International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2021; 9(2): 01-10
Received: 12-12-2020
Accepted: 22-01-2021

Ankita Mishra
PG Scholar, PG Department of Kaumarbhritya, National Institute of Ayurveda, Jaipur, Rajasthan, India

Rashmi Pareek
PhD Scholar, PG Department of Kaumarbhritya, National Institute of Ayurveda, Jaipur, Rajasthan, India

Nisha Kumari Ojha
Associate Professor & HOD, PG Department of Kaumarbhritya, National Institute of Ayurveda, Jaipur, Rajasthan, India

Corresponding Author:
Ankita Mishra
PG Scholar, PG Department of Kaumarbhritya, National Institute of Ayurveda, Jaipur, Rajasthan, India

Role of ayurveda drugs in the management of psychological distress in adolescents: Evidences

Ankita Mishra, Rashmi Pareek and Nisha Kumari Ojha

Abstract
Adolescent age group constituting 21% of India's population is the period of rapid physical, sexual, psychological growth. Increased parental and peer pressure can put this age group into lots of stress. Poor mental health is strongly related to other health and development concerns in young people notably, lower educational achievements, substances abuse, violence and poor reproductive and sexual health. Unfortunately, modern medicine based neurological drugs have met with unsatisfactory success in treatment of various neuropsychiatric disorders due to multi-factorial nature of these diseases.
The *Medhya Rasayanas* are a special class of *Ayurvedic* nutraceuticals which are specific to brain and nervous system. They are claimed to promote cognitive functions of the brain and are specifically indicated for maintenance of psychological well being. *Medhya rasayana* drugs play an essential role in the treatment of psychiatric and psychosomatic diseases. The mode of this therapy involves the individual to attain sedation, calmness, tranquility or a stimulation of activities of brain. Based on the experimental and clinical research, it is known that these drugs have varying degree of psychotropic action and are known to possess antidepressant, sedative and tranquilizing action. These plants are used both in herbal and conventional medicine and offer benefits that pharmaceutical drugs lack. Present review entails the evidences of medhya rasayana drugs in management of psychological distress in adolescents and reveals that these drugs have potential to alleviate the distress among adolescents.

Keywords: Adolescence, Psychological distress, *Medhya rasayan*, Nootropics

1. Introduction
Adolescence comes from the Latin word meaning "to come to maturity''. It is a period of transition between childhoods to adulthood. It is crucial and dynamic time when most of a person's biological, cognitive, psychological and social characteristics are changing. WHO defined adolescence at the age group of puberty [begin between 13 to19 years] refers to the maturational, hormonal and growth process and also changes with emotional, cognitive and behavioral changes. India has the largest population of adolescent in the world with 20% the world's adolescent [1].
Adolescent age group constituting 21% of India's population is the period of rapid physical, sexual, psychological growth. Increased parental and peer pressure can put this age group into lots of stress. Poor mental health is strongly related to other health and development concerns in young people notably, lower educational achievements, substances abuse, violence and poor reproductive and sexual health [2].
On the other hand, stress becomes distress" when the individual is unable to cope with it. Thus, distress is known to induce a number of clinical manifestations, like hypertension, coronary artery disease, peptic ulcer, asthma, migraine, ulcerative colitis, irritable bowel syndrome, diabetes mellitus, thyrotoxicosis, behavioral disorders like anxiety and depression and the list is very long.
Promoting adolescents wellbeing and education is of vital significance for the future of the Nation. As these adolescents stand in the threshold of adulthood, they need authentic and accurate guidelines that would help them for smooth and safe transition from childhood to adult. The problems of adolescent are multi-dimensional in nature and require holistic approach.
The *Medhya Rasayanas* are a special class of *Ayurvedic* nutraceuticals which are specific to brain and nervous system. They are claimed to promote cognitive functions of the brain as related to brain aging. *Ayurveda medhya rasayana* are specifically indicated for maintenance of mental/psychological well being. Studies also document that these drugs have nootropic as well as psychotropic effect and work variously to improve the psychological functioning of an individual [3].
Medhya rasayana drugs play an essential role in the treatment of psychiatric and psychosomatic diseases.

The mode of this therapy involves the individual to attain sedation, calmness, tranquility or a stimulation of activities of brain [4]. Based on the experimental and clinical research, it is known that these drugs have varying degree of psychotropic action and are known to possess antidepressant, sedative and tranquilizing action. These plants are used both in herbal and conventional medicine and offer benefits that pharmaceutical drugs lack.

2. Methodology

Ayurveda classics are reviewed for the therapeutic role of *medhya rasayana* drugs. Also, with the help of PubMed, Scopus, Web of science and Google Scholar, a comprehensive database of published research was collected on evidences of *Ayurveda medhya* drugs for their effect on various psychopathological states like, anxiety, depression and for neuroprotection, nootropic action, learning and memory etc.

3. Evidences

3.1 *Yastimadhu* [5]

Latin Name-*Glycyrrhiza glabra Linn.*
Family- Leguminosae

Chemical Constituents- Glycyrrhizin, glycyrrhetinic, deglycyrrhizinated licorice (DGL), flavonoids, isoflavonoids, calcones, aumarins, titerpenoids, sterols, starch, sucrose, glucose, lignin, amines, gum, volatile oil.

Properties and Actions

Rasa	:	*Madhura*
Guna	:	*Guru, Snigdha*
Virya	:	*Sheeta*
Vipaka	:	*Madhura*
Karma	:	*Balya, Chakashusya, Varnya, Vrasya, Vatapittajit, Raktaprasadana*

Formulations - *Eladi Gutika, Yastimadhuka Taila, Madhuyastyadi Taila*

Therapeutic Uses - *Kasa, Kshaya, Svarabheda, Vatarakta, Vrana*

Part Used - Dry root

Dose - 2-4 g

3.1.1 Neuroprotective Effect

Systemic administration of *Glycyrrhiza glabra* (GL) 30 minutes before kainic acid administration significantly suppressed neuronal cell death and drastically decreased gliosis and proinflammatory marker inductions [6] Another study suggested neuroprotective properties of glycyrrhizin(GL) following occlusion of the middle cerebral artery (MCAO) in the postischemic rat brain. .*Glycyrrhizin*, a triterpene found in licorice roots and rhizomes. GL has been reported to bind directly to HMGB1, inhibiting its chemo attractant and mitogenic activities. GL (10mg / kg) administration intravenously at 3 or 6h after MCAO reduced volumes of infarction to 12.9±4.2 percent and 46.2±9.9 percent of untreated control, respectively. Improvements in motor dysfunction and neurological disorders and inhibition of microglia activation and proinflammatory cytokine production followed this neuroprotective impact [7]. Improvement in learning and memory of mice was observed when they were administered aqueous extract of liquorice in a dose of 150mg/kg. This is probably due to facilitation of cholinergic transmission in mouse brain [8].

3.1.2 Anti convulsant Effect

In one experimental study, the anti-convulsant potential of aqueous and ethanol extract of *Glycyrrhiza glabra* (AEGG and EEGG) and its action on markers of oxidant stress is shown in pentylenetetrazole (PTZ)-induced seizure in albino rats. This is mediated via suppression of gliosis and induction of proinflammatory markers (COX-2, iNOS, and TNF-α) [9].

