



Review Article

ROLE OF AYURVEDIC MEDICINAL PLANTS IN CHILDHOOD NEUROPSYCHIATRIC DISORDERS: AN EVIDENCE BASED APPROACH

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ABSTRACT

The concept of mental health has been dealt in Ayurveda with great emphasis. In our classical texts, the equilibrium of *Satva-Raja-Tama* is considered as foundation for perfect health status. The principles of Ayurveda still hold very true in managing childhood neuropsychiatric disorders. *Medhya* drugs has been used since antiquity for the effective management of the disorders. But in this era of scientific aptitude, it is the need of hour to practice evidence based medicine by the use of various *Medhya* drugs described in Ayurvedic texts for the management of neuropsychiatric disorders.

Medhya herbs provide special nourishment to neuronal tissue and are thus used to enhance memory, cognition, and help in coping various neuropsychiatric problems. In this context, the present paper will focus on scientific exploration of *Medhya dravyas* like *Brahmi* (*Bacopa monneri*), *Mandukparni* (*Centella asiatica*), *Shankhpushpi* (*Convolvulus pleuricaulis*), *Jatamansi* (*Nordostachys jatamansi*) and *Vacha* (*Acorus calamus*) to validate the ancient views regarding effective management of neuropsychiatric disorder.

KEYWORDS: Medicinal Plants, *Brahmi* (*Bacopa monneri*), *Mandukparni* (*Centella asiatica*), *Shankhpushpi* (*Convolvulus pleuricaulis*), *Jatamansi* (*Nordostachys jatamansi*) and *Vacha*, Childhood Neuropsychiatric Disorders.

INTRODUCTION

Neuropsychiatric disorders constitute the greatest stress on the children in most of the developed and developing countries. Problem of Neuropsychiatric disorders are increasing throughout world at an alarming rate. Neuropsychiatric disorders are common in the united state and internationally. An estimated of 22% of Americans aged 18 and older (about 1 in 5 adults) suffer from a diagnosable Neuropsychiatric disorder in a given year.^[1]

Cerebral dysfunction from any physical cause manifested by changes in mood behaviour, perception, memory, cognition, or judgments and/or psycho-physiology indicates Neuropsychiatric disorders.^[2] Neuropsychiatric disorder not only causes a terrible reduction in quality of life of the sufferer, it also places tremendous burden on both the carrier and welfare systems. Epidemiological studies of Indian children reveal that Neuropsychiatric disorder is largely a hidden problem in the country.

There is a paucity of modern drugs/agents facilitating acquisition, retention, and retrieval of

information and knowledge. Nootropic agents such as pircetam^[3], nefiracetam, aniracetam^[4] and choline esterase like inhibitors like donepezil are being primarily used to improve memory, mood, behaviour.

However the resulting adverse effects associated with these agents have limited their use^[5,6]. Beyond physically locating areas of damage and deficit, there is a great need to understand to work in prevention, treatment and rehabilitation efforts.

Ayurveda, The Indian system of medicine had developed therapeutic measures to rejuvenate whole functional dynamics of the body organs. This rejuvenation is known as *Rasayana Chikitsa*^[7] (Rejuvenation therapy). Ayurveda claims that several plants, the "*Medhya*" plants (intellect promoting) herbs such as *Brahmi* (*Bacopa monneri*), *Mandukparni* (*Centella asiatica*), *Shankhpushpi* (*Convolvulus pleuricaulis*), *Jatamansi* (*Nordostachys jatamansi*) and *Vacha* (*Acorus calamus*) are beneficial in cognitive disorders.^[8] Thus, it is supposed that these drugs can prove beneficial and provide effective and long term solution to Neuropsychiatric

disorders and thereby improve the quality of life and school performance in children.

Clinical and Experimental Evidences Regarding the Role of Various Ayurvedic Drugs in Neuropsychiatric Disorders.

