

# Role of Medicinal Plants in Neurodegenerative Diseases

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**Abstract :** Neurodegenerative disease are characterized by severe memory loss, unusual behaviour, personality changes, and a decline in cognitive function. No definitive cure for most of these diseases exist, even though they are life threatening and the drugs presently available to treat these diseases have limited efficacy. Herbal medicines have attracted considerable attention in recent years, especially for treatment of neurodegenerative disorders. This review summarizes the role of natural plant compounds and herbal formulations investigated in animal models and clinical investigations for treatment of neurological diseases. The relevant compounds and herbal extracts with CNS activities have been listed and pharmacological activities have been included. These herbal medicines can be an alternative and a valuable source for future neurodegenerative drug discovery. Some of the plant species in these genera and families may be the most promising candidates for further investigation and require serious consideration in clinical trials. Active components in some of the herbal extracts are not clearly known and the compatibility law of herbal formulations remains to be further investigated. The unique ways of Ayurveda to cross the blood brain barrier and deliver the plant extracts at the site of defect have also been given attention in this review.

## INTRODUCTION

Herbs, which have always been the primary source of medicines in developing countries, are once again resurfacing throughout the developing and developed world. Statistics show that people not only in India but in Europe, North America and Australia are also consulting trained herbal professionals and using the plant medicines that were taken by ancestors, centuries ago. In India natural compounds have always been used as medicines. Traditional therapies have now been backed by scientific evidence and have given these plant compound credibility<sup>1</sup>. Being very different from the Allopathic system of medicine, Ayurveda-based drug discovery uses 'reverse pharmacology', in which drug are first identified based on large-scale use in the population, then validated in clinical trials. This approach reduces the time for drug discovery by almost a decade, and much less than the usual cost. Neurological disorders especially the ones involving degeneration have found very few cures in the Allopathic system of medicine. Hence these plants compounds are being focused again to look for agents which can reverse or halt if not cure many of the neurodegenerative disorders.

Ancient Ayurveda texts extensively deal with the nervous system and disorders associated with it. Nervous system disorders, called 'VataVyadhi' in Sanskrit, were thought to be brought on by imbalances of Vata, the biological air humour, the energy that moves through the brain and the nerves controlling both voluntary and involuntary functions. Hence, Vata derangements always include weakness, disturbance, or hypersensitivity of the nervous system. Included in these texts are direct mentions of age-associated memory loss, preventive care, and therapeutic interventions<sup>2</sup>. Apoptosis (programmed cell death) along with oxidative stress have been reported as pathological cause for aging and neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Multiple Sclerosis (MS) and Amyotrophic lateral sclerosis (ALS). Neurodegeneration is also caused by genetic and environmental factors. Oxidative stress and free radical generation catalyzed by redox metals have been shown to play crucial role in regulating redox reactions in vivo contributing RNS and ROS, main culprits in neurodegeneration<sup>3</sup>. A classic example which is also widely prevalent in geriatric population is Alzheimer's disease (AD). AD is a typical disorder of neurodegenerative disease seen as a progressive inexorable loss of cognitive function along with the presence of senile plaques in the hippocampal area of the brain. Memory loss, forgetting names, loss of recent memory results in frustration, hostility, and irritability which are common emotional features exhibited by patients with AD. In severe cases, patients pass urine and stools in bed, memory is completely lost, and there is no sense of time and place. Patients become totally dependent upon others and finally need comprehensive care in hospitals and by another person at home. Herbal medicine offers several options to modify the progress and symptoms of such disorders. Hence presented below is a comprehensive review of various plant compounds which have the ability to retard the progress of various life threatening neurodegenerative

diseases.

