EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

MEDICINAL PLANTS EXPENDED IN THE TRADITIONAL AND AYURVEDA FOR THE ENHANCEMENT OF LEARNING AND MEMORY DISORDERS: AN OVERVIEW

Chintha Venkataramaiah and Wudayagiri Rajendra*

Department of Zoology, Sri Venkateswara University, Tirupati, Andhra Pradesh, India.

*Corresponding Author: Wudayagiri Rajendra

Department of Zoology, Sri Venkateswara University, Tirupati, Andhra Pradesh, India.

ABSTRACT

Learning and memory disorders, in general, are associated with brain trauma, neurodegenerative, or as a part of physiological aging. Aging in humans is generally associated with deterioration of cognitive performance and, in particular, learning and memory. Different therapeutic approaches are available to treat cognitive impairment and neurodegenerative or psychiatric disorders. However, a very few synthetic drugs are currently approved by regulatory authorities for treating multi-factorial ailments and disorders of cognition. Synthetic drugs are known to cause undesirable adverse effects, whereas natural products are considered safe and effective. Ayurveda has quite sophisticated divergence of medicinal plants with dominant pharmacological / therapeutic activities on cognition and mental functions etc. Traditional herbal medicines, either directly as supplements or indirectly in the form of food, improve brain functions including learning, memory and attention and quality of life with either no or limited side effects. More than a hundred herbal medicinal plants have been traditionally used for learning and memory improvement, but only a few have been tested in randomized clinical trials and remaining have to be systematically evaluated through a multidisciplinary approach. Keeping in the view of relative importance of medicinal plants, here we will enumerate those medicinal plants that show positive effects on various cognitive functions in learning and memory and discuss briefly the specific medicinal plants that have promising experimental data or initial clinical data and might have potential to reach a clinical trial in near future.

KEY WORDS: Ayurvedic & Traditional medicine; Cognition; Human ailments; Synthetic drugs.

INTRODUCTION

Learning is the experience-dependent acquisition of knowledge and skills, whereas memory is the retention and retrieval of facts or events composed of experiences. Memory disorders can range from mild to severe and can be progressive (neurodegenerative disease) or immediate (brain injury). Almost all are linked with some damage to neuroanatomical structures, either in part or full, which hinders acquisition (learning), consolidation (storage of labile stable memory), and retrieval (recall). Forebrain and hippacampal atrophy, decreases in acetylcholine levels, cholinergic hypo function, preferential age-dependent degeneration of basal forebrain cholinergic neurons, and attenuation of neurotrophic signaling in sensory neurons 5-HT, Dopamine (DA) and other neurotransmitters are some of the important factors that might contribute to learning and memory impairment.[1,2,3]

Nature is the best combinatorial chemist and possibly has answers to all diseases of mankind. Failure of some synthetic drugs and their side effects has prompted many researchers to unfold the ancient healing methods which use herbal medicines for the treatment of different human ailments. Plant species have been identified to solicit a direct pharmacological action on the body.[4] Herbal treatment is a natural form of healing or alternative therapy where plants are being used in the form of extracts, pills, syrup or powder to cure ailments or diseases of human beings and in some cases animals too. Today herbal remedies are back into prominence. The efficacy of many conventional medicines which once had near universal effectiveness against serious infections is on the wane.

Ayurveda and Traditional Medicine (TM) are based on the use of herbal compounds to treat learning and memory loss. More than 150 plants have been used to improve learning and memory, based on the direct or indirect traditional belief of various preparations and mixtures.[5] Synthetic drugs are known to cause undesirable adverse effects, whereas natural products are considered safe and effective.[6] Herbal medicines are becoming popular for improving quality of life with either no or limited side effects. The influence of natural products is quite marked in drug discovery; of 1,335 approved drugs from the 1940s to date, 59 (4%) are derived from natural products, and 299 (22%) are derived from a semi synthetic modification of natural product.[7]

A major revolution in clinical neuropharmacology and psycho pharmacology was heralded during 1980s when effective drugs were discovered for psychosis, depression and anxiety and natural products have played a significant role in the management of neuropsychiatric disorders.[8] Man has used plant derived drugs for health delivery over centuries and remedies from plants sources for mankind are as old as human history and still in use till date.[9] It is estimated that about 85% of useful bioactive plant derived pharmaceuticals used globally are discovered by systematic investigation of leads from traditional medicines (Tomoko et al., 2002). Medicinal plants are used in treatment and prevention of various health problems from simple to complex disease situations among rural populations globally, thereby improving the quality of life. It is estimated that over 80% of people in developing countries are peasant farmers, live in rural areas and use medicinal plants for their health care needs. (Birhan et al., 2011).

