants who were seen to improve following starting treatment. Effect sizes not included due to unavailable data.

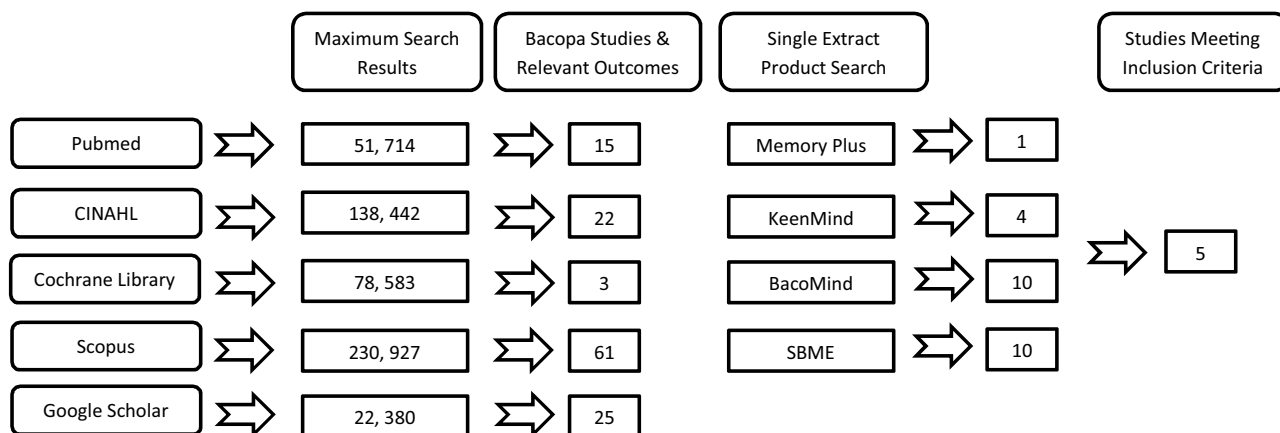


Fig. 1. Flow chart of trials investigating *Bacopa monnieri* in children and adolescents.

Table 2

Classification of true cognitive abilities and behavioural constructs of reviewed *Bacopa monnieri* trials.

Cognitive Ability/Behaviour	Sharma et al. ⁴⁰	Negi et al. ⁴¹	CDRI ⁴²	Dave et al. ⁴³	Dave et al. ⁴⁴
Reasoning	Raven's Coloured Progressive Matrices				
Visual Perception	WISC Maze ^a ; Bender Gestalt Test for Children				
Auditory Perception					
Language behaviour		Sentence Repetition^{**} ; Logical Memory (IR)^{**}	Sentence Repetition^{***} ; Logical Memory (IR)^{***}	Repeating Words^a ; Repeating Sentences^a	
Number Facility		Delayed Response Learning	Delayed Response Learning ^{**}		
Mental Speed		Mental control	Mental control^{***}	Mental Control^a	
Memory					
Free recall Memory		Word Recall (Non-Meaningful)	Word Recall (Non-Meaningful)^{**}	Orientation	
Associative Memory		Paired Associate Learning^{**}	Paired Associate Learning		
Memory Span	DS Forward^b ; DS Backward^b	Digit Span Test	Digit Span Test^{***}	Digit Span Test^a	
Visual Memory		Picture Recall	Picture Recall[†]	Visual Reproduction^a ; Recognition	
Auditory Memory				Verbal Retention (Similar Pairs)^a ; Verbal Retention (Dissimilar Pairs)^a	
Meaningful Memory		Word Recall (Meaningful)	Personal Information Test; Word Recall (Meaningful)^{**}	Information^a	
Behaviour					
Hyperactivity			Parent Rating Scale –Hyperactive Subscale^{***}		Restlessness Subscale^a
Inhibition/Impulsivity			Parent Rating Scale – Impulsive Subscale		Impulsivity Subscale^a ; Self-Control Subscale^a
Attention			Parent Rating Scale – Inactive Subscale^{**}		Attention-deficit Subscale^a
Learning					Learning Problems Subscale^a
Peer Relations					Social Problems Subscale

All significant results are in bold.

