

Evidence based Ayurveda for revitalization of mental health

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Abstract

Mental health is an integral part of health. Mentally healthy people are able to function well in home and society and meet the ordinary demands of daily life. They enjoy a positive quality of life and are free of disabling symptoms of psychopathology. On the other hand, any type of mental disorder is associated with a totally disturbed life. According to the World Health Organization, 10% of the world's population has some form of mental disability and 1% suffers from severe incapacitating mental disorders. In India community-based surveys conducted during the past two decades showed that the total prevalence of psychiatric disorder was around 5.8%. For children, only a few studies have reported a prevalence rate ranging from 8.17-35.6% in India. Although the current used drugs are the first choice medication, however, these agents produce various unacceptable side effects like, loss of appetite, stomach aches/ cramps, headache, dizziness, irritability, drowsiness, staring, tics etc., which should be a matter of concern in both adults and children. In this area, Ayurvedic herbs having Medhya property may prove safe and effective. Review of various experimental and clinical studies offer clue to use different Medhya drugs, judiciously for the management of psychiatric and behavioural disorders.

Introduction

Mental health may be defined as a state of emotional and psychological well being in which an individual is able to use his or her cognitive and emotional capabilities, function in society and meet the ordinary demands of everyday life [1]. According to World Health Organization mental health is defined as "a being of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community" [2]. The World Health Organization states that 10% of the world's population has some form of mental disability and 1% suffers from severe incapacitating mental disorders [3]. In India community-based surveys conducted during the past two decades showed that the total prevalence of psychiatric disorder was around 5.8% [4]. Another study reports the prevalence rate for mental disorders in India as 65.4 per 1000 population [5].

Mental health in children is defined by the achievement of expected developmental cognitive, social

and emotional milestones and at the same time satisfying social relationships and effective coping skills. Mentally healthy children enjoy a positive quality of life; function well at home, in school, and in their communities; and are free of disabling symptoms of psychopathology [6]. For children, only a few studies have reported a prevalence rate ranging from 8.17-35.6% in India [7-11].

The most commonly occurring mental disorders are anxiety disorders, mood disorders, personality disorders, dementia and that of children as mentioned in DSM-IV, include anxiety disorders, attention deficit and disruptive behaviour disorders, autism and other pervasive disorders, eating disorders, learning and communication disorders, mood disorders, tic disorders etc. These disorders are characterized by abnormal behaviour, thoughts, emotions and relationship with others.

The current medications used in the treatment of mental disorders including children incorporate antipsychotic, antidepressants, anti anxiety drugs, stimulants and mood stabilizing groups. Although these drugs are the first choice medication, however, these agents produce various unacceptable side effects like, loss of appetite, stomach aches/cramps, headache, dizziness, irritability, drowsiness, staring, tics etc., which should be a matter of concern in both adults and children. In this area, Ayurvedic herbs having Medhya property may prove safe and effective. The drugs promoting Medha (intellect) are termed as Medhya drugs.

Review of various experimental and clinical studies offer clue to use different Medhya drugs, judiciously for the management of psychiatric and behavioural disorders. The review is taken from articles cited on Pubmed and in MAPA (Medicinal and Aromatic Plant Abstracts) by using the key words learning and memory, cognition, Bacopa, Centella etc.

Nootropic activity

In a study, daily administration of *Ashwagandha* root extract (50,100 and 200 mg/kg orally) for 6 days significantly improved memory consolidation in mice receiving chronic electroconvulsive shock (ECS) treatment. *Ashwagandha* administered on day 7, also attenuated the disruption of memory consolidation, produced by chronic treatment with ECS. On the elevated plus maze *Ashwagandha* reversed the scopolamine (0.3

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mg/kg) induced delay in transfer latency on day 1. On the basis of these findings it is suggested that *Ashwagandha* exhibits a nootropic like effect in naive and amnesic mice [12]. A study indicate that treatment during postnatal developmental stage with *Centella asiatica* extract can influence the neuronal morphology and promote the higher brain functions of juvenile and young adult mice [13].

Regeneration of nerves/ Induction of Axon-or Dendritic outgrowth

Sub fractions of *Centella asiatica* 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 (GKF 4). Relatively polar fractions (GKF 10 and GKF 13) also showed activity, albeit less than GKF 4. The findings indicate that components in *Centella* ethanolic extract may be useful for accelerating repair of damaged neurons [14].