## ASHWAGANDHA (*WITHANIASOMNIFERA*)

Ashwagandha has been commonly used in Ayurvedic formulations as a nerve tonic, aphrodisiac, and 'adaptogen' and helps the body fight stress. Ashwagandha is a member of the Solanaceae family, and the root is the part that is widely used. The roots extract is called a Rasayana (rejuvenative) and is believed to possess antioxidant activity, free radical scavenging activity, and is thought to give a healthy immune system<sup>4</sup>. Ashwagandha has a calming effect in people with agitation and hence may be useful in patients with neurodegenerative diseases. An extract of Ashwagandha root produces a calming effect on the central nervous system (CNS) in experimental animals, and hence is a potential calming agent. A recent double-blind, randomized, placebo controlled study using 500mg of the root extract of Ashwagandha on stress showed it to be useful in stress as well as memory preservation<sup>4</sup>. Ashwagandha contains several steroidal compounds such as the ergostane-type steroidal lactones, including Withanolides A to Y, dehydroWithanolide R, Withasomniferin A, Withasomnidienone, Withasomniferols A to C, Withaferin A, and Withanone. One of these Withanolides, is a very effective free radical scavenger and shows positive effects in several neurodegenerative diseases. It also preserves neuronal cells longevity<sup>5</sup>. Aqueous extracts of this herb have been found to increase cholinergic activity, including increases in the acetylcholine content and cholineacetyl transferase activity in rats and this might partly explain the cognition-enhancing and memory-improving effects. Dendritic regeneration is hastened in neurons as shown by the levels of two dendritic markers, MAP2 and PSD-95, with Ashwagandha, suggesting that it stimulates dendrite formation. Oral administration of a semipurified extract of the Ashwagandha root reversed behavioural deficits, plaque load, and accumulation of beta-amyloid peptides in mouse models of AD. In summary Ashwagandha has been found to be helpful in patients with paralysis, anxiety, memory loss, weakness all of which are seen in neurodegenerative diseases.

## BRAHMI (*BACOPAMONNIERI*)

Brahmi (also known as Bacopamonnieri, BM) is a bitter-tasting creeper plant found in damp and marshy areas and is grown all over India especially in Kerala and is commonly used in Ayurvedic medicine. It is as a nerve tonic, diuretic and strengthens the heart. It is also used as a drug for treatment of epilepsy, sleeplessness, asthma, and bone and joint pains<sup>6</sup>. The main constituents of this plant are Saponins and triterpenoid Bacosaponins that include bacosides A and B, bacosides III to V and bacosaponins A, B and C. Other Saponin glycosides include the Jujubogeninbisdesmosides bacosaponins D, E and F. Antioxidant constituents include alkaloids, plant sterols, Betulic acid, polyphenols, and sulfhydryl compounds<sup>7</sup>. Thus, BM could act by reducing divalent metals, scavenging reactive oxygen species, inhibiting lipoxigenase activity and decreasing the formation of lipid peroxides. Traditionally, BM was used to improve memory and cognitive function. The extract of the plants have been tried extensively for their effects on the neurological disorders<sup>8</sup>. Memory loss due to aging has been shown by the effect of the drug on the hippocampus, by increasing protein kinase activity that gives it the nootropic action. In rodent model BM also inhibited cholinergic degeneration and resulted in better cognitive functions<sup>9</sup>.

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BM extracts protected neurons from beta-amyloid-induced cell death by suppressing cellular acetylcholinesterase activity. A team of researchers also reported that a standardized extract of BM reversed the cognitive deficits induced by intracerebroventricularly administered colchicines and ibotenic acid into the nucleus basalis magnocellularis. In the same study, BM also reversed the (a) depletion of acetylcholine, (b) reduction in choline acetyltransferase activity, and (c) decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus<sup>9</sup>. In addition, BM extract-treated neurons expressed a lower level of reactive oxygen species, suggesting that Brahmi restrained intracellular oxidative stress. BM has now been introduced in the Indian market for treatment of memory and attention deficit disorders. One study at Michigan showed thyroid disorder with its use hence it may be best to monitor thyroid function while using it<sup>10</sup>.