1) **Brahmi (*Bacopa monnieri*)**

i. **Nootropic activity**

In a study, *Bacopa monnieri* (BM) was evaluated alone and in combination with phenytoin for its effect. Phenytoin (PHT, 25mg/kg PO x 14 days) adversely affected cognitive function in the PA task. BM extract, (40 mg/kgx7 days), given along with phenytoin in the second week of the two week regimen, significantly reversed PHT – induced impairment. Both acquisition and retention of memory showed improvement without affecting its anticonvulsant activity.^[9]

ii. **Memory enhancing effect**

1. In a study on the effects of *Brahmi* (*Bacopa monnieri*) on human memory. The results show a significant effect of the *Bacopa monnieri* on a test for the retention of new information. Follow up tests showed that the rate of learning was unaffected suggesting that *Bacopa monnieri* decreases the rate of forgetting of newly acquired information tasks assessing attention verbal and visual short term memory and the retrieval of preexperimental knowledge were unaffected.^[10]
2. *Bacopa* has also demonstrated a significant memory promoting effect in animal models of Alzheimer's disease.^[11]

iii. **Effect on cognitive function**

1. In a study, the chronic effects of an extract of *Bacopa* on cognitive function in healthy human subjects were examined. *Bacopa* significantly improved speed of visual information processing measured by the IT task learning rate and memory consolidation compared to placebo, with maximal effects evident after 12 weeks. These findings suggest that *Bacopa monnieri* may improve higher order cognitive process that are critically dependent on the input of information from our environment such as learning and memory.^[12]
2. Extensive pharmacological studies, mostly conducted with standardized extract have shown that *Bacopa* improved the acquisition, retention and retrieval of learned tasks.^[13]
3. Bacoside A and B were found to facilitate the capacity for mental retention in rats and were active in both positive and negative reinforcement experiments.^[14]
4. In an open 4 week trial of *Bacopa* in 35 patients with anxiety neurosis 12g/day of dried *Bacopa*

herb was given in the form of syrup. Significant improvement in anxiety ($P<0.05$), concentration ($P<0.05$) and immediate memory span ($P<0.01$) were seen as a result of the treatment. No major side effects were observed.^[14]

5. In a study to investigate the effect of *Bacopa* in school children aged 6-8 years, 40 children were given *Bacopa* syrup equivalent to 1g dried herb daily for 3 months, in a single-blind design. Immediate memory, perception and reaction/performance times improved with *Bacopa* treatment. No side effects were observed.^[15]

iv. **Antidepressant activity**

In a study, the standardized methanolic extract of *Bacopa monnieri* (bacoside A) was investigated for potential antidepressant activity in rodent models of depression. The effect was compared with the standard antidepressant drug imipramine. The *Bacopa monnieri* extract was given in the dose of 20 and 40 mg/kg, orally once daily for 5 days was found to have significant antidepressant activity in forced swim and learned helplessness models of depression and was comparable to that of imipramine.^[16]

v. **Antistress effect**

The antistress effect of bacosides of *Brahmi* (*Bacopa monnieri*) was studied in adult male Sprague Dawley rats by administering oral doses of 20 and 40 mg/kg for 7 consecutive days. The data indicate that *Bacopa* has potential to modulate the activities of HSP 70, P450 and SOD (super oxide dismutase) thereby possibly allowing the brain to be prepared to act under adverse conditions such as stress.^[17]

vi. **Improvement of mean reaction time**

In a placebo control, double-blind study to test the efficacy of *Bacopa* on children for six weeks, 50 normal school children split into two groups were given either *Bacopa* or placebo. At the conclusion, they were evaluated for attention, concentration, and memory. *Bacopa* was shown to improve mean reaction time (Auditory and visual) significantly.^[18]

vii. **Effect on behavior & increase in serotonin level**

In an experimental study, rats were individually trained in a simple T- maze until they reached a predetermined level of performance. They were then divided into three groups and given either nothing, diazepam (Valium), or *Bacopa*. At the end of 10 days, they were evaluated by repeating the T- maze trial. Those animals given *Bacopa*, showed remarkable learning and memory enhancement compared with the control and Valium groups. Furthermore, the neurochemical content of their

brain tissue showed an increase in the level of serotonin. Serotonin has been identified with improved spatial memory as well as anxiolytic benefits.^[19]

viii. Revitalization of intellectual functions

In a study, Sharma and colleagues gave one half of a group of 40 healthy children (ages 6-8) Bacopa in a syrup base three times a day (a total of 1.05g/day) over the course of four weeks, while giving the other half a placebo. Those children taking Bacopa were superior in matters of speed and accuracy in solving maze problems. Overall, these improvements "Vitalized" the children's efficacy and their propensity to choose exploratory behavior and to opt for novel experiences in preference to familiar ones.^[20]