In a study, it was found that six of the 18 compounds isolated from the methanol extract enhanced neurite outgrowth in human neuroblastoma SH-SY5Y cells. In Withanolide A-treated cells, the length of NF-H-positive processes was significantly increased compared with vehicle treated cells, whereas, the length of MAP2-positive processes was increased by Withanosides IV and VI. These results suggest that axons are predominantly extended by Withanolide A, and dendrites by Withanosides IV and VI [15].

Treatment with Withanolide A (WL-A) isolated from *Ashwagandha*, induced significant regeneration of both axons and dendrites, in addition to the reconstruction of pre and post synapses in the neurons. WL-A (10 micro mol Kg⁻¹ day⁻¹), for 13 days, p.o.) recovered A beta (25-35) induced memory deficit in mice. At that time, the decline of axons, dendrites and synapses in the cerebral cortex and hippocampus was almost recovered. WL-A is therefore an important candidate for the therapeutic treatment of neurodegenerative diseases, as it is able to reconstruct neuronal networks [16].

Effect on cognitive function

In a study, *Bacopa monnieri* 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 [17].

In an experimental study, an extract of *B. monnieri* was given to albino rats to measure its effect on three newly acquired behavioural responses: brightness discriminating, condition avoidance and continuous avoidance. The facilitating effect of the *Bacopa* was clearly discernible in all three learning responses, augmenting both the rat's cognitive function and mental retention capacity. The rats learned faster, retained more of what they had learned, and remembered it longer. The chemical

constituents responsible for the facilitating effect of *Bacopa* on learning schedules were identified as a mixture of bacosides A and B. The bacosides also enhanced vital protein activity and produced an increase in protein synthesis in the hippocampus, a part of the brain that is important for long-term memory [18].

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. Work related mental fatigue, measured as total work output and errors committed per unit time, also improved significantly with *Bacopa* treatment (P<0.001). Improvements were also seen in symptoms such as insomnia, headache, palpitation and irritability [19]. To investigate the effect of *Bacopa* in school children aged 6-8 years, 40 children were given *Bacopa* syrup equivalent to 1 g dried herb daily for 3 months, in a single-blind design. Immediate memory, perception and reaction/ performance times improved with *Bacopa* treatment [20].

Neonatal rat pups (7 days old) were given different doses of fresh leaf juice of *C. 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 [21].

In a study on the effects of Brahmi (*B. monnieri*) on human memory, seventy six adults aged between 40 and 65 years took part in a double blind randomized, placebo control study in which various memory functions were tested and levels of anxiety measured. The results showed a significant effect of the *B. monnieri* on a test for the retention of new information. Follow up tests showed that the rate of learning was unaffected suggesting that *B. monnieri* decreases the rate of forgetting of newly acquired information [22]. *Bacopa* has also demonstrated a significant memory promoting effect in animal models of Alzheimer's disease [23].

In an experimental study, fresh *C. asiatica* plant extract was given orally to rat pups (n=5), from P7-P49 (6 weeks, 2 ml/kg/day). These and age matched normal control (n=5) rats were subjected to learning tests in T-maze and passive avoidance test. Following this, rats were sacrificed and amygdaloid nucleus was processed for Golgi staining. 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. This may be the neural basis for enhanced learning in *Centella asiatica* treated rats [24].

A study undertaken to assess the potential of *Nordostachys 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 200 mg/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. Hence, *N. jatamansi* might prove to be a useful memory restorative agent in the treatment of dementia seen in elderly persons [25].

A study undertaken with the objective of studying the effect of *Tinospora cordifolia* (Tc) on learning and memory in normal rats and on cyclosporine induced memory deficits, both alcoholic and aqueous extract of *T. cordifolia* enhanced the cognition in normal rats as were seen in behavioural tests – Hebb William maze and the passive avoidance task [26].

To investigate the effects of *Glycyrrhiza glabra*, on learning and memory, the elevated plus- maze and passive avoidance paradigm were employed to evaluate learning and memory parameters. Three doses (75, 150 and 300 mg/kg p/o) of aqueous extract of *G. glabra* were administered for 7 successive days in separate groups of mice. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. Furthermore, this dose reversed the amnesia induced by diazepam 1mg/kg i.p.), scopolamine (0.4 mg/kg i.p) and ethanol (1mg/kg i.p) [27].