^a Significant treatment effect at $p < 0.05$ level.

^b Significant treatment effect at $p < 0.01$ level.

^{*} Significant at $p < 0.05$ level over placebo.

^{**} Significant at $p < 0.01$ level over placebo.

^{***} Significant at $p < 0.001$ level over placebo.

ple flavoured syrup, whereas subsequent trials used capsules of Bacopa or Bacopa extract.^{41–44} The added pineapple flavouring might account for the lack of dropouts in the trial as the taste of the supplement may have appealed to the children, encouraging compliance. This syrup equated to 1050 mg of active treatment per day;

an amount significantly higher than any subsequent studies have used, with the exception of a poly-herbal study by Ramarao et al.⁴⁶ Overall, dropouts were well documented. Only one study did not report explanations for dropouts, the authors reasoned that parents withdrew their child due to a lack of improvement in symptoms.⁴²

4. Discussion

This review investigated the efficacy of the Ayurvedic medicine *Bacopa monnieri* in children and adolescents in both clinical and non-clinical populations. This is the first systematic review of its kind to investigate the benefits and safety of this herb in a younger cohort. The outcomes of the included studies demonstrate significant consistent improvements in the language behaviour cognitive domain,^{41–43} and in a number of the memory sub-domain particularly in *memory span*.^{40,42,43} Significant improvements were seen in both studies that measured behavioural outcomes,^{42,44} with improvements in hyperactivity and attention-deficit domains consistent across both trials. ADHD is one of the most common psychiatric illnesses in the world with an estimated 8–12% school-aged children being diagnosed with the disorder.⁴⁷ These and similar developmental disorders need structured, multi-dimensional forms of treatment for the best possible academic, social and mental health outcomes for children and adolescents.⁴⁸ Singh and Dhawan,⁷ Stough,^{5,12} Roodenrys,²⁵ Barbhैया,²⁶ Calabrese,²⁷ Nathan,^{10,11} and most recently Morgan²⁰ and Downey⁹ have investigated the benefits of a single-extract of *Bacopa* on human cognitive function in adult populations. Despite these encouraging results, limited research has examined the beneficial effects of *Bacopa* in children and adolescents. The studies contained within the scope of this review indicate that *Bacopa monnieri* has potential to thrive as a natural and safe option for treating symptoms associated with childhood mental health disorders.^{41–44}

Complementary and alternative medicines are fast becoming viable standalone or adjunctive treatment preferences in place of pharmaceutical treatment for a range of developmental disorders. Child and adolescent health is being targeted by alternative treatment companies on the grounds that natural intervention measures can treat a variety of common mental health and medical conditions within this population. Without crucial safeguards, some treatments may end up doing more harm than good. In the context of Ayurveda, practitioners prescribe *Bacopa* on a patient by patient basis, so it is rare that a single extract would suit all individuals.⁴ The strength of this review is that a rigorous systematic investigation was conducted and detailed analysis of each included study was undertaken. The use of the Carroll framework in this review allowed the authors to consolidate distinct outcomes into true cognitive abilities.³⁹ Previous work by Pase and Stough emphasizes the use of the Cattell-Horn-Carroll (CHC) model of intelligence to support the clear understanding of cognitive processes across multiple studies in nutrition research.⁴⁹ Future systematic reviews would benefit from utilising this model to understand what impact nutritional treatments may have within the cognitive framework. A weakness of this review is that only studies published in English were included. *Bacopa* is native to India and following 3000 years of its use in the Ayurvedic medicinal system, studies in languages other than English must exist. In addition to this, the authors did not access the Digital Helpline for Ayurveda Research Articles (DHARA), which allows researchers to search for Ayurveda specific articles; upon inspection there were no further articles that required inclusion into this review. Furthermore, the inclusion of an unpublished report may weaken the overall outcomes of the review. Lead author (JDK) statistically analysed the raw data from the report and verified its outcomes; however, this data would best serve the scientific community as a peer reviewed publication.