2) Mandukparni (*Centella asiatica*)

i. Neuroprotective effect

In an attempt to prepare neuroprotective compounds that were more efficacious than Asiatic acid itself, the chemical structure of Asiatic acid was modified and 36 derivatives were obtained. The neuroprotective activities of these derivatives were evaluated using primary cultures of rat cortical neurons insulted with the neurotoxin, glutamate, as an in vitro screening system. These results showed that these derivatives of Asiatic acid exerted significant neuroprotective effects on cultured cortical cells by their potentiation of cellular oxidative defense mechanism. That is, these may prove to be efficacious in protecting neurons from the oxidative damage caused by exposure to excess glutamate.^[21]

ii. Regeneration of nerves

In a study, sub fractions of *Centella* ethanolic extract were tested (100 microg mL - 1) for neurite elongation in the presence of nerve growth factor (NGF). Greatest activity was found with a non-polar fraction (GKF4). Relatively Polar fractions (GKF 10 and GKF 13) also showed activity, albeit less than GKF4. Thus, *Centella* contains more than one active component. Asiatic acid (AA). Male Sprague Dawley rats given *Centella* ethanolic extract in their drinking water (300-330 mg/kg-1daily) demonstrated more rapid functional recovery and increased axonal regeneration (larger caliber axons and greater number of myelinated axons) compared with controls, indicating that the axons grew at a faster rate. Taken together the findings indicate that components in *Centella* ethanolic extract may be useful for accelerating repair of damaged neurons.^[22]

iii. Learning and memory enhancing effect

1. In an experimental study, fresh *Centella asiatica* plant extract was given orally to rat pups (n=5). Results showed a significant increase in the percent correct response (control: 86.44 + 2.33 percent Vs Expt. 93.44 + 3.90 percent) in plant extract treated rats. Passive avoidance retention test revealed a significantly memory retention, dendritic intersection was significantly increased at all concentric circles, except at 100 micron. Dendritic branching points also significantly increased in the inner three zones. These results indicate a correlation between improved learning capacity and increased dendritic arborization in amygdaloid nucleus.^[23]
2. In an experimental study to evaluate the nootropic effect of *Centella asiatica*, animals were tested in radial arm maze to assess the learning and memory performance. Performance of juvenile and young adult mice was significantly improved in radial arm maze and hole board tests, but locomotor activity did not show any change compared to control. Treatment resulted in increased acetylcholine esterase activity in the hippocampus. Dendritic arborization of hippocampal CA3 neurons was also increased in terms of intersections and branching points both at month and 6 months. Results of the present investigation show that treatment during postnatal developmental stage with *C.asiatica* extract can influence the neuronal morphology and promote the higher brain functions of juvenile and young adult mice.^[24]

iv. Antidepressant activity

In a study to evaluate the antidepressant activity of total terpenes from gotu kola in forced swimming test. The effect of total terpenes from gotu kola on the immobility time in forced swimming mice and ameliorated the imbalance of amino acid level. Thus, it may be concluded that the total terpenes from gotu kola had antidepressant activity. (Chen Y, Han T, Qin L, Rui Y, Zheng H).

v. Effect on cognition and oxidative stress

1. In the present study, the effect of an aqueous extract of *C.asiatica* (100, 200 and 300 mg/kg for 21days) was evaluated in i.c.v. STZ induced cognitive impairment and oxidative stress in rats. Male wistar rats were injected with STZ (3 mg/kg, i.c.v.) bilaterally on the days 1 and 3. Cognitive behavior was assessed using passive avoidance and elevated plus maze paradigms on the days 13,14 and 21. Rats were killed on the day 21 for estimation of oxidative stress parameters (Malondialdehyde (MDA), glutathione, superoxide

dismutase and catalase) in the whole brain upon completion of the behavioral task. Rats treated with *C.asiatica* showed a dose dependant increase in cognitive behavior in both paradigms. A significant decrease in MDA and an increase in glutathione and catalase levels, were observed only in rats treated with 200 and 300 mg/kg *C.asiatica*. The present findings indicate that an aqueous extract of *C.asiatica* is effective in preventing the cognitive deficits, as well as the oxidative stress, caused by i.c.v. STZ in rats. [25]