The effect of *Withania somnifera* extract prepared by two different methods were assessed on behavioral parameters using open field exploratory behavior, behavior despair and passive avoidance tests and were compared in young and old stressed Wistar rats. *W. somnifera* extracts prepared with 50% methanol and solvent containing water, ghee and honey were administered orally as fine suspension, during the shock period. The results revealed that stress produced depression anxiety and retention deficit in young and old rats. Administration of *W. somnifera* methanolic extract 250 mg/kg during shock period in young and old rats attenuated the stress-induced depression and enhanced memory. *W. somnifera* traditional extract 250mg/kg produced memory enhancement in both control and stressed young and old rats [28].

Isolated constituents of *W. somnifera* (Sitoindosides VII-X and Withaferine – A) increased cortical muscarinic acetylcholine receptor capacity partly explaining the cognition enhancing and memory improving effects traditionally attributed to *Ashwagandha* [29].

In a study, one half of a group of 40 healthy children (ages 6-8) were given *Bacopa* in a syrup base three times a day (a total of 1.05 g/day) over the course of four weeks, while the other half were given 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 behaviour and to opt for novel experiences in preference to familiar ones [30].

Effect in ADHD

In a study 36 children in the 8-10 year age group were selected for a double blind, randomized trial. 19 were given 50 mg of *Bacopa* twice daily, 17 others received placebo. After 12 weeks of treatment, the children were subjected to a battery of specialized tests. The data revealed a significant improvement in the areas of sentence repetition, logical memory and pair associative learning (matching things that go together, e.g. “test” and “grade”) in all 19 ADHD children who took *Bacopa* [31].

A 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 [32].

Effect on behaviour

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 [33].

Antidepressant activity

In a study, *B. monneiri* extract 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 [34].

A 15 day treatment with *N. jatamansi* resulted in a significant increase in the levels of NE, DA, 5-HT, 5-HIAA and GABA. These data indicate that the alcoholic extract of the roots of *N. jatamansi* causes an overall increase in the levels of central monoamines and inhibitory amino acids [35].

In an experimental study a bioassay-guided isolation of the ethanol extract from the fruits of *Piper longum* yielded, a known piperidine alkaloid, piperine, which

showed an inhibitory effect against monoamine oxidase (MAO). The results suggest that piperine possesses potent antidepressant-like properties that are mediated in part through the inhibition of MAO activity and therefore represent a promising pharmacological therapeutic candidate as an antidepressant agent [36].

Anxiolytic/ antistress activity

The bioactive glycowithanolides (WSG), isolated from *W. somnifera* roots WSG (20 and 50 mg/kg) was administered in rats orally once daily for 5 days and the results were compared by those elicited by the benzodiazepine lorazepam (0.5mg/kg, i.p.), for the antidepressant investigations. WSG induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus-maze test, social interaction and feeding latency in an unfamiliar environment. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim induced 'behavioral despair', and 'learned helplessness', tests [37].

In a study, mice received varying doses [10-300mg/kg i.p.] of hydroalcoholic extract of roots and rhizomes of *G. glabra* and anxiolytic activity was assessed using different paradigms like elevated plus maze, foot shock-induced aggression and amphetamine induced stereotypy. In all the animal models of anxiety, lower doses of hydroalcoholic were more effective in alleviating anxiety. The extract and standard anxiolytic agents increased duration of occupancy of mice in open arm, increased latency to foot shock-induced aggression and reduced number of fighting bouts and delayed the onset of amphetamine induced grooming, biting, sniffing and repetitive head movements [38].

The antistress effect of bacosides of Brahmi (*B. 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 indicated 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 [39].

A number of herbal drugs mostly in the form of their extracts (holistic approach) or in some, as active principles isolated from them, were evaluated for their antistress activity by a number of tests. *W. somnifera*, *Ocimum sanctum*, *T. cordifolia*, *C. asiatica*, *G. glabra* were reported with encouraging results [40].

Neuroprotective effect

The effect of an aqueous extract of *C. asiatica* (100, 200 and 300 mg/kg for 21 days) was evaluated in i.c.v. STZ induced cognitive impairment and oxidative stress in rats. The findings indicated 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 [41].

The protective effect of *N. jatamansi* (NJ) on neurobehavioural activities was studied in middle cerebral artery (MCA) occlusion model of acute cerebral ischaemia in rats. 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 [42].

CNS Depressant/ sedative effect

The methanol extract of the whole plant of Shankhapushpi, *Convolvulus microphyllus sieb ex spreng* (convolvulaceae), was found to produce alternations in the general behaviour pattern, reduction in spontaneous motor activity, hypothermia, and potentiation of phenobarbitone-sleeping time, reduction in exploratory behavioural pattern and suppression of aggressive behaviour. The extract also showed an inhibitory effect on conditioned avoidance response and antagonism to amphetamine toxicity. The findings explicitly suggested that the whole plant extract of *C. microphyllus* possesses a potential CNS depressant activity [43].