In the current review, *Bacopa monnieri* was investigated in terms of its use in child and adolescent populations with focus on its use as an individual extract. The five studies included in this review continue to support the hypothesis that *Bacopa monnieri* improves elements of human cognition.^{5,9,11,12,15,20} Further to this, the current review provided some of the first evidence of the use of *Bacopa* in behavioural and attention-deficit disorders,

such as ADHD.^{42,44} This unique area of research requires stronger more focused trials investigating the benefits of *Bacopa monnieri* on elements of mental health and within the context of developmental dysfunction. Two of the trials included in this review employed significance testing on only those who responded to the treatment in open-label designs.^{43,44} Replicating these results is difficult due to the imprecise understanding of what constitutes a treatment-responder. Furthermore, the lack of a control group from these two studies weakens the cognitive⁴³ and behavioural⁴⁴ improvements reported following *Bacopa* supplementation. Standardized, easily replicated trial designs in clinical and non-clinical child and adolescent populations are essential to ensure the outcomes of *Bacopa* administration on behaviour, cognition, attention, memory and intelligence are reliable and valid.

Clinical significance

Bacopa monnieri is a plant based nootropic that may provide cognitive and behavioural improvements in children and adolescents.

Conflicts of interest

None declared.

References

- Pellow J, Solomon EM, Barnard CN. Complementary and alternative medical therapies for children with attention-deficit/hyperactivity disorder (ADHD). *Altern Med Rev*. 2011;16(4):323–337.
- Sinn N. Nutritional and dietary influences on attention deficit hyperactivity disorder. *Nutr Rev*. 2008;66(10):558–568.
- Dodge T, Litt D, Kaufman A. Influence of the Dietary Supplement Health and Education Act on consumer beliefs about the safety and effectiveness of dietary supplements. *J Health Commun*. 2011;16(3):230–244.
- National Center for Complementary and Integrative Health N. *Ayurvedic Medicine In Depth*; 2005. <https://nccih.nih.gov/health/ayurveda/introduction.htm>. Accessed 14.07.16.
- Stough C, Downey LA, Lloyd J. Examining the nootropic effects of a special extract of *Bacopa monnieri* on human cognitive functioning: 90 day double-blind placebo-controlled randomized trial. *Phytother Res*. 2008;22:1629–1634.
- Malhotra CL, Das PK. Pharmacological studies of *Herpestis monnieri*, Linn. (Brahmi). *Indian J Med Res*. 1959;47(3):294–305.
- Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monnieri* Linn. (Brahmi). *Indian J Pharmacol*. 1997;29:359–365.
- Singh HK, Rastogi RP, Srimal RC, Dhawan BN. Effect of bacosides A and B on avoidance responses in rats. *Phytother Res*. 1988;2(2):70–75.
- Downey LA, Kean J, Nemeš F, et al. An acute, double-blind, placebo-controlled crossover study of 320 mg and 640 mg doses of a special extract of *Bacopa monnieri* (CDRI 08) on sustained cognitive performance. *Phytother Res*. 2013;27(9):1407–1413.
- Nathan PJ, Clarke J, Lloyd J, Hutchison CW, Downey L, Stough C. The acute effects of an extract of *Bacopa monnieri* (Brahmi) on cognitive function in healthy normal subjects. *Hum Psychopharmacol*. 2001;16(4):345–351.
- Nathan PJ, Tanner S, Lloyd J, et al. Effects of a combined extract of *Ginkgo biloba* and *Bacopa monnieri* on cognitive function in healthy humans. *Hum Psychopharmacol*. 2004;19(2):91–96.
- Stough C, Lloyd J, Clarke J, et al. The chronic effects of an extract of *Bacopa monnieri* (Brahmi) on cognitive function in healthy human subjects. *Psychopharmacology*. 2001;156(4):481–484.
- Das A, Shanker G, Nath C, Pal R, Singh S, Singh H. A comparative study in rodents of standardized extracts of *Bacopa monnieri* and *Ginkgo biloba*: anticholinesterase and cognitive enhancing activities. *Pharmacol Biochem Behav*. 2002;73(4):893–900.
- Neale C, Camfield D, Reay J, Stough C, Scholey A. Cognitive effects of two nutraceuticals Ginseng and *Bacopa* benchmarked against modafinil: a review and comparison of effect sizes. *Br J Clin Pharmacol*. 2013;75(3):728–737.
- Pase M, Kean J, Sarris J, Neale C, Scholey A, Stough C. The cognitive-enhancing effects of *Bacopa monnieri*: a systematic review of randomized, controlled human clinical trials. *J Altern Complement Med*. 2012;18(7):647–652.
- Asthana OP, Srivastava JS, Ghatak A, Gaur SPS, Dhawan BN. Safety and tolerability of bacosides A and B in healthy human volunteers. *Indian J Pharmacol*. 1996;28(1):37.
- Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of *Bacopa monnieri* in Alzheimer's disease model. *J Ethnopharmacol*. 2010;127(1):26–31.

