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BacoMind®: A Cognitive Enhancer in Children Requiring Individual Education Programme

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Abstract: *Bacopa monnieri* belonging to family Scrophulariaceae has been used since time immemorial by Ayurvedic medical practitioners in India as brain tonic. In the present clinical trial, efficacy of BacoMind®, an enriched phytochemical composition from *Bacopa monnieri* on cognitive function in children requiring individual education programme was evaluated. Twenty-eight volunteers with Intelligent Quotient between 70-90 were enrolled in the clinical trial. The study was conducted as outpatient procedure in hospital settings with close monitoring. BacoMind® at 225 mg as single oral dose for a duration of four months showed significant change in the baseline value of working memory and short term verbal memory from 5.21±0.32 to 6.38±0.25 ($p \leq 0.05$) and 5.33±0.44 to 6.54±0.35 ($p \leq 0.05$), respectively in 70.83% of study population. Significant improvement ($p \leq 0.05$) was also seen in logical memory, memory related to personal life and also in visual as well as auditory memory. BacoMind® was also found to be well tolerable with no major side effects. The findings of the current study revealed the cognitive enhancing effect of the BacoMind® in children requiring individual education programme.

Key words: BacoMind®, low intelligent quotient children, cognitive enhancement

INTRODUCTION

Children with intelligence level in the low average or borderline Intelligent Quotient (IQ) range 70-90 can be grouped together as slow learners and these children are eligible for Individual Education Programme (IEP) (Krishnakumar *et al*., 2006). There is no standard definition of the slow learner who can be given IEP. The Texas Education Agency (1989) defined them as students who have regularly met with failure in the schools, whose intellectual functioning level, IQ 70-89, has affected their ability to keep up with the pace in learning. Krishnakumar *et al*. (2006) grouped them as children with intelligence level in the low average or borderline IQ range.

Data compiled by Office of Special Education Programs (OSEP) in US Department of Education show that since 1976-77 the number of children served annually under special education has increased from 1.6 to 5.3 million in 1993-94 (Lewitt and Baker, 1996). This alarming increase in the prevalence of number of children requiring IEP adds to the socio-economic burden of the country. With limited help from conventional medicine, possible adverse effects of allopathic medicine and the unpredictability and uncontrollability of exacerbations make complementary and alternative medicine appealing in case of children requiring IEP.

In recent years, researchers have identified a number of natural compounds that could potentially help to retard memory deterioration. Most of this research is based on plants used in the ancient

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systems of medicine to promote brain health. One of the earliest chronicled plants in the Ayurvedic treatise, the Charaka Samhita (100 A.D.), is *Bacopa monnieri* (*B. monnieri*) which is recommended in formulations for the management of a range of mental conditions including anxiety, poor cognition and lack of concentration. *B. monnieri* (Family: Scrophulariaceae) is also known as Water Hyssop, Brahmi, *Herpestis monniera* and is a creeping annual plant found throughout the Indian subcontinent in wet, damp and marshy areas (Chopra *et al*., 1956). *B. monnieri* being one of the most popular Indian herbal remedies has been studied repeatedly in the past not only for bioactive constituents (Deepak and Amit, 2004), but also for pharmacological attributes (Singh and Dhawan, 1997). Preliminary studies have shown *B. monnieri* extract improved memory performance of rats in various learning situations (Singh and Dhawan, 1982) and useful in treatment of dementia (Das *et al*., 2002). Behavioural study showed that *B. monniera* improved motor learning (Prakash and Sirsi, 1962), acquisition, retention and delayed extinction in rats (Singh and Dhawan, 1982). Studies indicated that cognition facilitating effect was due to two active saponins viz., bacosides A and B (Singh *et al*., 1988) and bacosides were reported to inhibit the amnesic effects of scopolamine, electroshock and immobilization stress (Dhawan and Singh, 1996). Standardised extract of *B. monnieri* showed antioxidant activity in rat frontal cortex, striatum and hippocampus (Bhattacharya *et al*., 2000).