2. Neonatal rat pups (7 days old) were given different doses of fresh leaf juice of *Centella asiatica* (CeA) orally for different period of time. These rats were then subjected to spatial learning (T-Maze) and passive avoidance tests along with the age matched normal saline control rats. The result showed improvement in spatial learning performance and enhanced memory retention in neonatal rats treated with higher doses. These results indicate that treatment with CeA fresh leaf juice during growth spurt period of neonatal rats enhances memory retention. [24]

3) *Shankpushpi* (*Convolvulus pleuricaulis*)

i. CNS Depressant Activity

Neuropharmacological activities of the methanol extract of the whole plant of *Shankpushpi*, *Convolvulus microphyllus* sieb ex spreng (convolvulaceae), were studied in experimental animals. The extract was found to produce alternations in the general behavior pattern, reduction in spontaneous motor activity, hypothermia, and potentiation of phenobarbitone-sleeping time, reduction in exploratory behavioral pattern and suppression of aggressive behavior. The extract also showed an inhibitory effect on conditioned avoidance response and antagonism to amphetamine toxicity. These findings explicitly suggest that the whole plant extract of *C. microphyllus* possesses a potential CNS depressant activity. [26]

ii. Increase in Acquisition efficiency

The ethanolic extract of the plant when administered to rats through gastric intubation at different time intervals showed enhanced neuropeptide synthesis of the brain. It induces an increase in brain protein content thus increasing acquisition efficiency. [27]

iii. Effect on Behavior

The alcoholic extract reduced the spontaneous motor activity of mice, the reduction being more marked in amphetamine treated hyperactive mice. The extract also exhibited potentiation of phenobarbitone (pentobarbitone) hypnosis in

mice and morphine analgesia in albino rats. The extract caused a reduction in the fighting response of mice and abolished conditioned avoidance response without affecting the escape response. The electrically induced convulsive seizures in rats and tremorine-induced tremors in mice were antagonised by the extract. [28]

iv. Cytoprotective effect on Hippocampal cells

Effects of *Shankpushpi* on hippocampal neuron cells were studied in stressed adult Swiss albino white female mice. After treatment with alcoholic extract there was a significant increase in cells of CA1 and Dg. *Sankpushpi*, in addition to improving memory has also been suggested to have cytoprotective antistress effect. [29]

4) *Jatamansi* (*Nordostachys jatamansi*)

i. Neuroprotective effect

The protective effect of *Nordostachys jatamansi* (NJ) on neurobehavioral activities, thiobarbituric acid reactive substance (TBARS), reduced glutathione (GSH), thiol group, catalase and sodium potassium ATPase activities was studied in middle cerebral artery (MCA) occlusion model of acute cerebral ischemia in rats. MCA occlusion caused significant depletion in the contents of glutathione and thiol group and a significant elevation in the level of TBARS. The activities of Na (+) K (+) ATPase and catalase were decreased significant by MCA occlusion. The neurobehavioral activities (spontaneous motor activity and motor coordination) were also decreased significantly in MCA occlusion group. All the alternations induced by ischemia were significantly attenuated by 15 days pretreatment of NJ (250 mg/kg p.o.) and correlated well with histopathology by decreasing the neuronal cell death following MCA occlusion and reperfusion. The study provides first evidence of effectiveness of NJ in local ischemia most probably by virtue of its antioxidant property. [30]

ii. Improvement of Learning and Memory

In a study undertaken to assess the potential of *N. Jatamansi* as a memory enhancer, elevated plus maze and the passive avoidance paradigm were employed to evaluate learning and memory parameters. Three doses (50, 100, and 200 mg./kg. p.o.) of an ethanolic extract of *N.jatamansi* were administered for 8 successive days to both young and aged mice. The 200mg/kg dose of *N.jatamansi* ethanolic extract significantly improved learning and memory in young mice and also reversed the amnesia induced by diazepam (1 mg/kg, i.p.) and scopolamine (0.4mg/kg.i.p.). Furthermore, it also reversed aging induced amnesia due to natural aging of mice. As scopolamine induced amnesia was reversed, it is possible that the memory

improvement may be because of facilitation of cholinergic transmission in the brain. Hence, *N.jatamansi* might prove to be a useful memory restorative agent in the treatment of dementia seen in elderly persons. The underlying mechanism of action can be attributed to its antioxidant property. [31]

iii. Sedative and tranquilizing action

The sesquiterpene valeranone present in *Nardostachys jatamansi* was pharmacologically investigated in animal experiments of sedative, tranquilizing and antihypertensive properties. In some experiments, typical for tranquilizers, certain activities could be demonstrated such as the prolongation of barbiturate hypnosis, the impairment of rotarod performance, an anticonvulsive activity on electric shock and potentiation of the body-temperature lowering activity of reserpine. [32]