Although herbs have always been the principal form of ayurvedic medicine in developing countries, they have become popular throughout the developing and developed countries in recent times. Ayurvedic based drug discovery uses "reverse- pharmacology", in which drug candidates are first identified based on large scale use in population, then validated in clinical trials.[10] Although the clinical efficacy of several herbal extract's based remedies have been explored by proper clinical trials conducted during the past three decades, the development of novel psychotherapeutics based on acquired knowledge from herbal remedies continue to be rare.[11]

The famous Charaka Samhitha written in 1st century refers brahmi (nerve tonic) for curing mental retardation leading to psychosis. Pharmacological properties of several medicinal plants have been clearly mentioned as having properties of cognitive enhancement and anxiolytic effect.[12] Many plant based medicines are known to be economical and are found to be free from side effects. In India plant based indigenous knowledge and traditional medicines are being used in various cultures and tribes.[13] In India itself, there are more than 1100 medicinal plants grown, of these some 60 genuses are used immensely in medical preparations and almost 95% of the prescriptions have been reported to be plant based in the traditional system of medhya, Unani, Ayurveda, Homeopathy and Siddha.[14,15]

During the past few years, interests have been revived in the study and use of bioactive factors extracted from Ayurvedic medicinal plants in different parts of the world. As a result countries have sought cooperation in identifying and using safe positive components of traditional medicine in their national health systems.[16] The awareness of the role of medicinal plants in healthcare delivery in developing countries resulted in exploring the natural herbal medicines, with a view to integrate it with the modern orthodox medicine.[17]

Medicinal Plants, thus, have been serving a source material for drug development and provide valuable clues for pharmacological evaluation of herbal medicine which certainly open up the new class of drugs for learning and memory disorders.[18,15]

Keeping in view the relative importance of medicinal plants, the present review is aimed at documenting the ethnomedical information of medicinal plants used for the learning and memory improvement.[9] The selected medicinal plants which are being used in cognitive improvement, have been classified as "Medhyarasayanas". The word medhya means "intellect or cognition and rasayana means "rejuvenation". In addition the clinical efficacy of some currently popular cognitive active herbal remedies, which stimulate interest in evaluating these herbs as potential sources for structurally and functionally novel cognitive active drugs lead or hits.

Medicinal plants produce different kinds of bioactive metabolites also known as natural products as they bring forth cognitive enhancement, antipsychotic and different kinds of neuropharmacological effects.[19] This appears to be a particularly rewarding approach because it has been reported that, of 122 drugs derived from medicinal plants which are in use worldwide, 80% can be traced back to their ethanomedical uses.[20] In this present communication, we will discuss available clinical data of medicinal plants for disorders involving learning and memory impairment. We have chosen those herbs for which substantial clinical data are available for improving cognition. Besides natural products in clinical trials, we have listed those plants whose experimental data or initial clinical data seem promising and have potential to reach a clinical trial in the near future.

POTENTIAL MEDICINAL PLANTS THAT IMPROVE LEARNING AND MEMORY

The human brain is one of the most sophisticated organs nature has ever made. The most interesting aspects of the brain is its power to retain information, which we call as memory. A vast number of natural, plant based extracts and chemicals are purported to have beneficial effects on human brain function. "Zhang" (2002 identified extracts and constituents from 85 individual medicinal plants that have demonstrated potential efficacy for treating cognitive, psychiatric disorders on the basis of animal behavioral models alone. However, few medicinal plants have been assessed in methodologically adequate human trials.

Bacopa monnieri
Bacopa monnieri Linn (Brahmi) has been used since times immemorial as nerve tonic for Improvement of memory. The chemical constituents responsible for the effect of brahmi on learning schedules was identified as a mixture of two saponins designated as bacosides A and B. They also enhanced protein kinase activity in hippocampus. Bacosides were also found to be safe in

regulatory pharmacological and toxicological studies.[21]

Acorus calamus
The neuropsycho-pharmacological effect of a poly herbal formulation Bramhi Ghrita (BG) on learning and memory processes were authenticated in rats by elevated plus maze and in mice by Morris water maze model. BG contains Acorus calamu Which acts as a memory enhancer formulation and may also be useful as a supportive adjuvant in the treatment of impaired memory functions.[22]

Withania somnifera
Withania somnifera, popularly known as Ashwagandha is widely considered as the Indian ginseng. In Ayurveda, it is classified as arasayana (rejuvenation) and expected to promote physical and mental health, rejuvenate the body in debilitated conditions and increase longevity. The use of *W. somnifera* in various disorders of central nervous system, neurodegeneration, cerebral ischemia, and even in the management of drug addiction.[23]

Evolvulus alsinoides
Evolvulus alsinoides (EA), considered as Shankhpushpi. Learning and memory enhancing activities were analyzed by using Cook and Weidley's pole climbing apparatus, passive avoidance paradigms and active avoidance in rodents. The ethanol extract of EA and its ethyl acetate and aqueous fractions were evaluated for their memory enhancing properties.[24]

Embelica officinalis
The effects of Anwala churna (*Emblica officinalis Gaertn.*), an Ayurvedic preparation of *Emblica officinalis*, which increases the total serum cholesterol levels and brain cholinesterase activity in mice. Elevated plus maze and passive avoidance apparatus served as the exteroceptive behavioral models for testing memory. Anwala churna (50, 100 and 200 mg/kg, p.o.) produced a dose-dependent improvement in memory scores of young and aged mice. Anwala churna may prove to be a useful remedy for the management of neurological disorders, on account of its multifarious beneficial effects such as, memory improving property, cholesterol lowering property and anti-cholinesterase activity.[25]

Centella asiatica
Centella asiatica (L.) is a perennial, creeper, faintly aromatic and is one of the chief herbs for treating skin problems, to heal wounds, for revitalizing the nerves and brain cells. Hence it is known as a "Brain food" in India. *Centella asiatica* is one of the important medicinal plants in the International market of medicinal Plant Trade.[26]