Negi *et al.* (2000) reported significant memory enhancing effect of phytocomposition containing *B. monnieri* in children with Attention Deficit Hyperactivity Disorder (ADHD). Exploratory study revealed *B. monnieri* renovating and improving the perceptual motor function during the developmental phase of children (Sharma *et al*., 1987). Further, safety aspect of *B. monnieri* extract, no mutagenic effect was observed in Ames test (Dipanwita *et al*., 2008) and no incidence of genotoxicity was also reported as well (Giri and Khan, 1996). A no-observed adverse effect level of 500 mg kg^{-1} day^{-1} was established in subchronic oral toxicity study for 90 days (Joshua *et al*., 2007). Phase I clinical trial on BacoMind™ reported it safe in healthy human volunteers (Pravina *et al*., 2007). A double blind placebo controlled trial with 450 mg daily dose of BacoMind® for 12 weeks in elderly volunteers showed it to be safe (unpublished data).

The present study was designed with the primary objective of evaluating the intellect and memory functions of BacoMind® in children requiring IEP and to provide scientific evidence for the clinical use of proprietary formulation of *B. monnieri* supplementation as a cognition enhancer. The secondary objective was to assess an overall safety of BacoMind® in children requiring IEP.

MATERIALS AND METHODS

Study Design

An open labelled clinical trial was conducted at Centre for Research in Mental Retardation (CREMERE), Mumbai, India. Institutional Ethical Committee approval was obtained.

BacoMind®

BacoMind®, an enriched phytochemical composition of *B. monnieri*, developed by Natural Remedies Pvt. Ltd. (patent pending) was standardised to the content of the following bioactive constituents viz., bacoside A_3 (>5.0% w/w), bacopaside I (>7.0% w/w), bacopaside II (>5.5% w/w), jujubogenin isomer of bacopasaponin C (>7.0% w/w), bacopasaponin C (>4.5% w/w), bacosine (>1.5% w/w), luteolin (>0.2% w/w), β-sitosterol-D-glucoside (>0.3% w/w) and apigenin (>0.1% w/w). It was further standardised using the following *in vitro* bioassays viz., lipoxygenase inhibition assay (IC_{50}<600 μg mL^{-1}), ABTS radical scavenging assay (IC_{50}<100 μg mL^{-1}), DPPH assay (IC_{50}<200 μg mL^{-1}) and butyrylcholinesterase inhibition assay (IC_{50}<3000 μg mL^{-1}).

HPLC finger print of BacoMind® is shown in Fig. 1 and 2; Fig. 3 describes the HPTLC profile of BacoMind®. The individual compounds present in this formulation were identified and quantified using respective standards. Quantification of the compounds was carried out on dry weight basis.

