

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

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ABSTRACT

Context • Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity or difficulty in controlling behavior. Psychostimulant medications remain the mainline treatment for children with ADHD; however, the average response rate to these medications is 70%, and up to 30% of children do not respond to these medications or are unable to tolerate such potential adverse effects as nausea, insomnia, and weight loss.

Objective • The study investigated the effectiveness of standardized *Bacopa monnieri* extract (SBME) in ameliorating the severity of the symptoms of ADHD in children.

Design • The clinical trial was conducted as an open-label study.

Setting • The study was conducted at the Center for Research in Mental Retardation (CREMERE) in Mumbai, India, from 2008 to 2010.

Participants • Thirty-one children were participants in the trial. They were 6-12 y of age, with an age of onset of ADHD before 7 y of age, as defined by the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* criteria for ADHD.

Intervention • The children received SBME at a dose of

225 mg/d for a period of 6 mo. The specific SBME used in the study was BacoMind (M/s Natural Remedies, Bangalore, India).

Outcome Measures • Subsequent to the screening of participants, the research team administered the Parent Rating Scale to assess the ADHD symptom scores at baseline, and the team administered it again at the end of the 6 mo of treatment.

Results • SBME significantly reduced the subtests scores of ADHD symptoms, except for social problems. The symptom scores for restlessness were reduced in 93% of children, whereas improvement in self-control was observed in 89% of the children. The attention-deficit symptoms were reduced in 85% of children. Similarly, symptom scores for learning problems, impulsivity, and psychiatric problems were reduced for 78%, 67%, and 52% of children, respectively. It was observed that 74% of the children exhibited up to a 20% reduction, while 26% of children showed between a 21% and a 50% reduction in the total subtests scores.

Conclusion • Standardized extract of *B monnieri* was found to be effective in alleviating the symptoms of ADHD and was well-tolerated by the children. (*Adv Mind Body Med.* 2014;28(2):10-15.)

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Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity or difficulty in controlling behavior¹ that in almost 60% of cases lasts into adulthood.² The symptoms may lead to functional impairments affecting education and family and social interactions.³ Psychostimulant medications remain the mainline treatment for children with ADHD; however, the average response rate to these medications is 70%,⁴ and up to 30% of children do not respond to these medications or are unable to tolerate such potential adverse effects as nausea, insomnia, and weight loss.⁵ In addition to these reasons, the growing popularity of complementary and alternative medicine is contributing to the desire of many parents to seek alternative medicines for ADHD. Complementary or alternative treatments, such as massage, dietary supplements, and herbal medicines are being used.⁶⁻⁹ Various herbs like *Hypericum perforatum*, *Echinacea* spp, *Ginkgo biloba*, *Humulus lupulus*, *Valeriana officinalis*, *Passiflora incarnata*, *Melissa officinalis*, and *Bacopa monnieri* have been reported to possess effects that can ameliorate ADHD symptoms.¹⁰⁻¹²

B monnieri—also known as *Herpestis monnieri*, water hyssop, or Brahmi—has been used since time immemorial in the traditional and ayurvedic systems of medicine as a nerve tonic to enhance and improve learning, memory, and concentration and to provide relief to individuals with anxiety or epileptic disorders.¹³ *B monnieri* has been reported to possess antioxidant effects on specific brain areas, namely the hippocampus, frontal cortex, and striatum,¹⁴ which are frequently reported to be abnormal and smaller in neuroimaging studies in ADHD patients.¹⁵ Alterations in catecholaminergic transmitter functions, mainly dopaminergic, are related to ADHD symptoms,¹⁶⁻¹⁸ and researchers have demonstrated that *B monnieri* has had protective effects against dopaminergic degeneration¹⁹ and has increased dopamine levels in rats.²⁰ Moreover, clinically, formulations containing *B monnieri* have improved attention, cognition, and impulse control and have been well-tolerated, indicating promise for ADHD treatment in children.^{18,21} Though a pilot study by Negi et al²² on the effects of *B monnieri* in children with ADHD is available, no other evidence-based literature has appeared so far on the efficacy of *B monnieri* as a monoherbal preparation in the management of symptoms of ADHD. Hence, the present study was conducted to evaluate the effect of a standardized phytochemical composition of *B monnieri* in improving ADHD symptoms in children.