Prunus amygdalus
Prunus amygdalus (PA) nuts used as cognitive enhancer. Total cholesterol levels and cholinesterase (ChE) activity, learning and memory parameters were evaluated using elevated plus maze (EPM), passive avoidance and motor activity paradigms. PA reduced the brain ChE

activity in rat and proves to be a useful memory-restorative agent. It is potentially used in the management of cognitive impairment.[27]

Zingiber officinale
The ayurvedic rasayana (rejuvenator) extracted from *Zingiber officinale* Roscoe has been used as a memory enhancer. Elevated plus maze and passive avoidance paradigm were employed to evaluate learning and memory parameters. *Z. officinale* significantly increased whole brain acetyl cholinesterase inhibition activity. *Z. officinale* has been used as a useful memory restorative agent in the treatment of dementia.[28]

Celastrus paniculatus
Celastrus paniculatus Willd. (Celastraceae) is used for learning memory. In elevated plus maze model, *Celastrus paniculatus* extract showed statistically significant improvement in memory process. The estimation of acetylcholinesterase enzyme in rat brain supports the plus maze and passive avoidance test by reducing acetylcholinesterase activity which helps in memory performance.[29]

Foeniculum vulgare
Foeniculum vulgare Linn. extract used as a nootropic and anticholinesterase agent in mice. Treatment of this plant extract increased the step-down latency and acetylcholinesterase inhibition in mice significantly. *F. vulgare* is employed in treatment of cognitive disorders.[30]

Panax ginseng
Crude ginseng extracts enhance performance on shock motivated tasks due to its memory- enhancing (nootropic) properties of ginseng. Nootropic and anxiolytic effects of the ginseng were attributed to the presence of saponins, Rb1. Which can improve memory for a visual discrimination task and that the nootropic effect may be related to changes in anxiety.[31]

Vitis vinefera
The aerial parts of *Vitis vinifera* (common grape or European grape) have been widely used in ayurveda to treat a variety of common and stress related disorders. The seed extract of *V. vinifera* was evaluated for antistress activity in normal and stress induced rats. The nootropic activity of v.vinifera was evaluated by using the conditioned avoidance response in rats as described by cook and weidly.[32]

Albizzia lebbeck
The effect of saponin containing n- butanolic fraction (BF) extracted from dried leaves of Albizzia lebbeck on learning and memory was studied in albino mice using passive shock avoidance paradigm and the elevated plus maze. Which demonstrated that the nootropic activity of this plant extract was correlated to the anti-oxidant potential of the bioactive factors present in the plant.[33]

Clitoria ternatea

Clitoria ternatea L. commonly known as 'Butterfly pea', a traditional Ayurvedic medicine, has been used for centuries as a memory enhancer, nootropic, antistress, anxiolytic, antidepressant, anticonvulsant, tranquilizing and sedative agent. It's extracts possess a wide range of pharmacological activities including antimicrobial, antipyretic, anti-inflammatory, analgesic, diuretic, local anesthetic, antidiabetic, insecticidal, blood platelet aggregation-inhibition and for use as a vascular smooth muscle relaxing properties.[34]

Amazonian herbal

Promnesic, anti-amnesic and AChEI properties were identified in a standardized ethanol extract from Ptychopetalum olacoides (POEE), a medicinal plant favored by the elderly in Amazon communities. The Anticholinesterase activity compatible with the observed promnesic and anti-amnesic effects of PO in mice. Reaffirming the potential of this extract for treating neurodegenerative conditions where a hypo-functioning of cholinergic neurotransmission is prominent.[35]

Tabernaemontana divaricata

Tabernaemontana divaricata (TD), a Thai medicinal herb, has been widely used as an analgesic, sedative, or a cough syrup. It has been used for preventing forgetfulness and improving the memory.[36]

Leontopodium alpinu

Leontopodium alpinum ('Edelweiss') enhance cholinergic neurotransmission. The potency to increase synaptic availability of acetylcholine (ACh) in rat brain Isocomene investigated with behavioural tasks in mice. It restored object recognition in scopolamine-impaired mice and showed nootropic effects in the T-maze alternation task in normal and scopolamine-treated mice. Additionally, this sesquiterpene reduced locomotor activity of untreated mice in the open field task, while the activity induced by scopolamine was abolished.[37]

Hypericum perforatum

St. John's wort extract is commonly used as a wound healing, anti- inflammatory, anxiolytic, diuretic, antibiotic, antiviral and cancer chemoprotective agent. It also has nootropic and/or antiamnestic effects that single administration of St. John's wort extract (500 mg/kg) caused PPI disruption in rats. The effect of antiamnestic doses of the extract on PPI has not been investigated despite the coexistence of impaired memory and PPI deficit in some neurological disorder.[38]

Thespesia populnea

Thespesia populnea (Malvaceae) is a large tree found in the tropical regions and coastal forests of India. Various parts of *T. populnea* are found to possess useful medicinal properties, such as antifertility, antibacterial, and anti-inflammatory. The learning and memory parameters were assessed using elevated plus maze and passive avoidance test. It showed significant improvement in memory of young and aged mice. T. populnea bark possessed a powerful memory enhancing activity in mice.[39]

Rubia cordifolia

Effect of alcoholic extract of roots of *Rubia cordifolia* was investigated on cold restraint induced stress and on scopolamine-induced memory impairment. Alcoholic extract enhanced brain gamma- amino-n-butyric acid (GABA) levels and decreased brain dopamine and plasma corticosterone levels. Acidity and ulcers caused due to cold restraint stress were inhibited by alcoholic extract. Animals treated with alcoholic extract spent more time in open arm in elevated plus maze model. It also antagonized scopolamine induced learning and memory impairment.[40]