3.1.3 Effect on Learning and Memory

Glabridin, isolated from the roots of *Glycyrrhiza glabra* (Gg) was tested in mice for its effects on cognitive functions and cholinesterase activity. Glabridin (1, 2and 4 mg Kg, P. O.) and piracetam (-1) (400 mg kg), i. P.), a commonly used nootropic drug, was administered to different classes of mice daily for 3 consecutive days. The higher doses (2 and 4 mg kg (-1), P. O.) of glabridin and piracetam significantly antagonized the amnesia induced by scopolamine (0.5 mg kg (-1), I. P.) in both the, elevated plus maze test and passive avoidance test. Furthermore, glabridin (2 and 4 mg kg (-1), P. O.) and metrifonate (50 mg kg (-1), I. P.), used as a standard drug, both remarkably reduced the brain cholinesterase activity in mice compared to the control group. Therefore, glabridin appears to be a promising candidate for memory improvement [10]. The aqueous root extract of cc has shown spatial learning and memory enhancing activities in all the selected doses, but it was more significant in the doses of 150 and 225 mg/kg [11].

3.1.4 Antidepressant activity

Liquorice extract may possess an antidepressant-like effect. Antidepressant activity of *Glycyrrhiza glabra* is demonstrated in mouse models of immobility tests. This is mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin. This suggests that antidepressant like effect of liquorice extract seems to be mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin. Monoamine oxidase inhibiting effect of liquorice may be contributing favorably to the antidepressant-like activity [12].

3.1.5 Antioxidant Activity

The isoflavones glabridin and hispalglabridins A and B of *Glycyrrhiza. glabra Linn*. Have significant antioxidant activity. The antioxidants protect susceptible brain cells from the oxidative stress, resulting in reduced brain damage and improved neuronal function, thereby enhancing the memory [13].

3.2 Mandukparni [14]

Latin Name-*Centella asiatica* (Linn.)
Family- Apiaceae

Chemical Constituents- Indocentelloside, brahmoside, brahminoside, asiaticoside, kuniside, isothamkuniside, brahmic, asiatic, thankunic acid, isothankunic acid, mesoinositol, oligosaccharide centellose, kaempferol, quercetin, stigmasterol.

Properties and Action

Rasa	:	*Tikta, Kasaya, Madhura, Katu*
Guna	:	*Laghu, Sara*
Virya	:	*Shita*

Vipaka : *Madhura*
Karma : *Kaphapittahara, Hridya, Medhya, Svarya, Rasayana, Deepana, Varnya, Vishaghna, Aayushya, Balya, Smritiprada*

Important Formulations - *Brahma Rasayana*
Part used – *Panchang* (whole plant)
Dose - 3-6 gm

3.2.1 Effect on learning and Memory
Study demonstrated the ameliorating effect of ethanolic extract of *Centella asiatica* on learning and memory impairment in mice induced by either transient bilateral common carotid arteries occlusion (T2VO) or an intraperitoneal injection of scopolamine. It is likely that the positive effect of *Centella asiatica* observed could be, at least partly, accounted by its antioxidative property [15].

3.2.2 Antioxidant & Cognitive Action
The neuroprotective effect of *Centella asiatica* (CA) on chronic aluminum exposure induced mitochondrial enzyme alteration, oxidative stress, apoptosis and cognitive dysfunction in rat was investigated. Aluminum (100 mg/kg) and CA (150 and 300 mg/kg) were administered daily for a period of 6 weeks in male Wistar rats. Different behavioral, biochemical and cellular estimations and aluminum concentration were evaluated. Chronic aluminum administration resulted in memory impairment and caused marked oxidative damage associated with mitochondria impairment. It also caused a significant increase in caspase-3 activity, acetylcholine esterase activity and aluminum concentration in hippocampus and cerebral cortex of rat brain. Chronic administration of CA significantly improved memory performance, oxidative defense decreased aluminum concentration, caspase-3, acetyl cholinestrease activity and reversal of mitochondrial enzyme activity as compared to aluminum-treated animals. The study demonstrated neuroprotective potential of CA against aluminum-induced cognitive dysfunction and mito-oxidative damage [16].

3.2.3 Decreasing Oxidative Stress
Various study reported the neuroprotective activity of *Centella asiatica* by different modes of action such as enzyme inhibition, prevention of amyloid plaque formation in Alzheimer's disease, dopamine neurotoxicity in Parkinson's disease, and decreasing oxidative stress [17].

3.2.4 Cognitive Effect
Study report that, Asiatic acid (AA), a pentacyclic triterpene in *Centella asiatica*, possesses neuroprotective effects both in vitro and *in vivo*. AA was shown to attenuate glutamate-induced cognitive deficits of mice and protects SH-SY5Y cells against glutamate-induced apoptosis in vitro **[18]**. The effect of *Centella asiatica* fresh leaf extract treatment on the dendritic morphology of hippocampal CA3 neurons, one of the regions of the brain concerned with learning and memory during the rat growth spurt period was investigated. Neonatal rat pups (7 days old) were fed with 2, 4 or 6 ml kg^{-1} body weight of fresh leaf extract of *Centella asiatica* for 2, 4 and 6 weeks. After the treatment period their brains were removed and the hippocampal neurons were impregnated with silver nitrate (Golgi staining). Hippocampal CA3 neurons were traced by using a camera lucida, dendritic branching points and intersections were quantified. These data were compared with data for age-matched control rats. The results showed a significant increase in the dendritic length (intersections) and dendritic branching points along the length of both apical and basal dendrites in rats treated with 4 and 6 ml kg^{-1} body weight per day of *Centella asiatica* for longer periods of time (i.e. 4 and 6 weeks). The study conclude that the constituents present in *Centella asiatica* fresh leaf extract have a neuronal dendritic growth stimulating property; therefore, the extract can be used for enhancing neuronal dendrites in stress and neurodegenerative and memory disorders [19].

3.2.5 Anxiolytic Effect
A study demonstrated the anxiolytic effect of ECa 233 (a standardized extract of *Centella asiatica* containing triterpenoids not less than 80%, in comparison to diazepam) in both acutely and chronically stressed animals. The effects could be mainly accounted by madecassoside and asiaticoside, suggesting a potential use of ECa 233 for the treatment of both acute and chronic anxiety in the pathological state [20].

3.3 *Sankhpushpi* [21]
Latin Name-*Convolvulus pluricaulis choisy*
Family-Convolvulaceae

Chemical Constituents-
Shankhapushpin, convolvine, phyllabine, convolidine, confoline, subhirsine, convosine, convolvidine, scopoline, B-sitosterol.

Properties and Action
Rasa : *Tikta, Katu, Kasaya*
Guna : *Sara*
Veerya : *shita*
Vipaka : *Katu*
Karma : *Pittahara, Kaphahara, Rasayana, Medhya, Balya, Mohanasaka, Aayushya*

Formulations – *Agastyaharitaki Rasayana, Brahma Rasayana, Brahmi Ghrita, Manasamitra Vataka, Gorocanadi Vati, Brahmi vati*

Part used- *Panchang* (whole plant)
Dose - 3-8 g

3.3.1 Antidepressant Activity
The effect of the petroleum ether, chloroform, and ethyl acetate fractions of the total ethanolic extract of *Convolvulus pluricaulis choisy* on depression in mice was examined. The petroleum ether (25, 50 mg/kg), chloroform (25,50,100 mg/kg), and ethyl acetate (25, 50, 100 mg/kg) fractions were administered orally for 10 successive days to separate groups of Swiss young male albino mice. The effects of the extracts on the mice's immobility periods were assessed in the forced swim test (FST) and tail suspension test (TST). The chloroform fraction of the total ethanolic extract of *Convolvulus pluricaulis* exhibited a significant antidepressant like effect in mice by interaction with the adrenergic, dopaminergic, and serotonergic systems [22].