### SHANKHPUSHPI (*CONVOLVULUS PLURICAULIS*)

There are several species for Shankpushpi, including *Convolvulus pluricaulis* (CP), *Convolvulus microphyllus*, *Evolvulus alsinoides* and *Clitoria ternatea* (CT), which have shown medicinal properties. *Convolvulus pluricaulis* is a perennial herb that seems like morning glory. The herb is known to possess therapeutic benefits. The main reason for its popularity comes from its excellent results in treatment of insomnia effectively. It is believed to be the only herb that is capable of enhancing all the aspects related to cognitive function like learning, memory and the ability to recall. A wide range of secondary metabolites, including flavonol glycosides, triterpenoids, anthocyanins, and steroids, has been isolated and may be responsible for Shankpushpi's cognition and memory improving properties in addition to other pharmacological activities<sup>11</sup>. Regulation of stress hormones like adrenalin and cortisol is believed to be the reason behind Shankpushpi soothing effect on the nerves. It is recommended for nervous disorders such as anxiety, mental fatigue, stress and insomnia. The ethanolic extract of CP lead significantly improvement in learning and memory in rodent models<sup>12</sup>. The ethanolic extract of CP also possesses significant antioxidant activity when tested. The effect was incremental with increase of dose. Similarly, administration of CP extracts for 7 days enhanced memory in aged mice drastically. The same effect has been seen in monkey model of neurodegenerative disorders. Learning and memory functions are part of hippocampal region and showed a dose-dependent increase in acetylcholine esterase activity<sup>13</sup>. Specifically, administration of aqueous root extract of CT to neonate rats led to an improved spatial learning performance and retention, showing the memory-improving property of CT. In addition, a significant surge in acetylcholine content was observed in the hippocampi of CT-treated rats when compared with age-matched controls. Increase in acetylcholine in the hippocampus may be the basis for their improved learning and memory. Young adult rats fed with aqueous root extract of CT showed a stark increase in passive learning and retention. All this resulted in a significant increase in dendritic intersections, branching points, and dendritic processes arising from the soma of neurons in the amygdala region of CT-treated rats<sup>14</sup>. The extract of the plant slows the progress but not reverse disease. Several other diseases benefit by the plant extract, such as high or low blood pressure, anxiety neurosis, stress and mood disorders. It also works as psycho-stimulant and tranquilizer and a mental booster. *Convolvulus pluricaulis* is a brain tonic used to treat nervousness, insomnia, memory loss and both mental and physical fatigue.

### TURMERIC (*CURCUMA LONGA*)

Turmeric is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae. It is a tropical plant. Made from the rhizome and root, turmeric is used as a spice and colouring agent and in traditional medicine in Asia. The active constituents are thought to be turmerone oil and watersoluble curcuminoids, including curcumin<sup>15</sup>. It is commonly used as anti-inflammatory, antiseptic, and antibacterial for treating wounds both open and closed and has been used in the Indian system of medicine since a very long time to treat a variety of conditions both as a topical application and by mouth as well. This versatile spice helps detoxify the liver, balance cholesterol levels, fight allergies, stimulate digestion, and boost immunity. Epidemiologic studies show a 4.4-fold lower incidence of AD in Southeast Asian countries where turmeric is commonly used as a dietary spice<sup>16</sup>. Other studies indicate that the non-steroidal anti-inflammatory property of turmeric is associated with a reduced risk of AD. When orally given to aged mice with advanced plaque deposits as those seen in cases of AD, curcumin reduced the amount of plaque deposition, cascades involved in neuritic

plaque pathogenesis. Curcumin's ability to inhibit lipid peroxidation and neutralize reactive oxygen species is documented to be much superior to that of vitamin E<sup>17</sup>. Toxicity studies were conducted by the National Cancer Institute by administering turmeric oleoresin (organic extract of turmeric) in feed to groups of male and female rats and mice for 13 weeks and 2 years. No toxicities were reported<sup>18</sup>. Owing to the promising findings in animal models has prompted clinical trials of oral curcumin supplementation in patients with early AD. In a trial on humans the results of a six-month randomized, placebo controlled, double-blind, clinical trial of curcumin in 27 patients with AD found that oral supplementation with up to 4 g/day of curcumin not reported with any significant side effects<sup>19</sup>.

### GINKGO BILOBA

**Ginkgo** a unique of tree with no close living relatives is also known as the maiden tree. The ginkgo is a living fossil, recognisably similar to fossils dating back 270 million years. It is a tree native to China, but tree is grown all over. It is source of food and has various uses in ayurvedic system of medicine. Ginkgos are large trees (115-164 feet). Young trees are often tall and in trunked, but has few branches. The crown becomes broader as the tree ages. The ginkgos so resistant can be seen in Hiroshima, Japan, where six trees growing from 1–2 km from the 1945 atom bomb explosion were among the few living things in the area to survive the blast. All other life in the area was destroyed, but Ginkgos, despite being charred, survived and were soon healthy again and are alive to this day.