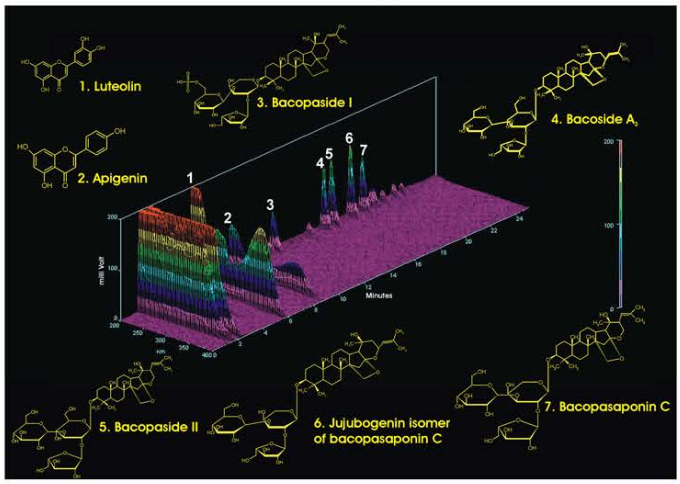

Fig. 1: HPLC fingerprint of BacoMind®, HPLC conditions: Column: Pinnacle DB C18 5 µm 250×4.6 mm, Restek; mobile phase: mixture of phosphate buffer (A) + Acetonitrile (B); in linear gradient from 70% (solvent A) to 60% in 25 min; phosphate buffer: 0.001 N potassium dihydrogen phosphate in HPLC grade water + 0.5 mL orthophosphoric acid; temperature: 25°C; flow rate: 1.5 mL min^{-1} throughout; UV (PDA): scanning range 200-400 nm

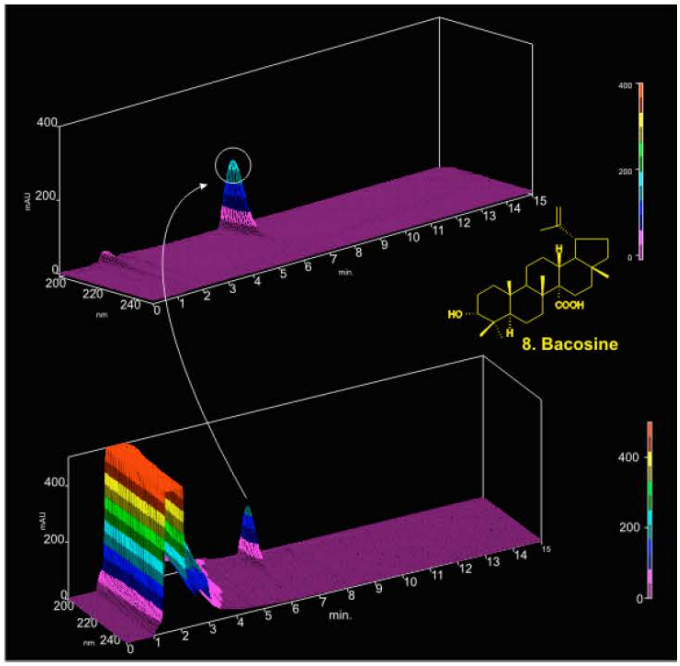

Fig. 2: HPLC fingerprint of BacoMind®, HPLC conditions: Column: Hibar, RP-18e (5 µm) 250×4.6 mm, Lichrospher; mobile phase: 5% Acetonitrile in 0.2% aqueous orthophosphoric acid and methanol (1:9); temperature: 25°C; flow rate: 1.5 mL min^{-1} throughout; UV (PDA): scanning range 200-400 nm