Commiphora whighitii

Gugulipid, a resin isolated from ethyl acetate extract of plant *Commiphora whighitii* is an established hypolipidemic agent in clinical practice. *Gugulipid* was investigated for its effect on learning and memory, parameters of oxidative stress (GSH and MDA) and AChE activity in the STZ treated mice. The study demonstrated that gugulipid has significant protective affect against streptozotocin-induced memory deficits model of dementia that can be attributed to anti-oxidant and anti-AChE activity of gugulipid.[41]

Glycyrrhiza glabra

Glabridin was isolated from the roots of *Glycyrrhiza glabra* and its effects on cognitive functions and cholinesterase activity were investigated in mice. Glabridin appears to be a promising candidate for learning and memory improvement and it is worthwhile to explore the potential of glabridin in the management of patients with neurological deficits.[42]

Pueraria tuberose

Nootropic effect of alcoholic and aqueous extracts of *P. tuberosa* was evaluated by using Elevated Plus Maze (EPM). A significant reversal effect was observed on rectal temperature in CIH model, reduction of head twitches in LIH models. However no significant reduction in catalepsy scores in HIC models were observed with test extracts and standard piracetam. The results indicate that nootropic activity observed in the tuber extracts of *P. tuberosa* could be through improved learning and memory either by augmenting the noradrenaline (NA) transmission or by interfering with 5-hydroxytryptamine (5-HT) release ALE and AQE extracts of tubers of *P. tuberosa* (Roxb) and these active principles may be responsible for nootropic activity. [43]

Murraya koenigii

Murraya koenigii leaves (MKL) commonly known as curry patta, are added routinely to Indian gravy and vegetarian dishes as a favorite condiment. The MKL diets produced a significant dose-dependent improvement in the memory scores of young and aged

mice and significantly reduced the amnesia induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). The underlying mechanism of action for the observed nootropic effect may be attributed to pro-cholinergic activity and a cholesterol lowering property. Therefore, it would be worthwhile to investigate specifically the therapeutic potential of MKL in the management of patients with learning and memory disorders.[44]

Anemarrhenaa sphodeloides
Anemarrhena asphodeloides Bunge. (AA, family Liliaceae), which primarily contains xantones, such as mangiferin, and steroidal saponins, such as timosaponin. The memory- enhancing effects of these saponins were investigated in scopolamine-treated mice. The memory-enhancing effect of timosaponin AIII (TA3) was greater.[45]

Cornus officinalis
The anti-amnesic activity of the methanolic extract of *Cornus officinalis* fruits (COT) and a major constituent, loganin were determined using scopolamine- induced (1 mg/kg body weight, s.c.) amnesic mice with both passive avoidance and the Morris water maze tests. Oral treatment of mice with COT (100 mg/kg body weight) and loganin (1 and 2 mg/kg body weight) significantly mitigated scopolamine-induced memory deficits in passive avoidance test. In the Morris water maze test, oral treatment of loganin significantly ameliorated scopolamine-induced memory deficits showing the formation of long-term and/or short-term spatial memory. Moreover, loganin (2 mg/kg body weight) significantly inhibited acetylcholinesterase activity by as much as 45% of control in the mouse hippocampus. These results indicate that loganin exerts antiamnesic activity in *in-vivo* through acetylcholine- esterase inhibition.[46]

Albizia julibrissin
The memory enhancement and antidepressant-like effects of the methylene chloride fraction of *Albizzia julibrissin* (MCAJ) have been demonstrated in mice.[47]

Marsilea minuta Linn
Marsilea minuta Linn. (Marsileaceae) has been referred in Indian traditional medicine system (Ayurveda) for the treatment of insomnia and other mental disorders. Marsilin, Isolated from *Marsilea minuta* also was found to elicit sedative and anticonvulsant properties. Antidepressant activity was studied using forced swimming test (FST), tail suspension test (TST), learned helplessness test (LHT) and 5-hydroxytryptophan (5-HTP) induced head twitches response in rodents.[48]

Artemisia absinthium l.
Artemisia absinthium L. has long been used as a traditional herbal medicine for the treatment of gastric pain, cardiac stimulation, to improve memory and for the restoration of declining mental function. The oxidative stress and behavioral deficits in the brain were significantly attenuated by pre-treatment with the methanol extract of *Artemisia absinthium* (100 mg/kg and 200 mg/kg,).[49]

Leuzea carthamoides
The effects of N- feruloyl serotonins, substances isolated from the seeds of *Leuzea carthamoides* (WILLD.), used as nociception and in anxiety. Anti-nociceptive responses were measured using the plantar and tail-flick tests which were administered before and after swimming stress (3 min, water temperature 32°C). Anxiety was evaluated using an elevated plus maze. N-feruloylserotonins have selective stress-reducing effects in stress-sensitive animals.[50]

Ptychopetalum olacoides
Homemade remedies with *Ptychopetalum olacoides* (PO) roots are used by Amazonian peoples for treating various age-related conditions. *Ptychopetalum olacoides* ethanol extract significantly improved step-down inhibitory avoidance long-term memory in adult and reversed memory deficits in aging mice. The acetyl cholinesterase inhibitory properties described for this extract may be of relevance for improving memory processes.[51]