3.3.2 Neuroprotective Effect
Neuroprotective effects of the aqueous extract from *Convolvulus pluricaulis* (CP) against aluminium chloride induced neurotoxicity in rat cerebral cortex was investigated. Daily administration of CP(150 mg/kg) for 3 months along with aluminium chloride (50 mg/kg) decreased the elevated

enzymatic activity of acetylcholine esterase and also inhibited the decline in Na(+)/K(+) AT Pase activity which resulted from aluminium intake. Along with prevention of accumulation of lipid and protein damage, changes in the levels of endogenous antioxidant enzymes associated with aluminium administration were also rectified. Oral administration of CP also preserved the mRNA levels of muscarinic receptor 1(M1 receptor), choline acetyl transferase (ChAT) and Nerve Growth Factor-Tyrosine kinase A receptor (NGF-TrkA). Further, it ameliorated the upregulated protein expression of cyclin dependent kinase5 (Cdk5) induced by aluminium. The potential of CPE to inhibit aluminium induced toxicity was comparable to rivastigmine tartrate (1mg/kg), which was taken as standard. The potential of the extract to prevent aluminium-induced neurotoxicity was also reflected at the microscopic level, indicating its neuroprotective effects [23].

3.3.3 Antioxidant Activity

The antioxidant effect of methanolic extract of whole plant of *Convolvulus pluricaulis choisy* (CP) was studied by using 1, 1-diphenyl-2-picryl- hydrazyl (DPPH) free radical scavenging model and anticonvulsant activity by using maximal electroshock seizure model. In antioxidant activity, ascorbic acid was used as standard agent while anticonvulsant studies were compared with phenytoin. Antioxidant activity have demonstrated significant free radical scavenging effect for methanolic extract of CP. IC50 value of methanolic extract was observed as 41.00µg/ml as compared to 2.03µg/ml of ascorbic acid. Methanolic extract of CP was evaluated for anticonvulsant activity at 250, 500 and 1000mg/kg. Experimental results have shown that at the dose of 500 and 1000mg/kg, *Sankhpushpi* didn't abolish the hind limb extension, but reduced the mean recovery time from convulsion [24]. *Shankhapushpi* inhibited acetylcholinesterase in a dose dependant manner, significantly scavenged DPPH radical and superoxide radical and chelated metal ions. Total antioxidant capacity (equivalent to ascorbic acid) of the plant extracts was also good. *Shankhapushpi* enhances memory function due to its Antioxidant and Acetylcholinesterase Inhibitory properties [25].

3.3.4 Nervine Tonic

Convolvulus pluricaulis choisy (CP) is a known drug for its action on boosting memory and improving intellect and beneficial for brain disorders like epilepsy. *Shankhapushpi* is found to be effective in anxiety, neurosis and used in cerebral abnormalities, insomnia, and serve as wonderful nervine tonic and memory invigorator [26].

3.3.5 Nootropic Effect

The nootropic effect of *Sankhpushpi* tablets prepared by three *bhavanaa* (levigation) of its *churna* (powder) with its own *Svarasa* (fresh juice) was evaluated. Results revealed that *Sankhpushpi* tablet shown highly significant results in improving memory, especially in long term memory loss in younger age group. In auditory immediate test and delayed test, 41.03% and 48% improvement was found which statistically highly significant (<0.001).Overall results for *Sankhpushpi* tablet were significant for all the subtests of Wechsler's Memory Scale. For long term retention (medha) and recollection (*smṛiti*), *bhavita sankhpushpi* tablet has shown highly significant results, because of its *rasayana*, *medhya* and *tridosasamaka* properties [27].

3.4 *Guduchi* [28]

Latin Name- *Tinospora cordifolia (Willd.) Miers*
Family- Menispermaceae

Chemical constituents

Tinosporin, Berberine, Choline, Tembertarine, Palmitine, Jatrorrhizine, Epoxycl Isoerodane, diterpen, mEpoxyclerodane, diteren, Isocolumbin, Mangoflin, Tetrahydropalmatine, Magnoflorine, Berberine, Choline, Aporphine alkaloids.

Properties and Action

Rasa : *Tikta, Kasaya*
Guna : *Laghu*
Virya : *Usna*
Vipaka : *Madhura*
Karma : *Balya, Deepana, Rasayana, Sangrahi, Tridoshsamaka, Raktashodhaka, Jvaraghna*

Formulations

Amritarishta, Amarottar kwath churna, Guduchi Tail, Guduchyadi churna, Guduchi Sattva, Chinnobhavadi kwath churna

Dose - 3-6 g of the drug in powder form
20-30 g of the drug for decoction

3.4.1 Neuroprotective activity

The neuroprotective activity ethanol extract of *Tinospora cordifolia* aerial parts (TCEE) against 6-hydroxyl dopamine (6-OHDA) lesion rat model of Parkinson's disease (PD). Animals were divided into five groups: sham operated, negative control, positive control (levodopa 6 mg/kg) and two experimental groups (n = 6/group). Experimental groups received 200 and 400 mg/kg of TCEE once daily for 30 days by oral gavage. Biochemical parameters including dopamine level, oxidative stress, complex I activity, brain iron asymmetry ratio and locomotor activity including skeletal muscle co-ordination and degree of catatonia were evaluated. TCEE exhibited major cerebroprotection by increasing the dopamine levels and complex I activity at 200 and 400 mg/kg respectively when compared with negative control group. Iron asymmetry ratio was significantly attenuated by TCEE at 200 and 400 mg/kg. Neuroprotection by TCEE was further supported by reduced oxidative stress and restored locomotor activity in treatment groups [29].

In a study, Monosodium salt of glutamate was used to induce neurotoxic injury in primary cerebellar neurons. Four extracts including Hexane extract, Chloroform extract, Ethyl acetate, and Butanol extract were obtained from fractionation of aqueous ethanolic extract of T. cordifolia and tested for neuroprotective activity. Out of the four fractions, Butanol extract of T. cordifolia (B-TCE) exhibited neuroprotective potential by preventing degeneration of neurons induced by glutamate. Expression of different neuronal, apoptotic, inflammatory, cell cycle regulatory and plasticity markers was studied by immunostaining and Western blotting. Neurite outgrowth and migration were also studied using primary explant cultures, wound scratch and gelatin zymogram assay. At molecular level, B-TCE pretreatment of glutamate-treated cultures normalized the stress-induced downregulation in the expression of neuronal markers (MAP-2, GAP-43, NF200) and anti-apoptotic marker (Bcl-xL). Further, cells exposed to glutamate showed enhanced expression of inflammatory (NF-κB, AP-1) and senescence markers (HSP70, Mortalin) as well

as the extent of mitochondrial damage. However, B-TCE pretreatment prevented this increase and inhibited glutamate-induced onset of inflammation, stress and mitochondrial membrane damage. Further, B-TCE was observed to promote regeneration, migration and plasticity of cerebellar neurons, which was otherwise significantly inhibited by glutamate treatment. These results suggest that B-TCE may have neuroprotective and neuroregenerative potential against catastrophic consequences of glutamate-,mediated excitotoxicity and could be a potential therapeutic candidate for neurodegenerative diseases [30].