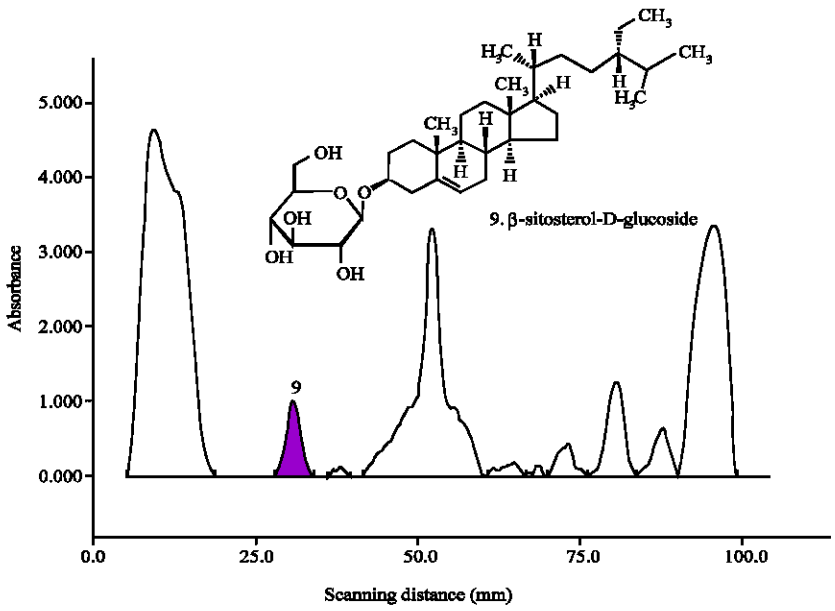

Fig. 3: HPTLC profile of BacoMind®, HPTLC conditions: TLC plate: Silica gel 60F254, 10×10 cm, Merck, Germany; spotting device: Linomat IV, Camag; mobile phase: Chloroform : Methanol (9:1); spraying agent: Anisaldehyde sulfuric acid reagent; Densitometer: CS 9301 PC, Shimadzu; UV: 530 nm. Reprinted from Phytomedicine, 5 (4) K. Pravina, K.R. Ravindra, K.S. Goudar, D.R. Vinod, A.J. Joshua, P. Wasim, K. Venkateshwarlu, V.S. Saxena and A. Amit. Safety evaluation of BacoMind™ in healthy volunteers: A phase I study, 301-308, 2007 with permission from Elsevier

BacoMind® (Batch No.: BM/03/LOT15) contained bacoside A_3 (80 mg g^{-1}), bacopaside I (89 mg g^{-1}), bacopaside II (68 mg g^{-1}), jujubogenin isomer of bacopa saponin C (90 mg g^{-1}), bacopa saponin C (52 mg g^{-1}), bacosine (23 mg g^{-1}), luteolin (4 mg g^{-1}), β-sitosterol-D-glucoside (9 mg g^{-1}) and apigenin (2 mg g^{-1}).

Participants

A total of 28 (13 males and 15 females) participants aged between 4-18 years (Age mean±SD; 10.54±3.02) were enrolled for the study following informed written consent. Parents of all the participants were asked to understand and sign the informed consent form on behalf of the participants as they were under 18 years of age. Demographic information of participants is presented in Table 1. The study was conducted as an outpatient procedure at CREMERE, Mumbai, India, between September 2004 and June 2005. The selection of participants was based on the following criteria.

Inclusion Criteria

The age group of 4-18 years, with an IQ between 70-90, proven to be healthy and parents willing to give written consent to participate in the study were considered.

Exclusion Criteria

Children having cerebral palsy, physical disability and children requiring IEP with epilepsy were excluded from the study.

Procedure

The study was conducted over a period of six months, which included a screening procedure, preparation of participants (prior to administration of BacoMind®) and finally supplementation of BacoMind® for a period of four months. Coded bottles provided by the sponsor were used to assign the allocation sequence. Clinical psychologist was responsible for enrollment of participant and assignment of BacoMind® to the participants.

All the parents of the participants were instructed to administer one capsule of BacoMind® (containing 225 mg of enriched phytochemical composition of *B. monnieri*) with a glass of water after the breakfast between 8.00 am and 9.00 am as single dose for the duration of four months. There was no restriction placed on routine activity or diet during the study period.

Compliance

In each follow up visit, along with medical examination, the participants were enquired about the compliance of medication, adverse events and willingness to continue the participation. If confirmed, they were issued the next container having capsules of BacoMind®. The compliance of study medication was ensured by counting of remaining capsules in the container along with the recording in the Medication Compliance Card (MCC). Volunteers taking 85% of study medication up to 4 months of treatment were considered to be compliant with therapy.

End Point Measurements

The clinical end point measurement was done by clinical psychologist and dispensing of the BacoMind® was on monthly basis so that the follow up could be well maintained and the parents could interact with the psychologist. At the same time the behavioural as well as school performance was enquired. The primary endpoint with respect to efficacy in children requiring IEP was the proportion of children achieving the improvement in scores of memory scale tests. The inclusion criteria adopted, Wechsler Intelligence Scale for Children (WISC) to assess the intelligence quotient of participants. The efficacy assessment of BacoMind® was done by performing a battery of memory scale tests.