Passiflora actinia
The leaves of *Passiflora actinia* resulted in anxiolytic-like effects in the elevated plus- maze. At higher doses, a sedative effect is produced and there is also an involvement of GABA system in this effect.[52]

Eclipta alba
Eclipta alba used for sedative, muscle- relaxant, anxiolytic, nootropic and anti-stress activities. The results point towards the potential neuropharmacological activity of the plant *Eclipta alba* as a nootropic and also having the property of attenuating stress induced alterations.[53]

Eclipta prostrate
Eclipta prostrata has been used as a traditional medicinal plant to prevent dementia and to enhance memory in Asia. It's potential as a nootropic and as an antioxidant has been reported in mice.[54]

Ficus religiosa
Ficus religiosa Linn. (Moraceae) is a variety of fig tree. Its figs contain a high serotonergic content, and modulation of serotonergic neurotransmission plays a crucial role in the pathogenesis of amnesia and also used in improvement of memory.[55]

Polygala tenuifolia
Cognition-enhancing activity and underlying mechanisms of triterpenoid saponins isolated from the roots of *Polygala tenuifolia* Willd. Have been reported to exhibit The Morris water maze was used to evaluate the spatial learning and memory. It improves hippocampus-dependent learning and memory, possibly through improvement of synaptic transmission.[56]

Ginkgo biloba

Ginkgo biloba is an herbal medicine being used in traditional Chinese medicine for thousands of years to treat a variety of ailments. It has been shown to reduce memory loss, enhance the brain activity and to slow down the degenerative effects of Alzheimer's disease.[57] The gingkolides present in *Ginkgo biloba* posses' activities pertinent to the disease mechanisms such as antioxidant, neuroprotective and cholinergic activities according to the studies conducted by medical Research Council of New Castle General Hospital.[58] Various clinical studies have indicated that 3- to 6-month treatment with 120- 240 mg of *G. biloba* has produced significant effect in patients with memory impairment, heart palpitations and restlessness.[59] *Gingko biloba* extract EGB761 has been found very effective in preventing the treatment Beta Amyloid toxicity in brain cells which accumulates in Alzheimer's disease.[60]

Galanthus caucasicus

Clinical studies on the efficacy of Galantamine have demonstrated its use in the treatment of mild to moderate memory impairments.[61] This drug has been found to be a competitive and selective acetylcholinesterase (AChE) inhibitor. This drug has also been shown to modulate the nicotinic ACh receptors in cholinergic neurons to increase acetylcholine release.[62] Galantamine has a half life of 5-6 hours and *in vitro* studies have shown that Hepatic CYP-450 enzymes (CYP2D6 and CYP3A4) are involved in galantamine metabolism. Galantamine has not been associated with hepatotoxicity in clinical trials. Pooled data from four randomized trials of this drug on patients with mild cognitive deficits have shown that patients who received galantamine 24 mg/d for six months had improved cognition more often than those who received placebo, and that a higher proportion receiving galantamine were globally improved.[63]

Huperzia serrata

Huperzine A is a natural cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata.* Huperzine A, an alkaloid has been shown to posses antioxidant and neuroprotective properties suggesting thereby it's potential in the treatment of learning and memory disorders.[64] This drug has been shown to inhibit acetyl cholinesterase and to improve memory and mental functioning in patients with cognitive disorder and other severe conditions.[65] Three Chinese double blind clinical trials of huperzine A on more than 450 patients, suggest that the use of huperzine-A may significantly improve the symptoms of neurological disease and other form of dementia.[66]

Catharanthus roseus

Vinpocetine, a chemical derived from vincamine is a constituent found in the leaves of *Catharanthus roseus*, (common name periwinkle; Vinca minor) as well as the seeds of various African plants.[67] It is used as a treatment for memory loss and mental impairments. Studies have demonstrated that Vinpocetine has thepotential to enhance cerebral blood flow also exhibit neuroprotective effects.[68,69] It is used as drug in Eastern Europe for the treatment of cerebrovascular disorders and age related memory impairment.[70]

Melissa officinalis

Melissa officinalis (LemonBalm) has been shown to improve cognitive function and to reduce agitation in patients with mild to moderate cognitive performance. Studies have demonstrated that *M. officinalis possesses* ACh receptor activity in central nervous system with both nicotinic and muscarinic binding properties.[58,71] This plant has also been reported to modulate mood and cognitive performance when administered to young, healthy volunteer.[72] The results of this study indicated that patients receiving M.*Officinalis extract* experienced significant improvements in cognition after 16 weeks of treatmen twith no side effects. The above clinical study also revealed that the frequency of agitation was higher in the placebo group compared to those receiving active treatment.[73]

Salvia officinalis

The extract of *Salvia officinalis* (sage) has been found to produce significant benefits in learning and memory to the patients with mild to moderate cognitive disorders after 16 weeks of treatment with S. officinalis.[74] The studies have demonstrated that the side effects associated with *S. officinalis* were similar to those observed with cholinesterase inhibitor.[75]