18. Bhattacharya SK, Kumar A, Ghosal S. Effect of Bacopa monniera on animal models of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. *Res Commun Pharmacol Toxicol*. 1999;4(3&4):1–12.
19. Holcomb LA, Dhanasekaran M, Hitt AR. Bacopa monniera extract reduces amyloid levels in PSAPP mice. *J Alzheimer's Dis*. 2006;9:243–251.
20. Morgan A, Stevens J. Does bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. *J Altern Complement Med*. 2010;16(7):753–759.
21. Katz M, Levine AA, Kol-Degani H, Kav-Venaki L. A compound herbal preparation (CHP) in the treatment of children with ADHD: a randomized controlled trial. *J Atten Disord*. 2010;14(3):281–291.
22. Dutta B, Barua TK, Ray J, et al. A study of evaluation of safety and efficacy of memomet, a multi herbal formulation (memomet) in the treatment of behavioural disorder in children. *Int J Res Pharm Sci*. 2012;3(2):282–286.
23. Bhalerao S, Munshi R, Nesari T, Shah H. Evaluation of Brahmi ghrtam in children suffering from Attention Deficit Hyperactivity Disorder (Study I). *Anc Sci Life*. 2013;33(2):123–130.
24. Kalra V, Zamir H, Pandey RM, Kulkarni KS. A randomized double blind placebo-controlled trial with Mentat in children with Attention Deficit Hyperactivity Disorder. *Neurosci Today*. 2002;6(4):223–227.
25. Roodenrys S, Booth D, Bulzomi S. Chronic effects of Brahmi (Bacopa monnieri) on human memory. *Neuropsychopharmacology*. 2002;27:279–281.
26. Barbhuiya HC, Desai RP, Saxena VS, et al. Efficacy and tolerability of BacoMind® on memory improvement in elderly participants—a double blind placebo controlled study. *J Pharmacol Toxicol*. 2008;3(6):425–434.
27. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. *J Altern Complement Med*. 2008;14(6):707–713.
28. Mandal AK, Hedge S, Patki PS. A clinical study to evaluate the efficacy and safety of 'Bacopa' caplets in memory and learning ability: a double blind placebo controlled study. *Aust J Med Herbal*. 2011;23(3):122–125.
29. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum and hippocampus. *Phytother Res*. 2000;14:174–179.
30. Russo A, Izzo AA, Borrelli F. Free radical scavenging capacity and protective effect of Bacopa monniera L. on DNA damage. *Phytother Res*. 2003;17:870–875.
31. Kapoor R, Srivastava S, Kakkar P. Bacopa monnieri modulates antioxidant responses in brain and kidney of diabetic rats. *Environ Toxicol Pharmacol*. 2009;27(1):62–69.
32. Dhanasekaran M, Tharakan B, Holcomb LA. Neuroprotective mechanisms of Ayurvedic antidementia botanical Bacopa monniera. *Phytother Res*. 2007;21:965–969.
33. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, double-blind, placebo-controlled cross-over study of 320 mg and 640 mg doses of Bacopa monnieri (CDRI 08) on multitasking stress reactivity and mood. *Phytother Res: PTR*. 2014;28(4):551–559.
34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*; 2013. <http://dsm.psychiatryonline.org/book.aspx?bookid=556>; Accessed 13.05.15.