Neuropsychological Tests

The battery of memory scale tests including WISC to assess IQ was performed as part of inclusion criteria.

Wechsler Intelligence Scale for Children

WISC consisted of 12 subtests, each measuring different aspects of child's cognition.
The subtests were divided in two groups:

- Verbal tests (assess the ability to understand, reason and express himself or herself through language)
- Performance tests (assess the individual's ability to perceive, organize and reason with visual/spatial stimuli)

Memory Scale Test

Memory scale for children was designed to assess different aspects of memory in children. The test comprises of 10 subtests and is as follows:

- Information: Assess the awareness of the child about self and the memory related to personal life
- Orientation: Assess the child's orientation to person, place and time
- Mental control: Checks child's working memory

- Digit span:
  - Repeating digits forward: subtest checks immediate memory
  - Repeating digits backward: subtest checks working memory
- Repeating the words: Checks the short term memory for verbal material
- Repeating the sentences: Gives idea about logical memory for verbal material
- Verbal retention of similar pairs: Gives idea about auditory memory for similar pairs
- Verbal retention of dissimilar pairs: Conveys about visual as well as auditory memory for dissimilar pairs of words
- Visual reproduction: Conveys about short term memory for non-verbal (graphic) material
- Recognition: Informs about short term memory for non-verbal material

Safety Measures

Participants and their parents/guardians in the study were instructed to report to the investigator in the event of any adverse effects for overall safety assessment on children. Thorough clinical-physical examination was done by physician before and after completion of the clinical study.

Statistics

The values were expressed either as percentage or mean±SEM. The scores of performance of memory tests conducted in pre and post (0th and 4th month) treatment periods were analysed by student's paired t-test using SPSS software. The statistical significance was set at $p \leq 0.05$.

RESULTS

A total of 28 subjects (13 males and 15 females) were enrolled, out of which 24 participants completed the study and were considered for statistical analysis (Table 1). Two participants dropped out following 4 months of treatment due to unknown reason.

Neuropsychological Tests

The memory scale test for children comprising of 10 subtests was designed to assess the different aspects of memory. The performance of children requiring IEP in various memory tests and each subtest were given in Table 3.

Four months treatment with BacoMind® showed a significant change in the baseline value of working memory (ST4/Digit span) and short term verbal memory (ST5/repeating words) from 5.21±0.32 to 6.38±0.25 ($p \leq 0.05$) and 5.33±0.44 to 6.54±0.35 ($p \leq 0.05$), respectively in 70.83% of study population.

Logical memory (ST6/repeating sentences) was improved from 3.21±0.31 to 4.04±0.23 ($p \leq 0.05$) in 50.00% of children. While memory related to personal life (ST1/Information) increased from 4.58±0.13 to 4.83±0.08 ($p \leq 0.05$) in 25% of children.

Also visual as well as auditory memory for similar (ST7) and dissimilar (ST8) words showed improvement from 4.25±0.21 to 4.63±0.16 ($p \leq 0.05$) in 29.17% of children and 2.88±0.32 to 3.13±0.30 ($p \leq 0.05$) in 25% of study subjects (Table 3).

Table 1: Demographic data of participants who enrolled and completed the study

	Enrolled		Completed	
Age group	Males	Females	Males	Females
Below 10 years	05	06	05	04
10-14 years	07	08	06	07
Above 14 years	01	01	01	01
Total	13	15	12	12

Table 2: Improvement in total score of memory scale test

Parameters	Groups I (±/no change)	II (upto 20%)	III (21-50%)	IV (51-75%)
No. of children	4	13	5	2
Percentage of children	16.67	54.17	20.83	8.33

n = 24

Table 3: Improvement in memory test scores and analysis of subtests for memory scale in BacoMind® treated children requiring IEP