Rosmarinus officinalis

The essencial oil of *Rosmarinus officinalis* has been shown to produce a significant decrement in performance of working memory, and impaired reaction times for both memory and attention based tasks.[76] The above three herbal plants, *Melissa officinalis*, *Salvia officinalis* & *Rosmarinus officinalis* have been evaluated using different *in vitro* and *in vivo* models to prove their efficacy and the studies have demonstrated that extracts from plants of the Lamiaceae family are active not only in inhibition of AchE or β-amyloid deposits *in-vitro* but also may have anti-BuChE (butyrylcholinesterase) activity. In addition, the antioxidant, cytoprotective, anti-apoptotic and anti-inflammatory activities have also been found in Lamiaceae plant extracts.[77]

Euphorbia royleana Boiss (Source of Shilajit)

Shilajit is used in the Ayurveda, the traditional Indian system of medicine, which has adaptogeni/anti- stress and immunomodulatory activities.[78] Studies have demonstrated the potential of Shilajit in the treatment of Alzheimer's disease.[79] The studies to assess its effectiveness in the management of Alzheimer's disease demonstrate that shilajit affects some events in cortical and basal forebrain cholinergic singnal

transduction cascade in rat brain.[80] The experimental studies in mouse animal model have revealed that Shilajit may be utilized safely in clinical practice up to a dose of 3 g/kg in mice (24 h mortality).[81]

Curcuma longa (Haldi)

The studies have demonstrated the role of Egr-1 in amyloid peptide-induced cytochemokine gene expression in monocytes. The anti-inflammatory action of Curcumin may be hypothesized due to inhibition of Egr-1 DNA-binding activity by curcumin.[82] Curcumin has been found to improve neurological deficit, decrease in mortality and reduce the water content in the brain.[83] The studies conducted on Alzheimer's disease mice model have shown that the levels of beta myeloid in AD mice that were given low doses of curcumin are significantly decreased as compared to those not treated with curcumin. Curcumin at low doses has also been found to decrease the "plaque burden" that these beta-amyloid plaques have on the brains of AD mice. These experimental studies have also revealed that the low doses of curcumin for longer periods is more effective rather than high doses in combating the neurodegenerative process, oxidative stress and inflammatory reactions.[84,85] Further, the studies have also revealed that curcumin is found to increase the activity of super oxide dismutase (SOD) and sodium-potassium ATPase that normally decreased with aging.[86] It has been observed that Curcumin given to APPswe/PS1dE9 mice for 7 days crosses the blood-brain barrier as demonstrated by muliti-photon microscopy and reduces the existing senile plaques.[87] In addition, the results of another study have demonstrated that curcumin increases phagocytosis of amyloid-beta, effectively clearing them from the brains of patients with neurodegenerative diseases.[88]

FUTURE PERSPECTIVE

The development of effective plant-based products for improving human brain function is constrained by a number of issues including a need to undeniably identify relevant active components and understand synergies within them and an inability to adequately standardize replicable plant extracts. Animal behavioral studies have only involved secondary metabolites either as a consequence of using them as simple tools for the modulation of specific neurotransmitter targets or involved secondary metabolites in rodent models of drug abuse and addiction. It would seem appropriate that animal models could be utilized as simple, economical, time efficient and ethically acceptable tools for investigating the neuronal and behavioral consequences of individual Phytochemical and complex mixtures. It is also evident that there are many medicinal plant extracts that may have beneficial effects on cognitive function without the association of toxicity induction. Many phytochemical simply do not function effectively as single molecules and there are many examples of synergies within and between the chemical groups. Animal models may provide ideal starting points for disentangling these synergies prior to human studies.

Today many developing countries have intensified their efforts in documenting the ethanomedical data on medicinal plants. Research to find out scientific evidence on Indian herbs has been intensified. Once these local ethanomedical preparations are scientifically evaluated and disseminated properly, people will be better informed regarding efficacious drug treatment and improved health status (Manandhar, 1987). Whereas determining the biological (activity) properties of medicinal plants used in traditional medicine is helpful to the rural communities and informal settlements. Several researchers and many phytopharmaceutical laboratories are currently being undertaken to isolate the active compounds and their mode of action by bioassay-guided fractionation from medicinal plants that showed high biological activity during screening. An innovative research effort is needed to define the advantage of traditional system of medicine with respect to their safety and efficacy could result in a better utilization of these complementary systems of medicine. Therefore, further research is deserved to isolate and characterize the bioactive compounds from medicinal plants which are responsible for the treatment of various learning and memory related disorders.

CONCLUSION

The use of herbal products has increased tremendously in developed and developing countries. Herbal medicines are perceived as natural, gentle and safe treatments compared to those of synthetic drugs. Numerous natural products have been used traditionally as learning and memory enhancers and provide promising effects to improve quality of life in terms of improving cognitive function associated with senescence. Contrary to traditional belief, some medicines do not fit and have failed to perform in the established test systems. This article summarizes some of the potential medicinal plants and their active constituents that have been used in traditional medicine, including Ayurveda, for their clinical cognitive-enhancing effects.

In the traditional practice of medicine, some of these plant products are already being used as dietary supplements in developed countries for their memory enhancing effects. Still many medicinal plants with the ability to improve memory function remain to be tested in clinical trials. These studies might provide therapeutic benefits in patients with cognitive disorders or increase the quality of life of people by improving their cognitive functions. A strong relationship exists between the traditional use of herbal plants and their mechanism of action, as identified in the current scenario using several pharmacological approaches. Several bioactive compounds have been isolated from these medicinal plants and their mechanisms of action on learning and memory have been well characterized. Hence, there is a need to perform more studies with differences in study designs, number of subjects, different fractions of the compound used, doses, differences in sensitivities or neurocognitive tests, and specific patient with memory

impairment for development of these herbal compounds as drug candidate in near future.