35. Pillow DR, Pelham Jr WE, Hoza B, Molina BS, Stultz CH. Confirmatory factor analyses examining attention deficit hyperactivity disorder symptoms and other childhood disruptive behaviors. *J Abnorm Child Psychol*. 1998;26(4):293–309.
36. Conners CK, Sitarenios G, Parker JDA, Epstein JN. The Revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. 1998;26(4):257–268.
37. National Institutes of Health. *What Are the Indicators of Learning Disabilities? Common Signs of Learning Disabilities*; 2014. Available at: <https://www.nichd.nih.gov/health/topics/learning/conditioninfo/pages/symptoms.aspx>; Accessed 10.02.16.
38. Gomez R, Burns GL, Walsh JA, De Moura MA. Multitrait-multisource confirmatory factor analytic approach to the construct validity of ADHD rating scales. *Psychol Assess*. 2003;15(1):3–16.
39. Carroll J. *Human Cognitive Abilities: a Survey of Factor Analytic Studies*. New York: Cambridge University Press; 1993.
40. Sharma R, Chaturvedi C, Tewari PV. Efficacy of Bacopa Monnieri in revitalizing intellectual functions in children. *J Res Educ Indian Med*. 1987;1:12.
41. Negi K, Singh Y, Kushwaha K, et al. Clinical evaluation of memory enhancing properties of Memory Plus in children with attention deficit hyperactivity disorder. *Indian J Psychiatry*. 2000;42(Suppl. 2).
42. Asthana OP, Srivastava JS, Gupta RC, et al. *Clinical Evaluation of Bacopa Monniera Extract on Behavioural and Cognitive Functions in Children Suffering from Attention Deficit Hyperactivity Disorder*. Central Drug Research Institute (CDRI); 2001. Unpublished.
43. Dave U, Wasim P, Joshua J, et al. BacoMind®: a cognitive enhancer in children requiring individual education programme. *J Pharmacol Toxicol*. 2008;3(4):302–310.
44. Dave UP, Dingankar SR, Saxena VS, et al. An open-label study to elucidate the effects of standardized Bacopa monnieri extract in the management of symptoms of attention-deficit hyperactivity disorder in children. *Adv Mind Body Med*. 2014;28(2):10–15.
45. Garvey CA, Gross D, Freeman L. Assessing psychotropic medication side effects among children: a reliability study. *J Child Adolesc Psychiatr Ment Health Nurs*. 1991;4(4):127–131.
46. Ramarao B, Shetty B, Srinivasan K, Rajagoplan V, Indurti J. *Clinical Evaluation of Certain Ayurvedic Formulations in the Management of Mental Retardation (Mānasa Mandatā)*. India, New Delhi: Central Council for Research in Ayurveda and Siddha, Dept. of AYUSH, Ministry of Health & Family Welfare; 2011.
47. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet*. 2005;366(9481):237–248.
48. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. Washington, DC: American Psychiatric Publishing; 2000.
49. Pase MP, Stough C. An evidence-based method for examining and reporting cognitive processes in nutrition research. *Nutr Res Rev*. 2014;27(2):232–241.