Subtest No.	Name of subtest	Test score before treatment (0th month)	Test score after treatment (4th month)	No. of children	Percentage of children
ST1	Information	4.58±0.13	4.83±0.08*	6	25.00
ST2	Orientation	4.50±0.18	4.71±0.13	4	16.67
ST3	Mental control	3.71±0.33	4.46±0.30*	11	45.83
ST4	Digit span	5.21±0.32	6.38±0.25*	17	70.83
ST5	Repeating words	5.33±0.44	6.54±0.35*	17	70.83
ST6	Repeating sentences	3.21±0.31	4.04±0.23*	12	50.00
ST7	Verbal retention of similar word pairs	4.25±0.21	4.63±0.16*	7	29.17
ST8	Verbal retention of dissimilar word pairs	2.88±0.32	3.13±0.30*	6	25.00
ST9	Visual reproduction	5.00±0.43	5.83±0.36*	14	58.33
ST10	Recognition	8.21±0.36	8.33±0.36	7	29.17

Values are expressed as mean±SEM; n = 24, *$p \leq 0.05$ significant vs pre-treatment values, ST-Subtest

The total score of 10 memory subtests was studied in terms of percentage increase in scores and four categories were made as shown in Table 2. It was observed that 54.17% of children have shown up to 20% increase in improvement in the total score, while 20.83% showed between 21-50% increase. Interestingly, 8.33% of the children requiring IEP revealed remarkable (51-75%) increase in the total score. No major side effects were observed except three children reported vomiting and stomach upset, but after two-three days of discontinuation of treatment no such side effects were reported and the treatment was thereafter continued. Overall, the BacoMind® was found to be well tolerated throughout the study with no major side effects.

DISCUSSION

In psychology, memory is an organism's ability to store, retain and subsequently recall information. Before an individual can remember something, the individual must first learn the information. Learning may be defined as the acquisition of new information, while memory is the capacity for storing and retrieving this information (Wickens, 2005). Children with below average intelligence have history of developmental delay in learning (Kaznowski, 2004). These children do not get sufficient attention in the mainstream education and they usually fail repeatedly in examinations and finally become school dropouts (Krishnakumar *et al*., 2006). With the exorbitant increase in the number of such children, it has become mandatory to find new therapy to treat them apart from IEP.

The present study was designed to validate the effect of chronic administration of BacoMind®, in children requiring IEP. BacoMind® was given at the dose of 225 mg single oral dose per day for four months in children requiring IEP. The dose was selected based on the published literature of *B. monnieri* and the preclinical *in vivo* efficacy studies of BacoMind® wherein optimum nootropic activity was observed at 40 and 60 mg kg^{-1} in Wistar rats and Swiss albino mice, respectively (Kasture *et al*., 2007).

Digit span tests device to measure immediate memory of subject, which is one of the vital psychological processes contributing in a normal continuum of behaviour. The observations from the present study indicated that BacoMind® can be useful in vitalizing specific psychological functions as exhibited by improvement of immediate and working memory in digit span tests. These findings were found to be in concordance with the study conducted in school going children supplemented with *B. monnieri*, which shares similarities with respect to digit span test (Sharma *et al*., 1987).

Working memory is a theoretical concept referring to a set of cognitive processes that provide temporary maintenance and manipulation of the information necessary for complex cognitive tasks (Baddeley, 1992). The results from the present study showed that treatment of BacoMind® significantly improved the subtest of the working memory and thereby improving mental control in 45.83% of children.

BacoMind® showed improvement in sentence repetition and logical memory in children requiring IEP, which were in accordance with the clinical study conducted in Attention Deficit Hyperactivity Disorder (ADHD) patients and healthy human volunteers (Negi *et al*., 2000; Stough *et al*., 2001).