CONFLICT FINTEREST
The authors declare that they have no conflict of interest in this regard.

REFERENCES
1. Lye TC, Piguet O, Grayson DA, Creasey H, Ridley LJ, Bennett HP, Broe GA. Hippocampal size and memory function in the ninth and tenth decades of life: The Sydney Older Persons Study. J Neurol Neurosurg Psychiat, 2004; 75: 548–554.
2. Ikarashi Y, Harigaya Y, Tomidokoro Y, Kanai M, Ikeda M, Matsubara E, Kawarabayashi T, Kuribara H, *et al*. Decreased level of brain acetylcholine and memory disturbance in APPsw mice. Neurobiol Aging, 2004; 25: 483-490.
3. Schliebs R, Arendt T. The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. J Neural Transm, 2006; 113: 1625-1644.
4. Nandan Kumarjha, Pandey K. Herbal formulation for psychiatric (*Nigella sativa*). Phytopharm, 2008; 9: 37-38.
5. Adams M. Gmunder F. Hamburger M. Plants traditionally used in age related brain disorders. A survey of ethnobotanical literature. J Ethnopharmacol, 2007; 113: 363-381.
6. Johnson WC. Williford WO. Benefits, Morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: A prospective randomized study. J Vasc Surg, 2002; 35: 413-421.
7. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod, 2012; 75: 311–335.
8. Duman RS, Heminger GR, Nestler ER. Molecular psychiatry. Adaptations to receptors -coupled signals transduction pathways underlying stress- and drug induced neural plasticity. J Nervous and Mental Dis, 1994; 182: 692-700.
9. Elufioye TO, et al. Ethnomedical study and screening of plants used for memory enhancement and antiaging in sagamu, Nigeria Eur J med Plants, 2012; 2(3): 262-275.
10. Vikas kumar. Potential medicinal plants for CNS disorders: an overview. Phytotheraphy research, 2006; 20: 1023-1035.
11. Padma TV. Ayurveda. Nature, 2005; 436: 486.
12. Debjit Bhowmik, Chiranjib, Pankaj Tiwari1, Tripathi KK and Sampath Kumar KP. Traditional Indian memory enhancer herbs and their medicinal importance. Annals of Biological Research, 2010; 1(1): 41-46.
13. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Phytother Res, 2002; 16: 639-45.
14. Rajani GP, Prasad KVSRG. Effect of *Eclipta alba* L.on Learning and memory enhancing in rats. Indian Journal of Pharmaceutical Edu Research, 2007; 41(4): 369-370.
15. Sathyavati B, Gupta AK, Tendon N. Medicinal plants of India. Indian Council of Medicinal Research New Delhi, 1987, India.
16. Shahriar M, Baha ANM, Hassain MI, Akhter S, Haque MA, Bhuiyan MA. Preliminary phytochemical screening, *invitro* anti-oxidant and cytotoxic activity of five different extracts of *withinia somnifera* root. International Journal of Pharmacy, 2012; 2: 450-453.
17. Sofowara A. Medicinal plants and traditional medicine in Africa. Spectrum books ltd. 1993; 298-300.
18. Edeoga HO, Okwu DE, Mbaebie O. Afr. J. Biotechnology, 2005; 4(7): 685-688.
19. Zwenger S and Basu C. Plant terpenoids: applications and potentials. Biotechnology and Molecular Biology Reviews, 2008; 3: 001-007.
20. Jones WP, Chin YW, Kinghorn AD. The role of pharmacognacy in modern medicine and pharmacy. Current drug targets, 2007; 247-264.
21. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monniera* Linn. Indian Journal of Pharmacology, 1997; 359-365.
22. Girish S Achliya, Barabde U, Wadodkar S, Dorle A. Effect of *Bramhi Ghrita*, a polyherbal formulation on learning and memory paradigms in experimental animals. Indian Journal of Pharmacology, 2004; 36(3): 159-162.
23. Kulkarni SK and Ashish Dhir. *Withania somnifera*: An Indian ginseng. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008; 32(5): 1093-1105.
24. Nahata A, Patil UK, Dixit VK. Effect of *Evolvulus alsinoides* Linn. On learning behavior and memory enhancement activity in rodents. Phyto Research, 2010; 24(4): 486-93.
25. Vasudevan M, Parle M. Memory enhancing activity of *Anwala churna (Emblica officinalis Gaertn.)*: an Ayurvedic preparation. Physiol and Behavior, 2007; 91(1): 46-54.
26. Sakshi Singh, Asmita Gautam, Abhimanyu Sharma and Amla Batra. *Centella asiatica*: A plant with immense medicinal potential but threatened. International Journal of Pharmaceutical Sciences Review and Research, 2010; 4(2): 003-0010.
27. Kulkarni KS, Kasture SB, Mengi S. Efficacy study of *Prunus amygdalus* (almond) nuts in scopolamine-induced amnesia in rats. Ind. J. of Pharmacology, 2010; 42(3): 168-73.
28. Hanumanthachar Joshi and Milind Parle. *Zingiber*

officinale: Evaluation of its nootropic effect in mice. African Journal of Traditional CAM, 2006; 3(1): 64-74.