In another study, the neuroprotective potential of butanol extract of *Tinospora cordifolia* (B-TCE) was investigated against glutamate-induced excitotoxicity using primary hippocampal neurons as in vitro and Wistar strain albino rats as *in vivo* model systems. B-TCE treatment was effective in prevention of anxiety, cognition, and motor-coordination deficits induced by glutamate. B-TCE pre-treatment protected the hippocampal neurons from glutamate-induced neurodegeneration and impaired plasticity. At molecular level, B-TCE was observed to attenuate overactivation of glutamate receptors. B-TCE promoted up regulation of ERK and AKT pathways of synaptic plasticity and cell survival in the hippocampus region of brain. This study provided the evidence of neuroprotective potential of B-TCE against glutamate-induced excitotoxicity in hippocampus region and suggested that B-TCE may act as a potential candidate for neuroprotective therapeutic approaches. A single compound 'tinosporicide' was also isolated from B-TCE, which was found to be effective at 800× lower concentration against glutamate-induced neurodegeneration under in vitro conditions [31].

3.4.2 Antidepressant Activity

The effect of petroleum ether extract of *Tinospora cordifolia* (Wild.) Miers, on depression in mice was examined. The extract (50, 100 and 200 mg/kg, p.o.) was administered for 14 successive days to Swiss young albino mice (either sex) and evaluated for antidepressant like activity using tail suspension test and forced swim test. Petroleum ether extract at all three doses produced significant antidepressant like effect in tail suspension test as well as in forced swim test and their efficacies were found to be comparable to imipramine (15 mg/kg, p.o.) and sertraline (20 mg/kg, p.o.). The extract at a dose of 50 mg/kg showed most potent effect and did not show any significant change in locomotor functions of mice as compared to control. The antidepressant-like effect of the extract was significantly reversed by pretreatment of animals with prazosin (a α_1-adrenoceptor antagonist), sulpiride (a selective dopamine D_2-receptor antagonist), p-CPA (a serotonin synthesis inhibitor) and baclofen (GABA-B agonist), when tested in tail suspension test. Petroleum ether extract also reduced the mouse whole brain monoamine oxidase (MAO-A and MAO-B) activities as compared to control, which resulted in increase in the levels of brain monoamines. The results prove that the extract have potential therapeutic value for the management of depressive disorders **[32]** .*Rasayana Ghana* tablet (RGT) comprising three herbs, *Guduchi*(*Tinospora cordifolia Miers)*, aamalaki (*Emblica officinalis)* and *Gokshura* (*Tribulus terrestris Linn),* along with *ghee* and honey as vehicle is found to be having antidepressant and anxiolytic activity in experimental animals **[33]**.

3.4.2 Anxiolytic activity

In a study, 50% ethanolic extract of *Tinospora cordifolia* (TCE) was investigated for attenuation of the negative effects of sleep deprivation (SD) in rats .Three groups of adult Wistar female rats-(1) vehicle treated sleep undisturbed (VUD), (2) vehicle treated sleep deprived (VSD) and (3) TCE treated sleep deprived (TSD) animals were tested behaviorally for cognitive functions, anxiety and motor coordination. TSD animals showed improved behavioral response in Elevated Plus Maze (EPM) and Novel Object Recognition (NOR) tests for anxiety and cognitive functions, respectively as compared to VSD animals. TCE pretreatment modulated the stress induced expression of plasticity markers PSA- NCAM, NCAM and GAP-43 along with proteins involved in the maintenance of LTP i.e., CamKII-α andcalcineurin (CaN) in hippocamous and PC regions of the brain. Contrary to VSD, TSD animals showed down regulated expression of inflammatory markers such as CD11b/c, MHC-1 and cytokines along with inhibition of apoptotic markers. This data suggests that TCE alone or in combination with other memory enhancing agents may help in managing sleep deprivation associated stress and improving cognitive functions. 15 days of TCE administration to these animals prior to SD ameliorate the anxiety-like behavior and also restored the exploratory behavior of these animals [34].

3.5. *Brahmi* [35]

Latin Name- *Bacopa monnieri Linn.*
Family- Scrophulariaceae

Chemical Constituents

Steroidal saponins, bacoside A &B, bacopasaonins, herpestine, brahmine, flavonoids glycosides, betulic acid and phytosterols.

Properties and Action

Rasa : *Tikta, kasaya, Madhura*
Guna : *Laghu, Sara*
Virya : *Shita*
Vipaka : *Madhura*
Karma : *Vatahara, Kaphahara, Rasayana, Aayushya, Medhya, Matiprada, Svarya, Prajasthapana, Vishahara, Mohahara*

Formulations - *Sarasvatarista, Brahmi ghrita, Ratnagiri Rasa, Brahmi vati, Sarasvata churna ¸ Smritisagar Rasa*
Part used- Whole plant
Dose - 1-3 g in powder form.

3.5.1 Effect on Learning and Memory

In a study, *Brahmi Rasayana* (BR) was administered in a dose of 100 and 200 mg/kg p. o for eight days to both young and aged mice. Scopolamine (0.4 mg/kg i.p.) was used to induce amnesia in mice. Elevated plus maze and passive avoidance paradigm were employed to evaluate learning and memory parameters. The effect of BR on whole brain AChE activity was also assessed. Piracetam (200mg kg^{-1} i. p.) was used as a standard nootropic agent.BR significantly improved learning and memory in young mice and reversed the amnesia induced by both scopolamine (0.4 mg kg–1 i. p.) and natural aging. BR significantly decreased whole brain acetyl cholinesterase activity that proves it to be a potent memory restorative agent in the treatment of dementia [36].

3.5.2 Neuroprotective Effect

The ability of *Bacopa* to inhibit the release of proinflammatory cytokines from microglial cells, the immune

cells of the brain that participate in inflammation in the CNS was investigated. The effect of *Bacopa* on signaling enzymes associated with CNS inflammatory pathways was also studied. The tea, infusion, and alkaloid extracts of *bacopa*, as well as Bacoside A significantly inhibited the release of TNF-α and IL-6 from activated N9 microglial cells in vitro. In addition, the tea, infusion, and alkaloid extract of *Bacopa* effectively inhibited caspase 1 and 3, and matrix metalloproteinase-3 in the cell free assay. *Bacopa* inhibited the release of inflammatory cytokines from microglial cells and enzymes associated with inflammation in the brain. *Bacopa* can limit inflammation in the CNS, and offers a promising source of novel therapeutics for the treatment of many CNS disorders [37].

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by loss of dopaminergic neurons in substantia nigra region and the presence of α-synuclein aggregates in the striatum and surrounding areas of brain. Evidences suggest that neuroinflammation plays a role in the progression of PD. We examined the neuro-protective effects of *Bacopa monnieri* (BM) in regulating neuroinflammation. Administration of BM suppressed the level of pro-inflammatory cytokines, decreased the levels of α-synuclein, and reduced reactive oxygen species (ROS) generation in PD animal model. Pre-treatment of BM showed more prominent results as compare to co- and post-treatment. Results recommend that *Bacopa* can limit inflammation in the different areas of brain, thus, offers a capable cause of novel therapeutics for the treatment of many CNS disorders [38].