5) Vacha (*Acorus calamus*)

i. Neuroprotective effect

In an experimental study, exposure of rats to acryl amide (ACR) caused hind limb paralysis in 58% of the animals on day 10 and decreased behavioral parameters, namely distance traveled, ambulatory time, stereotypic time and basal stereotypic movements compared with the control group. These rats also had a decrease in the reduced glutathione (GSH) content and glutathione-S-transferase (GST) activity in the corpus striatum and an increase in striatal dopamine receptors. As evident by an increase in the binding of 3H-spiperone to striatal membranes. Treatment with the ethanol: water (1:1) extract of the rhizomes of *Acorus calamus* (AC -002) increased the GSH content and GST activity in the corpus striatum while insignificant changes were observed in other parameters. Rats treated with ACR and AC-002 in combination had a lower incidence of paralysis (18%) compared with those treated with ACR alone on day 10 of the experiment. The rats also showed a partial recovery in other behavioral parameters. The levels of GSH content and GST activity increased in the corpus striatum, while the dopamine receptors decreased compared with the ACR treated rats. The results suggest that the neurobehavioral changes produced by ACR may be prevented following treatment with *Acorus calamus* rhizomes. [33]

ii. Effect on electrical activity & regional monoamine levels in brain

Effect of chronic administration of ethanolic extract of *Acorus calamus* (AC) was studied on spontaneous electrical activity and monoamine levels of brain. AC (200 mg/kg and 300 mg/kg) was administered

orally to adult Holtzman strain rats for 14 days. In AC treated rats, electrographic recording revealed that there was increase in activity together with an increase in norepinephrine level in the cerebral cortex but a decrease in the midbrain and cerebellum. Serotonin level was increased in the cerebral cortex but decreased in the midbrain. Similarly, dopamine level as increased in the caudate nucleus and midbrain but decreased in the cerebellum. Thus AC seems to exert its depressive action by changing electrical activity and by differentially altering brain monoamine levels in different brain regions. [34]

iii. Improvement of cognitive function

Methanolic extracts of seven herbs *Acorus calamus*, *Acorus graminens*, *Bupleurum falcatum*, *Dioscorea batatas*, *Epimedium koreanum*, *Poria cocos* and *Zizyphi jujuba* used in traditional Korean medicine for improvement of memory and cognition in old age were tested for cholinesterase inhibitory properties using the Ellman colorimetric methods significant inhibition of the enzyme at 200 micro g/ml was observed for extracts from *A. calamus* and *E. Koreanum*. [35]

iv. Monoamine oxidase inhibiting activity

A monoamine oxidase inhibiting activity has been observed in the all of the Asian species of *Acorus calamus* (Opdyke, 1977). Indian researchers found that the sedative effect of asarone was dependent on the depression of the ergotropic division of the hypothalamus. [36]

v. Sedative action

A sedative action and potentiation of barbiturate effect (increased sleeping time, reduced body temperature) was observed in small animals (mice, rats, rabbits and cats) following intraperitoneal administration of the aqueous and ethanolic extracts of both European and Asian varieties of *Acorus calamus*. [37]

vi. Effect on neurotransmitters

The Asian oil of *A. calamus* is reported to deplete levels of serotonin and norepinephine in the rat brain following intraperitoneal administration in a manner similar to that of reserpine. [37] In contrast the European variety has not been found to have the same activity upon the CNS. [37]

CONCLUSION

Increasing stress, depression, anxiety and increasing awareness of the disorder can be very well related to the alarming rise in the prevalence of Neuropsychiatric disorders in children. After reviewing these clinical and experimental studies, it can be concluded that all these drugs have memory enhancing, cognitive improvement, antistress, antidepressive, neuroprotective and cytoprotective

properties in the line of management of neuropsychiatric disorder. Thus, it can be concluded that these drugs have potential of effective management in Neuropsychiatric disorder.

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