The awareness of the child about self and the memory related to personal life was also seen to be improved. In addition, *B. monnieri* also improved memory, mental performance and reduced anxiety in patients with anxiety neurosis (Udupa and Singh, 1993). In healthy human volunteers *B. monnieri* improved information processing, verbal memory and memory consolidation (Stough *et al*., 2001). Another double blind placebo controlled trial in healthy volunteer reported *B. monnieri* reduces the amount of information lost from the memory (Roodenrys *et al*., 2002). Interestingly, 83.33% of children requiring IEP showed improvement in battery of memory tests. The findings also support the published literature (Stough *et al*., 2001; Udupa and Singh, 1993; Roodenrys *et al*., 2002).

It was apparent from the present study that BacoMind® could be useful for rejuvenating and improving the perception during the developmental phase of children. The exact mechanism of how these effects were caused is not known but previous research findings have postulated that bacosides may act by cholinergic modulation (Bhattacharya *et al*., 1999), enhancement of protein kinase activity in hippocampus, antioxidant activity (Bhattacharya *et al*., 2000; Tripathi *et al*., 1996) and also by their ability to reduce nitric oxide induced cellular alterations (Russo *et al*., 2003).

In conclusion, BacoMind® showed significant improvement in the working memory, logical memory, in memory related to personal life and also visual as well as auditory memory in children requiring individual education programme.

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REFERENCES

Baddeley, A., 1992. Working memory. Science, 255 (5044): 556-559.

Bhattacharya, S.K., A. Kumar and S. Ghosal, 1999. Effect of *Bacopa monniera* on animal models of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. Res. Commun. Pharmacol. Toxicol., 4 (3-4): 1-12.

Bhattacharya, S.K., A. Bhattacharya, A. Kumar and S. Ghosal, 2000. Antioxidant activity of *Bacopa monnieri* in rat frontal cortex, striatum and hippocampus. Phytother. Res., 14: 174-179.

Chopra, R.N., S.L. Nayar and I.C. Chopra, 1956. Glossary of Indian medicinal plants. Council of Scientific Industrial Research, New Delhi, pp: 32.

Das, A., G. Shankar, C. Nath, R. Pal, S. Singh and H.K. Singh, 2002. A comparative study in rodents of standardised extracts of *Bacopa monnieri* and *Gingko biloba* Anticholinestrase and cognitive enhancing activities. Pharmacol. Biochem. Behav., 73: 893-900.

Deepak, M. and A. Amit, 2004. The need for establishing identities of bacoside A and B, the putative major active saponins of Indian medicinal plant *Bacopa monnieri.* Phytomedicine, 11: 264-268.

Dhawan, B.N. and H.K. Singh, 1996. Pharmacological studies on *Bacopa monnieri*, an ayurvedic nootropic agent. Eur. Neuropsychopharmacol., 6: 144.

Dipanwita, D.D., P. Kapoor, R.P. Dighe, R. Padmaja, M.S. Anand, P. D'Souza, M. Deepak, B. Murali and A. Amit, 2008. *In vitro* safety evaluation and anticlastogenic effect of BacoMind™ on human lymphocytes. Biomed. Environ. Sci. (In Press).

Giri, A.K. and K.A. Khan, 1996. Chromosome aberrations, sister chromatid exchange and micronuclei formation analysis in mice after *in vivo* exposure to bacoside A and B. Cytologia, 61: 99-103.

Joshua, A.J., A. Damodaran, N.S. Deshmukh, K.S. Goudar and A. Amit, 2007. Safety evaluation of a standardised phytochemical composition extracted from *Bacopa monnieri* in Sprague Dawley rats. Food Chem. Toxicol., 45 (10): 1928-1937.

Kasture, S.B., V.S. Kasture, A.J. Joshua, A. Damodaran and A. Amit, 2007. Nootropic activity of BacoMind™, an enriched phytochemical composition from *Bacopa monnieri*. J. Nat. Remedies, 7 (1): 166-173.

Kaznowski, K., 2004. Slow Learners: Are Educators Leaving Them Behind? National Association of Secondary School Principals Bulletin. http://www.looksmart.com (accessed on 23 March 2007).