3.5.3 Anti Depressant Activity

A study examined the antidepressant like effect of methanolic extract of *Bacopa monniera* (MEBM) in all the classic models such as forced swimming test (FST),measurement of locomotor activity test (MLAT) and tail suspension test (TST), where it was found to possess significant antidepressant-like activity comparable to the standard drug imipramine hydrochloride. Findings demonstrated that the MEBM possesses antidepressant-like activity in the animal behavioral models [39]. Another study also investigated the antidepressant activity of *Bacopa monnierae* in rats with morphine mediated depression.The medicine was prescribed twice times for 8 successive days, at a dosage of 20–65 mg / kg. Forced swimming test (FST) was performed three days after last morphine administration to determine the drug's withdrawal effect. It was found that therapy with *Brahmi* was inhibiting the morphine-induced depression withdrawal effect [40].

The tea, infusion, and alkaloid extract of *bacopa*, as well as Bacoside A significantly inhibited the release of TNF-α and IL-6 from activated N9 microglial cells in vitro. In addition, the tea, infusion, and alkaloid extract of *Bacopa* effectively inhibited caspase 1 and 3, and matrix metalloproteinase-3 in the cell free assay. *Bacopa* inhibits the release of inflammatory cytokines from microglial cells and inhibits enzymes associated with inflammation in the brain. Thus, *Bacopa* can limit inflammation in the CNS, and offers a promising source of novel therapeutics for the treatment of many CNS disorders. *Bacopa* was found to significantly inhibit the release of IL-6 and TNF-α from LPS activated microglia and also notably inhibited the enzyme activity of MMP-3, and caspase 1 and 3. Thus, the study suggests that *bacopa* has the therapeutic potential for treating a wide range of CNS disorders that have a major neuroinflammatory component, including neurodegenerative diseases and psychiatric disorders such as depression, anxiety, and schizophrenia [41].

Behavioral experiments such as sucrose intake test, shuttle box escape test and open field test were used to examine the effect of *Brahmi* in depression. In rodents, stress was produced for 4 weeks. This resulted in decreased consumption of sucrose, locomotor activity and escape latency in the animals. In addition, both mRNA and protein content of brain derived neurotrophic factor (BDNF) showed down regulated expression in both the frontal cortex and hippocampus in chronic unpredictable stress (CUS) treated rats. Supplementation with *Brahmi* (80-120 mg/kg) greatly suppressed the behavioral changes and attenuated BDNF content to normal in the frontal cortex and hippocampus areas of the rat brain confirming its antidepressant activity [42].

A double blind, placebo-controlled clinical trial involving 17 healthy volunteers demonstrated acute effects of *Brahmi* (320 and 640 mg doses) on stress and mood swings developed by multitasking. *Brahmi* supplementation decreased stress as reported in those groups by decreasing cortisol levels and alleviating anxiety [43].

The methanol extract and different fractions of *Brahmi* were studied for antidepressant action in the forced swimming test (FST) and tail suspension test (TST) in mice. The results indicated that the methanol extract, ethanol and butanol fraction significantly reduced the immobility times both in FST and TST in mice after being administrated orally for 5 consecutive days. All tested samples, in the effective doses for FST and TST, showed no inhibitory effect against locomotor activity (LA) in mice [44].

3.5.4 Antioxidant Effect

Brahmi ameliorates the neuronal damage and physiological changes in rats upon smoke exposure. The group exposed the rats to smoke for 1h for 3 weeks and treated the animals with *Brahmi* with three different dosages *viz*., 10, 20, and 40 mg/kg body weight. This treatment quenched reactive oxygen species formed as a result of smoke exposure and normalized the pathological changes observed in rat brain. Also, the rate of acetylcholine esterase activity, lipid peroxidation and brain neurotransmitter levels were found to be normal upon *Brahmi* treatment. The herb also down regulated iNOS expression there by inhibited nitric oxide generation and HO-1 expression. Antioxidant enzyme concentration and monoamine oxidase action were also improved which were depleted upon smoke exposure [45] Oxidative stress generated by lead exposure is ameliorated by *Brahmi* in various areas of rat brain by virtue of its chelation and antioxidant property [46] Pretreatment of PC 12 cells with *Bacopa monniera* extract (BME) ameliorates the mitochondrial and plasma membrane damage induced by SNP (200µM) as evidenced by MTT and LDH assays. Also, BME pre treatment inhibited the generation of NO via down regulating iNOS expression. BME replenished the depleted antioxidant status induced by SNP treatment. SNP induced damage to cellular, nuclear and mitochondrial integrity was also restored by BME, which was confirmed by ROS estimation, comet assay and mitochondrial membrane potential assay respectively. BME pretreatment efficiently attenuated the SNP induced apoptotic protein biomarkers such as Bax, Bcl-2 cytochrome-c and caspase-3 which orchestrate the proteolytic damage of the cell. Q-PCR results further elucidated up-regulation of neuronal cell stress marker like HQ-1 and iNOS and down-regulated of BDNF upon SNP exposure was attenuated by BME pre-treatment. By considering all these findings, it is demonstrated that BME protects PC12 cells against SNP-induced toxicity via its free

radical scavenging and neuroprotective mechanism [47].
Brahmi also ameliorates decabrominated diphenyl ether (PBDE-209) provoked toxicity in neonate and young female mice. Different doses of *Brahmi* (40, 80, or 120 mg/kg) in combination with PBDE-209 (20 mg/kg body weight) were administered orally in mice from postnatal day 3 to day 10. Levels of oxidative stress indicators (malondialdehyde, and protein carbonyl) and antioxidant markers (superoxide dismutase and glutathione peroxidase) were measured. The results showed that the dose of 120 mg/kg of *Brahmi* restored the levels of oxidants and activities of antioxidant enzymes in the hippocampus and frontal cortex of neonates against PBDE-209-induced toxicity. This data suggests that *Brahmi* renders the brain resistant to PBDE-209 induced toxicity and thus may be better used as a preventive approach to protect against oxidative-mediated neuronal dysfunctions [48].

3.5.6 Anxiolytic Activity
Anxiety disorders are considered as one of the most prevalent psychiatric syndromes. They are associated with substantial impairments in both productive and social roles. Several clinical problems are associated with the anxiolytics being prescribed and therefore herbal medicines are being considered as an alternative to the complementary medicine. In the present study methanolic extract of *Centella asiatica* at the dose of 100, 200 and 400 mg/kg, (p.o) in male Sprague Dawley rats was studied for its anxiolytic property in widely accepted animals models *viz*. open field, elevated plus maze and hole board. The open field test marked increase in rearing, assisted rearing and number of square crossed and time spent in the center of arena. In the hole board test, enhanced time of head dipping and number of head dip in the treated animals was observed as compared to control. Similarly in elevated plus maze test, a marked increase in the number of entries and the time spent in open arms was noticed as compared to closed arms. Thus the results obtained indicate that *Centella asiatica* imparts potent anxiolytic activity [49].