The safety of the standardized *B monnieri* extract (SBME) used in the present study was confirmed in Sprague-Dawley rats. Toxicity studies revealed a median lethal dose of 2400 mg/kg on single oral administration. In a 14-day, repeated-dose, oral toxicity study in rats, the product was found to be well-tolerated at up to a dose of 500 mg/kg. In a subchronic, oral toxicity study in rats at the dose levels of 85 mg/kg, 210 mg/kg, and 500 mg/kg for 90 days, SBME revealed no major evidence of toxicity in a range of clinical

and laboratory evaluations.²³ Furthermore, in vitro studies also revealed no incidence of genotoxicity in Ames tests, chromosomal aberration assays, and micronucleus tests.²⁴ The safety and tolerability of SBME were established in a Phase I, randomized, open-label, dose-escalation study in 23 healthy adult volunteers, using 300 mg for first 15 days and 450 mg for next 15 days. Clinical and laboratory investigations conducted during pre- and posttreatment periods revealed no untoward effects. Mild, gastrointestinal side effects were observed in 3 of the volunteers evaluated in the trial.²⁵ SBME was found to be safe and tolerable in children as well.²⁶ Given that SBME has been shown to be safe and effective in the management of certain cognitive dysfunctions,^{26,27} the research team has conducted the present study with the objective of evaluating the effect of SBME in ameliorating the severity of ADHD symptoms in children.

MATERIALS AND METHODS

The current open-label clinical trial was conducted as an outpatient procedure at the Center for Research in Mental Retardation (CREMERE) in Mumbai, India, between 2008 and 2010. The research team obtained an institutional ethics committee approval for conduct of the study.

Participants

The research team recruited children between the ages of 6 and 12 years who had an IQ of 80 or higher and who met the criteria for ADHD in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. A screening was conducted to enroll the children, and children were diagnosed with ADHD based on structured interviews conducted by a clinical psychologist using the *DSM-IV* criteria. To be eligible, children must have had an onset of symptoms before 7 years of age. Autistic children, children with an intellectual disability (IQ < 80), and epileptic children were excluded from the study. A total of 31 children met the inclusion criteria and were recruited.

The parents or guardian of each child were informed that they were free to withdraw from the study at any time without any prior explanation. Parents of all enrolled children were briefed regarding the study's objective and procedures, received an informed-consent form, and were asked to sign that form on behalf of the children because they were under 12 years of age. Prior to signing the informed consent form, the parents and guardians were informed that they could communicate freely with the investigator to clarify any questions they had. No concomitant ADHD treatments were allowed during the study, including prescription pharmaceutical medications. Children were allowed to perform routine daily activities, and diet alteration was not recommended.

Intervention

BacoMind (M/s Natural Remedies, Bangalore, India) is a SBME. The extract was standardized in the content of the following bioactive constituents: (1) bacoside A₃ > 5.0% w/w;

(2) bacopaside I > 7.0% w/w; (3) bacopaside II > 5.5% w/w; (4) jujubogenin isomer of bacopasaponin C > 7.0% w/w; (5) bacopasaponin C > 4.5% w/w; (6) bacosine > 1.5% w/w; (7) luteolin > 0.2% w/w; (8) β -sitosterol-D-glucoside > 0.3% w/w; and (9) apigenin > 0.1% w/w. It was further standardized using the following in vitro bioassays: (1) lipoxygenase inhibition assay $IC_{50} < 600 \mu\text{g/mL}$; (2) ABTS radical scavenging assay $IC_{50} < 100 \mu\text{g/mL}$; (3) DPPH assay $IC_{50} < 200 \mu\text{g/mL}$; and (4) butyrylcholinesterase inhibition assay $IC_{50} < 3000 \mu\text{g/mL}$.

Each capsule of SBME contained 225 mg of *B monnieri* extract and 125 mg of microcrystalline cellulose. At the start of the study, parents and guardians were instructed to administer 1 capsule to their children once daily for the 6-month duration of the study. They received enough of the test substance (SBME) in a blister pack for 15 days of treatment and were advised to visit the center every 15 days with their children. At each visit, the research team counted any remaining capsules in the current blister pack to check compliance and recorded the count on the compliance card. After the team had ensured that the parents and guardians had complied with the medication, another fresh blister pack containing 15 capsules was issued. In each follow-up visit, the research team recorded the occurrence of any adverse events and confirmed willingness to continue participation, in addition to checking the compliance with medication.

Outcomes Measures

The primary outcome measured for the study was the change from baseline to 6 months in the ADHD symptom scores for 7 subtests of 3 domains related to the *DSM-IV* diagnostic criteria: inattention, hyperactivity, and impulsivity. These subtests were assessed pre- and posttreatment using the parent rating scale for ADHD. Each item on the scale was rated on a 1- to 4-point Likert scale (1 = not at all, 2 = just a little, 3 = pretty much, 4 = very much). The secondary outcome measure, the safety of the children, was assessed by monitoring the children for any adverse effects during the intervention. Parents were instructed to report any adverse effects to the investigator.