Early pharmacological studies revealed that Ginkgo biloba leaf specific flavonoids modulated the contractile functions of vascular smooth muscles, hence scientists subsequently made efforts to obtain a well standardized extract enriched in flavonoids. This extract is now often referred to as EGB 761. In the 1990s, almost all preclinical and clinical studies with this plant reported, were conducted with this extract only but it was soon realized though that flavonoids cannot be the sole therapy relevant bioactive constituents and that its clinical efficacy or pharmacological activity is not easily interpretable in terms of its effects on blood vessels only. Although, during the past two decades, the extracts from Ginkgo have remained the most well studied herbal remedies which have been commercialized to date in the developed world. However many questions regarding the active ingredients and the mode of action are yet to be clearly answered. Dementia as seen in Alzheimer's disease, as also in vascular dementia, is where the most important indication for Ginkgo biloba extract (EGb). The clinical efficacy of this extract is due to its neuroprotective metabolic and its effects on blood rheology. Some other studies also confirmed the role of Ginkgo biloba its benefits in some other forms of dementia and other memory disorders<sup>20</sup> [20]. Although our current knowledge on the active constituents and modes of actions of Ginkgo extracts remain far from being satisfactory, existing preclinical and clinical evidences available now are in agreement with the conviction that more than one active constituent and mode of action is involved in its observed clinical effects, and that the activity profile of a given Ginkgo extract cannot be predicted by the knowledge of its already known or proposed bioactive constituents only. Of the several known neuro active constituents of Ginkgo biloba leaf extracts, bilobalide is a unique, structurally and also pharmacologically. Although much has been published on the pharmacological properties of ginkgolides, by far the vast majority of them deal with their platelet active factor (PAF) antagonistic activity and that too with that of ginkgolide B only. Because of its role in function of platelets one of the side effects reported has been intracranial bleeding.

### JATAMANSI (*NARDOSTACHYS JATAMANSI*)

Jatamansi as a plant has a rich history of medicinal use and is used extensively in the Ayurvedic system of medicine. The rhizomes and roots of the plant have medicinal value and, therefore, have been the focus of chemical studies. They contain a variety of sesquiterpenes and coumarins. The sedative sesquiterpenevalerone, is a major component of the roots essential oil. Other terpenoids include spirojatamol, nardostachysin, jatamols A and B, and Calarenol. Jatamansi is the predominant coumarin. Studies on its role in the CNS revealed that extracts of *Nardostachys jatamansi* (NJ) alleviated all of the symptoms of chronic fatigue syndrome (CFS) in rats. As is seen in CFS the increase in lipid peroxidation, nitrite, and superoxide dismutase levels, and low catalase levels were all reversed by NJ extracts. This is due

to the powerful antioxidant property of NJ. Similarly, when an alcoholic extract of this plant was administered to both young and aged mice it significantly improved learning and memory and also reversed the amnesia induced by diazepam and scopolamine. In some other studies it reversed aging-induced memory loss due to the natural aging of mice, which suggests that the medicinal substrates in this plant may prove to be useful in restoring memory in older individuals as well as in patients with age-associated dementia<sup>21</sup>.

## GUGGULU

Guggulu is an oleogum resin exuding from the cracks and fissures in the bark or from incisions from several different plant species, including *Commiphoramukul*, *C. molmol*, *C. abyssinica*, *C. burseraceae*, and *C. whightii*. The oleogum resin of guggulu is a mixture of 30% to 60% water-soluble gum, 20% to 40% alcohol-soluble resins and about 8% volatile oils. There are several water-soluble constituents include mucilage, sugars, and proteins and also alcohol-soluble substances include the commiphoric acids, commiphorinic acid, and the heerabomyrrhols. Guggulu also contains ferulic acids, phenols, and other non-phenolic aromatic acids that are potent scavengers of superoxide radicals and could potentially be of importance for the treatment of Parkinson's disease and Alzheimer's disease and other oxidative stress-related disease<sup>22</sup>. The resin of the gum has been used for thousands of years in the treatment of arthritis, inflammation, obesity, and disorders of lipid metabolism. In several animals and human trials administration of guggulipid is reported to significantly lower both serum LDL cholesterol and triglyceride levels. Guggulu is an effective antagonist of the bile acid receptor farnesoid X receptor which seems the mechanism of action for its lipid lowering activity. Epidemiologic and biochemical data suggest a link between cholesterol, Parkinson's disease and AD. These studies indicate that there is a decreased prevalence of AD associated with the use of cholesterol-lowering drugs. Fall in neuronal cholesterol levels, in turn, inhibit the beta amyloid-forming amyloidogenic pathway, possibly by removing APP from cholesterol and sphingolipid-enriched membrane microdomains. Lowering of cholesterol may influence the progression of AD. Guggulipid has a significant protective effect against the streptozotocin-induced memory deficit model of dementia; the effect can be attributed to its cholesterol-lowering, antioxidant, and anti-acetylcholine esterase activity. These observations suggest Guggulipid as a potential anti-dementia drug.