35.6 Ashwagandha [50]
Latin Name-*Withania somnifera Dunal.*
Family-Solanaceae)

Chemical Constituents-
Withannolides A - Y, Dehydrowithanolide-R, Withasomniferin A, Withasomidienone, Withasomniferols A -C, Withaferin A, Withanone, Phytosterol, sitoindosides, B-sitosterol, ashwagandhine, cuscohygrine, tropine, pseudotropine, isopelletierine.

Properties and Action
Rasa : *Tikta, Kasaya*
Guna : *Laghu*
Virya : *Usna*
Vipaka : *Madhura*
Karma : *Rasayana, Vatakaphapaha, Balya, Vajikara*
Formulations - Asvagandhadyarista, Asvagandhadi Leha, Balasvagandha Lakshadi Taila
Therapeutic Uses - Sotha, Kshaya, Daurbalya, Vataroga, Klaibya
Part used – Root, leaves, fruit
Dose - 3-6 g of the drug in powder form

3.6.1 Neuroprotective Role
The review concludes the results of recent studies on *Ashwagandha* suggesting its extensive potential as neuroprotective in various brain disorders as supported by preclinical studies, clinical trials and published patents. However vague understanding of the mechanistic pathways involved in imparting the neuroprotective effect of *Ashwagandha* warrants further study to promote it as a promising drug candidate [51].
Research reports based largely on preclinical studies as well as few clinical trials have highlighted the neuroprotective role of *Ashwagandha* against many neurodegenerative diseases including Alzheimer's, Huntington's and Parkinson's disease. The protective effects of *Ashwagandha* were accomplished by restoring mitochondrial and endothelial function, mitigation of apoptosis, inflammation and oxidative stress mechanisms. In this review, we recapitulated neuroprotective properties of *Ashwagandha* extracts and/or its major constituents and discussed their mechanisms of action and potential therapeutic applications. The pre-clinical as well as clinical studies suggest the use of *Withania somnifera* (L.) against neurodegenerative disease. However, extensive studies are warranted to validate the use of extract or its single constituents for its clinical use [52].

3.6.2 Anti anxiety Effect
In this eight-week, prospective, randomized, double-blind, placebo-controlled study, the stress-relieving effect of *Ashwagandha* root extract was investigated in stressed healthy adults. Sixty male and female participants with a baseline perceived stress scale (PSS) score >20 were randomized to receive capsules of *Ashwagandha* extract 125 mg, *Ashwagandha* extract 300 mg or identical placebo twice daily for eight weeks in a 1:1:1 ratio. Stress was assessed using PSS at baseline, four weeks and eight weeks. Anxiety was assessed using the Hamilton-Anxiety (HAM- A) scale and serum cortisol was measured at baseline and at eight weeks. Sleep quality was assessed using a seven-point sleep scale. *Ashwagandha* is a medically important herb and has a proven impact on human health. The findings from this study suggest that eight weeks supplementation of aqueous *Ashwagandha* root extract was associated with a significant reduction of stress levels in individuals and improved the overall quality of life. Hence, the use of this herb as a supplement for stress and anxiety management could be an excellent alternative option. Further studies conducted with a larger cohort and in diverse populations and with more biochemical, physiological and psychological evaluation may confirm the present findings [53].

3.6.3 Anti stress effect
In this randomized, double-blind, placebo-controlled trial, the 60-day intake of an ashwagandha extract (Shodhen) in mild lyanxious, healthy adults resulted in significant emotional improvements over time. Compared with the placebo, *Ashwagandha* intake was associated with a statistically significant, greater reduction in the HAM-A, although changes in the DASS-21 failed to reach statistical significance, despite a strong positive trend. *Ashwagandha* intake was also associated with greater reduction in morning cortisol and DHEA-S; and a positive trend suggesting an increase in testosterone concentrations (the latter evidenced in men only). *Ashwagandha* was well tolerated with no significant reports of adverse events or changes in hematological measures (full blood count and lipid profile) over time. These findings suggest that *Ashwagandha's* stress-relieving effects may occur via its moderating effect on the hypothalamus-pituitary-adrenal axis [54].

The safety and efficacy of a high-concentration full-spectrum extract of *Ashwagandha* roots to reduce stress and anxiety was investigated on 64 subjects for 60 days with prospective, double blind, randomized, placebo-controlled design. In the study drug treatment group, each capsule contained 300 mg of high-concentration full spectrum extract from the root of the *Ashwagandha*. The treatment group exhibited a significant reduction ($P<0.0001$) in scores on all the stress-assessment scales compare to the placebo group. The serum cortisol levels were significantly reduced (P=0.0006) in the *Ashwagandha* group, in comparision to the placebo group. Findings suggest that a high-concentration full-spectrum *Ashwagandha* root extract safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life [55].

In another clinical trial, the effect of standardized *Withania somenifera* (WS) root and leaf extract (WSE) was evaluated in chronically stressed humans participants who were randomly assigned to WSE (125 mg QD, 125 mg BD, or 250 mg BID) or placebo groups. Stress levels were assessed at days 0, 30 and 60 using a modified Hamilton anxiety (mHAM-A) scale. Biochemical and clinical variables were measured at days 0 and 60. Between days 0 and 60 the WSE 125 mg QD group, significantly decreased the mean mHAM-A score, serum cortisol, serum C-reactive protein, pulse rate and blood pressure. The consumption of WSE significantly reduces experiential and biochemical markers of stress without adverse effects [56].

3.6.4 Effect on Memory

Withania somnifera's methanolic extract (50% menthol) and aqueous extract with honey and ghee was administered in a dose of 250 mg/kg in both control and stressed young and old rats. Both the extracts failed to reverse the stress-induced anxiety but traditional extract was found to be more active in memory enhancement than anxiolytic and antidepressant activity [57].

In a study, Withanoside IV (a constituent of WS; the root of WS) induced neurite outgrowth in cultured rat cortical neurons. Oral administration of withanoside IV significantly improved memory deficits in A beta-injected mice and prevented loss of axons, dendrites, and synapses. Sominone, an aglycone of withanoside IV, was identified as the main metabolite after oral administration of withanoside IV. Sominone induced axonal and dendritic regeneration and synaptic reconstruction significantly in cultured rat cortical neurons damaged by Abeta. Withanoside IV may ameliorate neuronal dysfunction in Alzheimer's disease and that the active principle after metabolism is sominone [58].

3.6.5 Nootropic activity

In a study *Ashwagandha* (*Withania somnifera L.*) root extract (50, 100 and 200 mg/kg; orally) were found to improve retention of a passive avoidance task in a stepdown paradigm in mice. Daily administration of *Ashwagandha* for 6 days significantly improved memory consolidation in mice receiving chronic electroconvulsive shock (ECS). *Ashwagandha*, administered on day 7 attenuated the disruption of memory consolidation produced by chronic treatment with ECS. On the elevated plus maze *Ashwagandha* reversed the scopolamine (0.3 mg/kg)-induced delay in transfer latency on day 1. On this basis it is suggested that *Ashwagandha* exhibits a nootropic like effect in naive and amnesic mice [59].