Statistical Reporting

The values were expressed either as a percentage or a mean \pm SEM. The scores of subtests of ADHD symptoms recorded in the pre- and posttreatment periods were analyzed by paired sample *t* test. The statistical significance was set at $P \leq .05$.

RESULTS

Thirty-one children participated in the study, of which 27 completed the trial and were considered for statistical analysis (Table 1). Four children dropped out of the trial for unknown reasons. The total score of 7 subtests of ADHD symptoms for each child was recorded in terms of percentage reduction in scores, based on 4 categories of improvement as shown in Table 2. The research team observed that 74% of

the children showed up to a 20% reduction, while 26% of children showed a 21% to 50% reduction in the total subsets scores.

Table 3 summarizes the subtests scores for ADHD symptoms recorded before and after treatment for all participants who completed the study. At the end of 6 months, treatment with SBME resulted in significant reduction in all the subtests scores of ADHD symptoms, except for social problems, for which a nonsignificant decrease in the symptom scores was observed. A remarkable reduction in the symptom scores for restlessness was observed in 93% of the children, while 89% showed improvement in self-control. In the attention-deficit attribute, improvement was observed in 85% of the children. Similarly, symptom scores for learning problems, impulsivity, and psychiatric problems were reduced in 78%, 67%, and 52% of the children, respectively.

DISCUSSION

ADHD is a childhood-onset condition and can have lifelong consequences leading to substantial problems in school, home, and community settings. Because a majority of children continue to manifest symptoms into adolescence and adulthood, the condition warrants treatment. Furthermore, because pharmacotherapeutic interventions are associated with side effects, an alternative safe and effective ADHD intervention that reduces the severity of its symptoms can potentially broaden the therapeutic options available. In systematic reviews on the assessment of evidence for complementary medicines for ADHD, Sarris et al¹² and Pellow et al²⁸ reported that only few CAMs were beneficial in ADHD, and *B monnieri* remains a promising future research candidate. However, use of *B monnieri* as an alternative intervention necessitates investigation of its benefits in clinical settings, and for this purpose, the present study was conducted to evaluate the effects of SBME in the management of ADHD symptoms.

It is possible that *B monnieri* works synergistically with other botanicals^{18,21}; however in the current trial, SBME was studied as a single botanical so that the results would pertain to the use of *B monnieri* in the management of symptoms of ADHD in children. To facilitate comparisons with the available interventions, the current trial used similar primary diagnostic criteria, as recommended by *DSM-IV*, as was used in earlier studies.^{29,30} The current study found that 74% of the children showed up to a 20% reduction, while 26% of the children exhibited a 21% to 50% reduction in total subtests scores. All the children responded to SBME treatment, whereas an average response rate of 70% has been observed for stimulant medications.⁴

Evidence suggests that the brains of ADHD children differ both morphologically and metabolically from normal children, and ADHD symptomatology relates to the disturbances in the prefrontal cortex. These regions of the brain are hypothesized to be involved in executive function (ie, attention and ability to exercise inhibition) and are

Table 1. Summary of the Study’s Population

Participants	Enrolled	Completed
Male	28	24
Female	3	3
Total	31	27

Table 2. Improvement in Total Scores on Subtests of ADHD Symptoms

Particulars	Improvement in Total Scores (n = 27)			
	I (No change)	II (0%-20%)	III (21%-50%)	IV (51%-75%)
No. of children	0	20	7	0
Percentage of children	0	74	26	0

Table 3. Improvement in Subtest Scores of ADHD Symptoms

ST No.	Name of Subtest	Test Score Before Treatment (Baseline)	Test Score After Treatment (6 Mo)	No. of Children Responded	Percentage of Children
ST1	Restlessness	17.44 ± 0.77	14.30 ± 0.63 ^a	25	93
ST2	Impulsivity	9.52 ± 0.43	8.70 ± 0.45 ^a	18	67
ST3	Attention-deficit	13.41 ± 0.60	10.89 ± 0.46 ^a	23	85
ST4	Social problems	6.85 ± 0.36	6.26 ± 0.41	16	59
ST5	Self-control	18.93 ± 0.79	15.85 ± 0.87 ^a	24	89
ST6	Psychiatric problems	7.81 ± 0.68	6.59 ± 0.41 ^a	14	52
ST7	Learning problems	16.41 ± 0.76	13.81 ± 0.59 ^a	21	78

Abbreviations: ST No. = subtest number.