## HYPERICUM PERFORATUM (ST JOHN'S WORT)

Scientist in Germany resulted current interest in the use of *Hypericum perforatum* (HP) for the treatment of mental health conditions. Low grade depression can benefit by the HP extracts as imipramine and that HP extracts were better tolerated by the patients than many synthetic antidepressants, extensive efforts were initiated in many German industrial and academic laboratories. Hyperforin, a prenylated chloroglucinol present in this plant, has been focused on as being primarily responsible for the antidepressant activity of HP<sup>23</sup>. Several studies in humans and animals have confirmed the antidepressant activity of hyperforin. Indian *Hypericum perforatum* (IHP) extract standardized for hyperforin lacked Monoamine Oxidase (MAO)-A and B inhibitory activity. In many animal models IHP showed antidepressant, anxiolytic, anti-amnesic, anti-inflammatory and analgesic and anti-stress activities. Some researchers recently found that HP had neuroprotective effects and diminished cognitive impairment and improved spatial learning and memory. The current widespread medicinal uses of HP extracts concentrate mainly on their therapeutic effects in patients with mild to moderately severe depression, and that too with hydro-alcoholic extracts only. The very first report on the efficacy of such an extract dates back much earlier than the fortuitous discovery of these effects of the synthetic tricyclic antidepressant imipramine or the MAO inhibitor iproniazide. HP has an excellent safety profile clearly superior to many conventional antidepressants. Photosensitivity and mania are two potentially serious adverse effects. Both side effects are seen very rarely and seem to reverse after stopping the extract. All properly controlled clinical trials of various types using HP extracts in patients with mild to moderately severe depression have all with consistency shown efficacy and a very high safety margin, and that it has no interaction with other medications, the extract can be considered as one of the safest known psychotherapeutic agents with proven clinical efficacy according to the modern concept of 'evidence based medicine'.

## GOTU KOLA (CENTELLAASIATICA)

*Centella asiatica*, is a small, herb annual plant of the family Mackinlayceae or subfamily Mackinlayoideae of family Apiaceae, and is native to India, and other Asian countries. It is used as a medicinal herb in Ayurvedic system. *Centella asiatica* grows in tropical swampy areas. The stems are slender, creeping stolons, green to reddish-green in colour, connecting plants to each other. The plant has long-stalked, green, reniform leaves around 2 cm with rounded apices which have smooth texture with palmate netted veins. The rootstock consists of rhizomes, growing vertically down. They are cream in colour and covered with root hairs. In the Ayurvedic system of medicine, gotu kola is one of the important rejuvenating herbs for nerve and brain cells and is believed to be capable of increasing intelligence, longevity, and memory<sup>24</sup>. The mechanism of action of the asiaticoside derivatives, including asiatic acid and asiaticoside, is believed to be by reducing hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death in vitro, suggesting a possible role for gotu kola in the treatment and prevention of AD and beta-amyloid toxicity. Gotu kola extracts reversed the beta-amyloid pathology in the brains of mice and improved the components of the oxidative stress response.

## JYOTISHMATI (CELASTRUS PANICULATUS)

*Celastrus paniculatus* is commonly also known as black oil plant, climbing staff tree, and intellect tree. Oil from the seeds is used as a traditional medicine. *C. paniculatus* is a deciduous vine with stems up to 10 centimetres in diameter and 6 meters long with rough, pale brown exfoliating bark covered densely with small, elongated lenticels. The leaves are simple, broad, and oval, obovate or elliptic in shape, with toothed margins. The plant is a climbing shrub found all over India.