Table 1: Showing pharmacological actions of drugs

S. No.	Drug	Pharmacological Action
1.	*Yashtimadhu (Glycyrrhiza Glabra)*	• Neuroprotective Effect [5-7] • Anti Convulsant Effect [8] • Effect On Learning And Memory [9, 10] • Antidepressant Activity [11] • Antioxidant Activity [12]
2.	*Mandukaparni(Centella Asiatica Linn.)*	• Effect On Learning And Memory [13] • Antioxidant & Cognitive Action [14] • Decreasing Oxidative Stress [15] • Cognitive Effect [17] • Anxiolytic Effect [18]
3.	*Sankhpushpi (Convolvulus pluricaulis choisy)*	• Antidepressant Activity [19] • Neuroprotective Effect [20] • Antioxidant Activity [21, 22] • Nervine Tonic [23] • Nootropic Effect [24]
4.	*Guduchi (Tinospora Cordifolia)*	• Neuroprotective Activity [25-27] • Antidepressant Activity [28, 29] • Anxiolytic Activity [30]
5.	*Brahmi (Bacopa Monnieri Linn.)*	• Effect on Learning And Memory [31] • Neuroprotective Effect [32] • Anti Depressant Activity [33-38] • Antioxidant Effects [39-42]
6.	*Ashwagandha (Withania somnifera Dunal.)*	• Neuroprotective Role [43-45] • Anti Anxiety Effect [46] • Anti Stress Effect [47-49] • Effect On Memory [50, 51] • Nootropic Activity [52]

4. Conclusion

Adolescence is the transitional period of development between childhood and adulthood. During this period, various types of psychological problems are common leading to distress in them. Ayurveda provides list of nootropic drugs, known as *medhya rasayana*, like *Yashtimadhu*, *Shankhpushpi*,

Guduchi, *Brahmi*, *Ashwagandha* having neuroprotective, antidepressant, anti stress, anxiolytic effects which help to overcome these problems by their multifold approach. Present review reveals that Ayurveda *medhya rasayana* have the potential to ameliorate the psychological distress in adolescents and help them to lead a successful life. The evidences prove that these drugs can be used effectively in psychological well being of adolescents.

5. References

1. United Nations Population Fund. The power of 1.8 billion adolescents, youth and the transformation of the future. New York: UNFPA State of World Population 2014.
2. http://www.nimh.nih.gov/about/director/2011/the-global-cost-of mentalillness. html.
3. Charaka Samhita commentary by vidhyotini edited by Pandit Rajeshwar data Shastri, Charaka chikitsa Rasayan aadhyaya 1/3-30-31
4. Chaudhari K, Murthy ARV. Effect of rasayana on mental health-a review study. International Journal of Ayurveda and Alternative medicine 2014;2:1-7
5. The Ayurvedic pharmacopoeia of india, Government of India, Department of Indian system of medicine &homeopathy, II(79):227-229.
6. Luo L, Jin Y, Kim ID, Lee JK. Glycyrrhizin suppresses HMGB1 inductions in the hippocampus and subsequent accumulation in serum of a kainic acid-induced seizure mouse model. Cell Mol Neurobiol 2014;34:987-997.
7. Kim SW, Jin Y, Shin JH, Kim ID, Lee HK, *et al*. Glycyrrhizic acid affords robust neuroprotection in the postischemic brain via anti-inflammatory effect by inhibiting HMGB1 phosphorylation and secretion. Neurobiol Dis .2012;46:147-156.
8. Muralidharan P. Cerebroprotective effect of Glycirrhyza glabra Linn root extract onhypoxic rat. J Bangladesh Pharmacol Soc 2009;4(60):4.
9. [1]Chowdhury B, Bhattamisra SK, Das MC. Anti-convulsant action and amelioration of oxidative stress by *Glycyrrhiza glabra* root extract in pentylenetetrazole-induced seizure in albino rats. Indian J Pharmacol 2013;45:40-43.
10. Cui YM, Ao MZ, Li W, Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. Planta Med 2008;74:[377-380].
11. Chakravarthi KK, Avadhani R. Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: An experimental study. Journal of Natural Science, Biology and Medicine 2013;4(2)
12. Dhingra D, Sharma A. Antidepressant-like activity of *Glycyrrhiyza glabra* L. in mouse models of immobilitytests. Prog NeuropsychopharmacolBiol Psychiatry 2006;30:449-454.
13. Reddy KY. Review on effect of Yastimadhu (*Glycirrhiza glabra* Linn.) on natural memory enhancing drugs on dementia. Int JPhytopharm 2010;1:17.
14. The Ayurvedic pharmacopoeia of india. Government of India, Department of Indian system of medicine &homeopathy I, II(29):99-102,
15. Doknark S, Mingmalairak S, Vattanajun A, Tantisira B, Tantisira MH. Study of ameliorating effects of ethanolic extract of Centella asiatica on learning and memory deficit in animal models. J Med Assoc Thai 2014;97:2:S68-76. PMID: 25518178.
16. Prakash A, Kumar A. Mitoprotective effect of *Centellaasiatica* against aluminum-induced neurotoxicity in rats: possible relevance to its anti-oxidant and anti-apoptosis mechanism. Neurol Sci 2013;34:1403-1409
17. Orhan IE. *Centellaasiatica* (L.) Urban: From Traditional Medicine to Modern Medicine with Neuroprotective Potential. Evid Based Complement Alternat Med 2012, 946:259.
18. Xu MF, Xiong YY, Liu JK, Qian JJ, Zhu L *et al*. Asiatic acid, a pentacyclic triterpene in Centella asiatica, attenuates glutamate-induced cognitive deficits in mice and apoptosis in SH-SY5Y cells. Acta Pharmacol Sin. 2012;33:578-587.
19. Mohandas Rao KG, Muddanna Rao S, Gurumadhva Rao S. *Centella asiatica* (L.) leaf extract treatment during the growth spurt period enhances hippocampal CA3 neuronal dendritic arborization in rats. Evidence-based complementary and alternative medicine 2006;3(3):349-357
20. Wijeweera P, Arnason JT, Koszycki D, Merali Z. Evaluation of anxiolytic properties of Gotukola--(Centella asiatica) extracts and asiaticoside in rat behavioral models. Phytomedicine 2006;13(9, 10):668-76
21. The Ayurvedic pharmacopoeia of india. Government of India, Department of Indian system of medicine &homeopathy I, II(66):218 219.
22. Dhingra D, Valecha R. Evaluation of the antidepressant-like activity of Convolvulus pluricaulis choisy in the mouse forced swim and tail suspension tests. Med Sci Monit 2007;13(7):155-61.
23. Bihaqi SW, Sharma M, Singh AP, Tiwari M. Neuroprotective role of Convolvulus pluricaulis on aluminium induced neurotoxicity in rat brain. J Ethnopharmacol 2009;30:124(3);[409-15].
24. Verma S, Sinha R, Kumar P, Amin F, Jain J, Tanwar S. Study of Convolvulus pluricaulis for antioxidant and anticonvulsant activity. Cent Nerv Syst Agents Med Chem 2012;12(1):55-9.
25. Nag G, De B Antioxidant and Acetylcholinesterase Inhibitory Properties of the Indian Medicinal Plant "Shankhapushpi" Used for Enhancing Memory Function, Journal of Complementary and Integrative Medicine 2006;5(1):3840-1158.
26. Sethiya NK, Nahata A, Mishra SH, Dixit VK. An update on Shankhpushpi, a cognition-boosting Ayurvedic medicine 2009;(7):1001-1022.
27. Amin H, Sharma R, Vyas H, Vyas M, Prajapati PK, Dwivedi R. Nootropic (medhya) effect of Bhāvita Śaṇkhapuṣpī tablets: A clinical appraisal. Ancient Sci Life 2014;(34):109-12.
28. The Ayurvedic pharmacopoeia of india. Government of India, Department of Indian system of medicine &homeopathy part I, I(27):70-72.
29. Kosaraju J, Chinni S, Roy PD, Kannan E, Antony AS *et al*. Neuroprotective effect of Tinospora cordifolia ethanol extract on 6-hydroxy dopamine induced Parkinsonism. Indian J Pharmacol 2014;(46):176-180.
30. Sharma A, Singh G. Tinospora Cordifolia as a Potential Neuroregenerative Candidate Against Glutamate Induced Excitotoxicity: An *in vitro* Perspective. BMC Complement Altern Med 2018;18(1):268.
31. Sharma A, Kalotra S, Bajaj P, Singh H, Kaur G. Butanol Extract of Tinospora Cordifolia Ameliorates Cognitive Deficits Associated With Glutamate-Induced Excitotoxicity: A Mechanistic Study Using Hippocampal