Note: Values are expressed as mean ± SEM (n = 27).

^aP ≤ .05 significant vs pretreatment value.

primarily regulated by catecholamine (dopaminergic, noradrenergic) pathways. A decrease in dopamine reserves in the prefrontal region has been reported to be associated with ADHD symptoms.^{31,32} The current frontline therapies for ADHD are stimulants of the central nervous system, such as dextroamphetamine, methylphenidate, and pemoline, which (1) target catecholamines, (2) act by inhibiting the reuptake of catecholamines (dopamine and norepinephrine), and (3) enhance release of presynaptic neuron dopamine and norepinephrine.⁴ *B monnieri*, similarly to the mode of action of synthetic stimulants of the central nervous system,

increases the dopamine levels in the cortex.²⁰ In addition to its effect on dopamine levels, *B monnieri* possess neuroprotective and antioxidant effects on the hippocampus and the frontal cortex.¹⁴ The effects of the SBME on the ADHD symptoms in the present study may be attributed to these modes of actions on the specific brain regions and neurotransmitters. Specifically, because these regions are associated with attention and the ability to exercise inhibition, the SBME may have significantly improved attention after the intervention period in 85% of the children.

Impulsivity, one of the core symptoms of ADHD, was significantly reduced in 67% of the children. This effect can be compared with results gleaned in a study using a combination herbal product containing *Panax quinquefolius* and *G biloba* extracts, which demonstrated improvement in 19 (53%) of 36 children after 2 weeks and 18 (53%) of 34 children after 4 weeks in the restless-impulsive attributes.³³ Restlessness or hyperactivity is an essential feature of ADHD, and following the intervention period in the current study, 93% of the children showed decreased restlessness. The mean subtest scores were significantly reduced post-SBME treatment.

Barkley³⁴ indicates that poor inhibition of behavior, often referred to as self-control, arises from ADHD, and the core symptoms of ADHD reflect problems with inhibiting behavior. It was postulated that normal levels of self-control are not possible when the brain systems are not functioning properly or become damaged. People diagnosed with ADHD often have a biologically based problem with self-control. SBME reduced self-control issues in 89% of the children. Malmberg et al³⁵ reported that a subthreshold diagnosis of ADHD was a major risk factor for several psychiatric problems, such as irritability, anger, and distress. SBME administration ameliorated the psychiatric disorders in children. Children with ADHD have difficulties in their relationship with other children in their classes and with siblings at home. The exact mechanism contributing to these social problems is not known³⁶; however, SBME was able to mitigate somewhat the children's social problems in the current study, but the result was not significant.

Academic and educational outcomes for children with ADHD were precisely reviewed by Loe and Feldman,³⁷ who concluded that the disorder has dramatic associations with poor grades and poor reading. This result could be owing to the memory impairments that are frequent in ADHD.^{38,39} In the current study, SBME administration significantly reduced learning problems in the children, and the effect of SBME on learning problems may be ascribed to the memory-enhancing effects of *B monnieri* that have been reported in studies by Negi et al²² in ADHD children and Usha et al²⁶ in children requiring an individualized education program. The overall effects of SBME on symptoms of ADHD may be ascribed to the neuroprotective,^{14,40} neurotrophic,⁴¹ and nootropic^{26,27,42} effects of *B monnieri* on the brain systems.

Pharmacotherapeutic interventions of ADHD have been reportedly associated with adverse effects. Adverse effects such as delay in growth, anorexia, insomnia, stomachache, and headache are associated with stimulant usage, whereas nonstimulant medications can cause issues such as cardiotoxicity, vertigo, orthostatic hypotension, tremor, constipation, and depression.^{43,44} No such treatment-related adverse effects were reported during the current study, which indicates that the SBME was safe and tolerable. The Phase I study in healthy human volunteers, the clinical trial in children, and the preclinical studies on SBME corroborate the safety of the test substance. The relatively short duration

of the trial in most of the earlier studies that evaluated efficacy of herbal interventions on the symptoms of ADHD remains a common limitation. In the present study, however, SBME was administered for 6 months and was well-tolerated in children with ADHD.

CONCLUSION

The current preliminary clinical trial revealed SBME (BacoMind) was effective in the management of ADHD symptoms and exhibited safety and tolerability in ADHD children. Further study is warranted on the potential use of the botanical substance as a replacement or adjunctive therapy for ADHD.

AUTHOR DISCLOSURE STATEMENT

Joshua Allan Joseph, MVS; Bharathi Bethapudi, MVS; and Amit Agarwal, PhD, are employed by Natural Remedies (Bangalore, India).

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