Krishnakumar, P., M.G. Geeta and R. Palat, 2006. Effectiveness of individualized education program for slow learners. Indian J. Pediatr., 73 (2): 135-137.

Lewitt, E.M. and L.S. Baker, 1996. Child indicators: Children in special education. The future of children. Spring, 6 (1): 139-151.

Negi, K.S., Y.D. Singh, K.P. Kushwaha, C.K. Rastogi, A.K. Rathi, J.S. Srivastava, O.P. Asthana and R.C. Gupta, 2000. Clinical evaluation of memory enhancing properties of memory plus in children with attention deficit hyperactivity disorder. Ind. J. Psychiatry, 42 (2): 4.

Prakash, J.C. and M. Sirsi, 1962. Comparative study of the effects of Brahmi (*Bacopa monnieri*) and chlorpromazine on motor learning in rats. J. Sci. Ind. Res., 21: 93-96.

Pravina, K., K.R. Ravindra, K.S. Goudar, D.R. Vinod, A.J. Joshua, P. Wasim, K. Venkateshwarlu and A. Amit, 2007. Safety evaluation of BacoMind™ in healthy volunteers: A phase I study. Phytomedicine, 14: 301-308.

Roodenrys, S., D. Booth, S. Buzomi, A. Phipps, C. Micallef and J. Smoker, 2002. Chronic effects of Brahmi (*Bacopa monnieri*) on human memory. Neuropsychopharmacology, 27 (2): 279-281.

Russo, A., F. Borrelli, A. Campisi, R. Acquaviva, G. Raciti and A. Vanella, 2003. Nitric oxide-related toxicity in cultured astrocytes: Effect of *Bacopa monniera*. Life Sci., 73: 1517-1526.

Sharma, R., C. Chaturvedi and P.V. Tewari, 1987. Efficacy of *Bacopa monnieri* in revitalizing intellectual functions in children. J. Res. Educ. Indian Med., 6 (1-2): 1-10.

Singh, H.K. and B.N. Dhawan, 1982. Effect of *Bacopa monniera* Linn. (Brahmi) extract on avoidance responses in rat. J. Ethnopharmacol., 5: 205-214.

Singh, H.K., R.P. Rastogi, R.C. Srimal and B.N. Dhawan, 1988. Effect of bacosides A and B on avoidance responses in rats. Phytother. Res., 2 (2): 70-75.

Singh, H.K. and B.N. Dhawan, 1997. Neuropsychopharmcological effects of the Ayurvedic nootropic *Bacopa monniera* Linn. (Brahmi). Indian J. Pharmacol., 29: S359-S365.

Stough, C., J. Lloyd, J. Clarke, L.A. Downey, C.W. Hutchison, T. Rodgers and P.J. Nathan, 2001. The chronic effects of an extract of *Bacopa monniera* (Brahmi) on cognitive function in healthy human subjects. Psychopharmacology, 156: 481-484.

Texas Education Agency, 1989. The slower learner: An advocate's view. Practitioner's guide series number two. Austin, TX: Author. (ERIC Document Reproduction Service No. ED346685) cited at http://eric.ed.gov/ERICWebPortal/custom/portlets/recordDetails/detailmini.jsp?_nfpb=true&_&ERICExtSearch_SearchValue_0=ED346685&ERICExtSearch_SearchType_0=eric_accno&accno=ED346685.

Tripathi, Y.B., S. Chaurasia, E. Tripathi, A. Upadhyay and G.P. Dubey, 1996. *Bacopa monniera* Linn. as an antioxidant: Mechanism of action. Ind. J. Exp. Biol., 34: 523-526.

Udupa, K.N. and R.H. Singh, 1993. Clinical and Experimental Studies on Rasayana Drugs and Panchkarma Therapy. 1st Edn. Central Council for Research in Ayurveda and Siddha, New Delhi.

Wickens, A., 2005. Foundations of Biopsychology. 2nd Edn. Pearson, Harlow, England.