The seeds contain fatty acids and alkaloids, having sedative and antidepressant actions. In Ayurvedic system the seeds are used to sharpen the memory and the oil of the seed is found to work as a tonic for memory loss attributed to its neuroprotective actions. A study in rats suggested that the aqueous extract of seed has dose-dependent activity, thereby leading to improvement of memory performance in rats<sup>25</sup>.

Jyotishmati is a long used medicinal plant that is known for ages for its effects on the brain and has been used in Ayurveda for sharpening the memory and improving concentration and cognitive function. Aqueous extracts of CP seeds have cognition-enhancing properties and antioxidant properties. CP extracts protected neuronal cells against H<sub>2</sub>O<sub>2</sub>-induced toxicity because of their antioxidant properties and their ability to induce antioxidant enzymes. CP extracts also protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function.

## PIPER METHYSTICUM (KAVA KAVA)

*Piper*, the pepper plant or pepper vines are important genus in the family Piperaceae and are both economical and medicinally significant. It contains about 1,000-2,000 species of shrubs, herbs, many of which are flourishing in their native habitat. *Piper methysticum* also called kava, continues to occupy a central place in everyday life in the Polynesian islands concerned. The first pharmacological evaluation of the kava pyrones was published in Lewin's admirable monograph. Kava has been shown to induce sleep from which subjects awake fully with no residual effects. Several preclinical or placebo-controlled double blind trials by many researchers demonstrated Kava's effectiveness in anxiety disorders and enhancing sleep quality<sup>26</sup>. One study investigated the acute effects of the herbal anxiolytic Kava-kava on emotional reactivity and cognitive performance through a double-blind randomized placebo-controlled trial involving healthy volunteers. The results of this study indicate that the mood-elevating effects of Kava were most prominent in cheerful subjects, indicating that trait cheerfulness moderated the drug-induced increase in cheerful mood<sup>27</sup>. Based on several tests Kava was shown to improve the accuracy and the speed of performing the partial report and the item recognition task, showing a beneficial effect of the phytopharmakon on visual-blind studies attention and short-term memory retrieval. Unlike conventional benzodiazepine-type anti-anxiety drugs, which tend to impair cognitive performance and to increase the occurrence of negative affective states, Kava is a potent anxiolytic agent, also can facilitate cognitive functioning and can increase positive effect on mood leading to exhilaration. Kava products are available all over in the USA in many health food stores, Polynesian grocery stores, and also in mass market outlets. Kava had rapidly gained popularity as a result of its reputed lack

of addictive properties, legal availability and claims by various authors (it induces 'deep restful sleep and clear, epic-length dreams', 'enhances psychic powers and visions' and 'relieves insomnia and nervousness' and because earlier it has been recognized by European health authorities as a relatively safe remedy for anxiety. Kava-kava is a well-established sleep inducing drug. It's also beneficial as an add-on therapy for drug resistant epilepsy have been demonstrated in several clinical trials, and its preclinical activity profile revealed that in addition to anticonvulsant activity it possessed a broad range of therapeutically interesting CNS function modulating properties. Toxicological and clinical studies have shown that kava extracts are virtually devoid of toxic side effects with the exception of the rare liver related side effects reported in some patients.