Effect of chronic administration of ethanolic extract of *Acorus calamus* (AC) was studied on spontaneous electrical activity and monoamine levels of brain. AC seemed to exert its depressive action by changing electrical activity and by differentially altering brain monoamine levels in different brain regions [44].

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 *A. calamus* [45].

CNS stimulating action

The effects of a 50% ethanol extract of the root of *Plumbago zeylanica* were investigated on locomotor behavior and central dopaminergic activity in rats. The results showed that the extract of the root of *P. zeylanica* specifically enhanced the spontaneous ambulatory activity without inducing stereotypic behaviour. The neurochemical estimations revealed elevated levels of DA and its metabolite homovanillic acid (HVA) in striatum compared with the control rats. These behavioural and biochemical results indicated stimulatory properties of the extract of the root of *P. zeylanica*, which may be mediated by dopaminergic mechanisms in the rat brain [46].

Discussion

Review of the various clinical and experimental studies of different Ayurvedic Medhya drugs reveals that these drugs possess nootropic, cognition enhancing, anti-stress, anxiolytic, antidepressant, anticonvulsant, CNS depressant, sedative and neuroprotective effect.

Ashwagandha and *Centella* possess nootropic activity. *Bacopa* and *Ashwagandha* have the potential for corrective effect in cognitive deficit, while *Centella* can influence the neuronal morphology and can thereby promote higher brain functions.

The drugs *C. asiatica* and *W. Somnifera* (*Ashwagandha*) are useful for repair of damaged neurons and in neurodegenerative disorders as these drugs have the capacity to reconstruct the neuronal networks.

Regarding the effect on cognition, the drugs *Bacopa*, *Centella*, *N. jatamansi*, *T. cordifolia*, *G. glabra* and *W. somnifera* may be useful. *Bacopa* has potential for revitalization of intellectual functions and may improve the higher order cognitive functions such as learning and memory. It has also showed effect on positive behavior modification by increasing the level of serotonin. *Centella* can induce memory retention an improved learning capacity by increasing dendritic arborization in amygdaloid nucleus.

N. jatamansi is useful as memory restorative agent as it facilitates cholinergic transmission in the brain. Both *T. cordifolia* and *G. glabra* are helpful in improving the learning capacity and memory restoration. *W. somnifera*, by increasing cortical muscarinic acetylcholine receptor capacity, can enhance memory.

Studies also indicate that *Bacopa* can produce significant improvement in different areas of child's functioning in ADHD children and it can also improve the mean reaction time (Auditory and Visual) significantly. *Bacopa* can also improve the behaviour by increasing the serotonin level in brain.

The drugs *B. monnieri*, *N. jatamansi* and *Piper longum* possess significant antidepressant activity. *N. jatamansi* can cause overall increase in the levels of central monoamines and inhibitory amino acids and therefore can be used as an antidepressant agent. *P. longum* also can be used as a promising antidepressant agent as it acts through the inhibition of MAO activity.

Studies regarding the anxiolytic or antistress activity revealed that *Bacopa*, *Centella*, *W. somnifera*, *T. cordifolia* and *G. glabra* have the potential to ameliorate the adverse conditions like stress. *W. somnifera* can be used as a mood stabilizer in clinical conditions of anxiety and depression. *G. glabra* possesses significant anxiolytic activity. *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.

C. asiatica by its potentiation of cellular oxidative defense mechanism acts as neuroprotective drug. Effectiveness of *N. jatamansi* in local ischaemia is most probably by virtue of its antioxidant property.

C. microphyllus shows potential CNS depressant activity by producing alternations in the general behaviour

pattern, reduction in spontaneous motor activity, hypothermia, and potentiation of phenobarbitone-sleeping time, reduction in exploratory behavioural pattern and suppression of aggressive behaviour. *A. calamus* seems to exert its depressive action by changing electrical activity and by differentially altering brain monoamine levels in different brain regions. *P. zeylanica* possesses CNS stimulant activity.

Conclusion

The studies indicate that Ayurvedic medhya drugs act in different way on the brain and different drug have specific action. Thus these drugs have potential to improve the overall mental system. Studies also reveal that Brahmi (*B. monnieri*) is the best intellect promoting drug which can prove safe and effective in promoting mental health in children. The review provides a clear view about the specific properties of different medhya drugs thus their judicious use will be very much helpful for the management of mental and behavioural disorders of adults and children.

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