Neurons 2020;22(1):81-99.
32. Dhingra D, Goyal PK. Evidences for the Involvement of Monoaminergic and GAB Aergic Systems in Antidepressant-like Activity of Tinosporacordifolia in Mice. Indian J Pharm Sci. 2008;(70):761-767.
33. Deole Y, Chavan SS, Ashok K, Ravishankar B, Thkar AB, Chandola HM. Evaluation of anti depressant and anxiolytic activity of Rasayaana Ghana Tablet (A compound Ayurvedic formulation) in albino mice .Ayu. 2011;32(3):375-379.
34. Mishra R, Manchanda S, Gupta M, Kaur T, Saini V, Sharma A *et al*. Tinospora cordifolia ameliorates anxiety-like behavior and improves cognitive functions in acute sleep deprived rats. Scientific Reports 2016;(6):255-64
35. The Ayurvedic pharmacopoeia of India. Government of India, Department of Indian system of medicine &homeopathy part I, I(11):44-46.
36. Joshi H, Parle M. Brahmi rasayana Improves Learning and Memory in Mice. Evid Based Complement Alternate Med 2006;3(1):79-85.
37. Michelle D, Nemetchek I, Andrea A Stierle, Donald B Stierle, Diana I Lurie. The Ayurvedic plant *Bacopa Monnieri* inhibits inflammatory pathways in the brain. J Ethnopharmacol 2017;02(197):92-100.
38. Singh B, Pandey S, Rumman M, Mahdi AA. Neuroprotective effects of *Bacopa monnieri* in Parkinson's disease model. Metab Brain Dis. 2020;35(3):517-525.
39. Antidepressant-like effects of methanolic extract of *Bacopa monniera* in mice Abdul Mannan, Ariful Basher Abir and Rashidur Rahman BMC Complement Altern Med 2015;(15):337.
40. Rauf K, Subhan F, Abbas M, Ali SM, Ali G, Ashfaq M *et al*. Inhibitory effect of bacopasides on spontaneous morphine withdrawal induced depression in mice. Phytother. Res 2014;(28):937-939.
41. Nemetchek, Stierle MD, Stierle AA, DB, Lurie DI. The Ayurvedic plant *Bacopa monnieri* inhibits inflammatory pathways in the brain. Journal of ethnopharmacology. 2017;(197:92):100.
42. Banerjee R, Hazra S, Ghosh Mondal, AK, Chronic AC. administration of *bacopa monniera* increases bdnf protein and mrna expressions: a study in chronic unpredictable stress induced animal model of depression. Psychiatry Invest 2014;(11):297-306.
43. Benson S, Downey LA, Stough C, Wetherell M, Zangara A, Scholey A. An acute, doubleblind, placebo controlled crossover study of 320 mg and 640 mg doses of *bacopa monnieri* (cdri 08) on multitasking stress reactivity and mood. *Phytother. Res* 2014;(28):551-559.
44. Shen YH, Zhou Y, Zhang C, Liu RH, Su J, Liu XH *et al*. Antidepressant effects of methanol extract and fractions of *Bacopa monnieri*. Pharmaceutical Biology 2009;47(4):340-343.
45. Pandareesh M, Anand T. Attenuation of smoke induced neuronal and physiological changes by bacoside rich extract in wistar rats via down regulation of ho-1 and inos. *Neurotoxicology* 2014;(40):33-42.
46. Velaga MK, Basuri CK, Robinson Taylor, Yallapragada KS, Rajanna PR Rajanna S *et al* effects of *bacopa monniera* on lead-induced oxidative stress in different regions of rat brain. Drug Chem. Toxicol 2013;(37):357-364.
47. Pandareesh MD, Anand T. Neuroprotective andanti-apoptotic propensity of *bacopa monniera* extract against sodium nitroprusside induced activation of inos, heat shock proteins and apoptotic markers in pc12 cells. *Neurochem. Res.* 2014;(39):800-814.
48. Verma P, Singh P, Gandhi BS. Neuromodulatory role of *bacopa monnieri* on oxidative stress induced by postnatal exposure to decabromodiphenyl ether (pbde-209) in neonate and young female mice. Iran. J. Basic Med. Sci 2014;(17):307.
49. Chandra J, Joshi H, Bahuguna P, Shanker K, Kumar R. Experimental studies on Centella asiatica for anxiolytic activity in rats.Scholars Academic Journal of Biosciences (SAJB) ISSN 2321-6883.
50. The Ayurvedic pharmacopoeia of india Government of India, Department of Indian system of medicine &homeopathy I, I(10):32-33.
51. Zahiruddin S, Basist P, Parveen A, Khan W, Ahmad G S. Ashwagandha in brain disorders: A review of recent developments. Journal of Ethnopharmacology Elsevier 2020;257(15):112876.
52. Dar NJ, Ahmad M. Neurodegenerative Diseases and *Withania Somnifera* (L.): An Update.J Ethnopharmacol 2020;(30):256:112769.
53. Salve J, Pate S, Debnath K *et al*. Adaptogenic and Anxiolytic Effects of Ashwagandha Root Extract in Healthy Adults: A Double-blind, Randomized, Placebo-controlled Clinical Study. Cureus 2019;11(12).
54. Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract A randomized, double-blind, placebo controlled study Lopresti *et al*. Medicine 2019;(98):37.
55. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration fullspectrum extract of Ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med 2012;(34)255-62.
56. Auddy B, Mitra A Hazra J. A standardized WS extract significantly reduces stress related parameters in chronically stressed humans: A double blind, Randomized, Placebo-controlled study. JANA, 2008;2:8.
57. Ramanathan M, Srinivasan J, Saravanbabu C, Viswanad B, Suresh B. Indian J Pharm, Sci 2003;65(6)601-604.
58. Zhao, Nakamura N, Hattori M, Kuboyama T, Tohda C, Komatsu K. Withanolide derivatives from the roots of *Withania somnifera* and their neurite outgrowth activities. Chem. Pharm. Bull. (Tokyo) 2002;50(6):760-765.
59. Dhuley JN. Nootropic-like effect of Ashwagandha (*Withania Somnifera* L.) in mice. Phytother. Res. 2001;15(6):524-528.