## CAMELLIA

*Camellia sinensis* is used as commonly available tea. The leaves of the plant are used to produce the popular beverage tea. It is of the genus of flowering plants in the family Theaceae. Depending on the oxidation state White tea, yellow tea, Green tea, black tea are all made from this species. Kukicha (twig tea) is also harvested from the plant, but uses twigs and stems rather than leaves. Common names include tea plant, tea shrub, and tea tree. Green tea is the product derived from the leaves of *Camellia sinensis* (Theaceae). Various health benefits, including anti-cancer potential, effects on cholesterol levels, antibacterial properties and positive effects for weight loss are all reported in recent medical research on tea (most of which has been on green tea). It is considered to have many positive health benefits due to tea's high levels of antioxidants of Catechins. A recent study indicated that the intake of Chinese and Japanese teas can reduce risk of Parkinsonism and Alzheimer's disease, such as oolong tea and green tea<sup>26</sup>. Green tea extracts can attenuate 6-OHDA-induced nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation and cell death. Polyphenolic Catechins derived from green tea have protective effects on neuronal cells and the rat model of PD through inhibition of ROS-nitrogen monoxide (NO) pathway, iNOS expression and cell death in the mice model of PD<sup>29</sup>. The biggest challenge of drug delivery into the CNS is bypassing the blood-brain barrier (BBB) as it limits access to the CNS. For decades, the BBB has prevented the use of many therapeutic agents for treating brain-related diseases and injuries, including AD, stroke, brain tumour, head injury, and other CNS disorders. Ayurveda relies on some novel methods of administering herbs or their preparations (or both) to treat CNS disorders. However, proper studies are lacking to demonstrate whether these herbs or their components given orally or by some other means cross the BBB and reach the CNS. One novel method of herbal delivery, called 'NASYA', involves intranasal delivery of dry herbal powders or medicated oils and is a practical, non-invasive, rapid, and simple method to deliver the therapeutic agents into the CNS. The use of medicated oils, which require that the herbs be cooked in four parts oil and 16 parts water over a low flame until all of the water evaporates, ensures the transport of lipophilic and lipid-soluble molecules across the BBB membrane, where hydrophilic compounds demonstrate minimal permeation. A second, simple method of administration involves application of the medicated oil on the body and massaging the areas with gentle or deep hand strokes. It is not clear whether this technique facilitates the transport and movement of the herbal components through the BBB. Indirect evidence from recent studies points to such a possibility. Significant brain functional activation changes together with increased cerebral blood flow were observed in participants who received a massage. Ayurveda also relies on several transcranial oleation therapies for nervous system disorders that are non-systemic and non-invasive. Procedures like Shirodhara (gentle dripping of the medicated oil on the forehead), Shirobasti (a special leather cap is placed over the shaved head of a patient and medicated oil is poured and retained over the head for 30 to 45 minutes), ShiroAbhyanga (medicated oil is smeared on the head followed by a gentle massage), and ShiroSeka (medicated oil is poured over the head in a continuous stream) may also influence hormonal and cerebral blood flow levels to a degree similar to that of Ayurvedic massage as mentioned above<sup>30</sup>. Aromatherapy, another popular method in the Ayurvedic system, involves the use of volatile plant materials known as essential oils for healing purposes for altering a person's mood and cognitive function. The essential oils are incorporated through steam inhalation or are topically applied to the face and arms. Aromatherapy used with massage may help to calm agitated people with dementia.

## CONCLUSIONS AND PERSPECTIVES

Although the therapeutic possibilities offered by herbs for diverse types of CNS disorders

have been known to mankind for centuries, until now little concentrated effort has been made to define and understand their most appropriate therapeutic uses, or to exploit them for identifying and developing CNS active drugs. Researchers interested in CNS active drug discovery projects have been, until recently, not paid due attention in using existing knowledge on herbal remedies. Such a situation is surprising because several modern therapeutically interesting concepts of modern pharmacology, in general, and psychopharmacology in particular, could be conceived through studies and efforts made to better understand the traditionally known herbal remedies only.

Concentrated efforts made to obtain a better chlorpromazine-like drug led, not only to many still therapeutically used antipsychotics, but also to the modern antidepressants. It is now becoming exceedingly apparent that the available psychotherapeutics do not properly meet the therapeutic demands of the vast majority of patients with mental health problems specially neurodegenerative disorders and that herbal remedies remain the ultimate therapeutic hope for many such patients all over the world. Current knowledge from most well thought out studies, CNS active medicinal plants reveal that many therapy relevant questions have not yet been properly answered for any of them. Consequently, therefore, many phytopharmaceutical laboratories are now concentrating their efforts on identifying the active constituents and modes of actions of these herbs. The ultimate goal of most such efforts has been to obtain a better therapeutically useful, or better standardized extract so that exact dosage can be established. However, until now, very little attention has been paid to the development of structurally and/or functionally novel CNS active drugs from psychoactive medicinal plants. It is hoped that the strong knowledge base of Ayurveda coupled with combinatorial sciences and newer techniques will improve the ease with which Ayurvedic products and formulations can be used in drug discovery campaigns and development process, thereby providing new functional leads for age-associated neurodegenerative diseases.

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