29. Bhanumathy M, Harish MS, Shivaprasad HN, Sushma G. Nootropic activity of *Celastrus paniculatus* seed. Pharmaceutical Biology, 2010; 48(3): 324-7.

30. Joshi H, Parle M. Cholinergic basis of memory-strengthening effect of *Foeniculum vulgare* Linn. Journal of Medicinal Food, 2006; 9(3): 413-7.

31. James D. Churchill, Jennifer L. Gerson, Kendra A. Hinton, Jennifer L. Mifek, Michael J. Walter, Cynthia L. Winslow and Richard A. Deyo. The Nootropic Properties of *Ginseng Saponin* Rb1 are linked to Effects on Anxiety. Integrative Physiological and Behavioral Science, 2002; 37(3): 178-187.

32. Satyanarayana Sreemantula, Srinivas Nammi, Rajabhanu Kolanukonda, Sushruta Koppula and Krishna M Boini. Adaptogenic and nootropic activities of aqueous extract of *Vitis vinifera* (grape seed): an experimental study in rat model. BioMed Ltd, 2005; 25: 104-112.

33. Chintawar SD, Somani RS, Veena S, Kasture S and Kasture B. Nootropic activity of *Albizzia lebbeck* in mice. Journal of Ethnopharmacology, 2002; 81(3): 299-305.

34. Pulok K, Mukherjee, Venkatesan Kumar N, Satheesh Kumar and Micheal Heinrich. The Ayurvedic medicine *Clitoria ternatea-* From traditional use to scientific assessment. Journal of Ethnopharmacology, 2008; 120(3): 291-301.

35. Figueiró M, Ilha J, Pochmann D, Porciúncula LO, Xavier LL, Achaval M, Nunes DS and Elisabetsky E. Acetylcholinesteras inhibition in cognition-relevant brain areas of mice treated with a nootropic *Amazonian herbal* (Marapuama). Phytomedicine, 2010; 17(12): 956-962.

36. Walika Nakdook, Onrawee Khongsombat, Pornnarin Taepavarapruk, Niwat Taepavarapruk and Kornkanok Ingkaninan. The effects of *Tabernaemontana divaricata* root extract on amyloid β-peptide 25–35 peptides induced cognitive deficits in mice. Journal of Ethnopharmacology, 2010; 130(1): 122-126.

37. Ariane Hornick, Stefan Schwaiger, Judith M. Rollinger, Nguyen Phung Vo, Helmut Prast and Hermann Stuppner. Extracts and constituents of *Leontopodium alpinum* enhance cholinergic transmission: Brain ACh increasing and memory improving properties. Biochemical Pharmacology, 2008; 76(2): 236-248.

38. Mariane G. Tadros, Mohamed R. Mohamed, Amal M. Youssef, Gilane M. Sabry, Nagwa A. Sabry and Amani E. Khalifa. Pro apoptotic and prepulse inhibition (PPI) disrupting effects of *Hypericum perforatum* in rats. J. of Ethnopharm, 2009; 122(3): 561-566.

39. Vasudevan M and Parle M. Pharmacological actions of *Hesperia populnea* relevant to Alzheimer's disease. Phytomedicine, 2006; 13(9-10): 677-687.

40. Patil RA, Jagdale SC, Kasture SB. Antihyperglycemic, antistress and nootropic activity of roots of *Rubia cordifolia* Linn. Indian J of Exp Biology, 2006; 44(12): 987-92.

41. Saxena G, Singh SP, Pal R, Singh S, Pratap R, Nath C. Gugulipid. An extract of *Commiphora whighitii* with lipid-lowering properties, has protective effects against streptozotocin- induced memory deficits in mice. Pharmacology Biochemistry and Behavior, 2007; 86(4): 797-805.

42. Cui YM, Ao MZ, Li W, Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. Planta Med, 2008; 74(4): 377-80.

43. Rao NV, Pujar B, Nimbal SK, Shantakumar SM, Satyanarayana S. Nootropic activity of tuber extract of *Pueraria tuberosa* (Roxb). Ind J Exp Bio, 2008; 46(8): 591-8.

44. Vasudevan M, Parle M. Antiamnesic potential of *Murraya koenigii* leaves. Phytotherapy Research, 2009; 23(3): 308-16.

45. Lee B, Jung K, Kim DH, Timosaponin AIII, a saponin isolated from *Anemarrhena asphodeloides,* ameliorates learning and memory deficits in mice. Pharmacology biochemistry and behavior, 2009; 93(2): 121-7.

46. Lee KY, Sung SH, Kim SH, Jang YP, Oh TH, Kim YC. Cognitive- enhancing activity of loganin isolated from *Cornus officinalis* in scopolamine-induced amnesic mice. Archives of Pharmacel Research, 2009; 32(5): 677-83.

47. Ji-Hyun Kim, Sun Yeou Kim, Seok-Yong Lee and Choon-Gon Jang. Antidepressant-like effects of *Albizzia julibrissin* in mice: Involvement of the 5-HT1A receptor system. Pharmacology Biochemistry and Behavior, 2007; 87(1): 41- 47.

48. Subrat Kumar Bhattamisra, Vinay Kumar Khanna, Ashok Kumar Agrawal, Paras Nath Singh and Sushil Kumar Singh. Antidepressant activity of standardized extract of *Marsilea minuta* Linn. Journal of Ethnopharmacology, 2008; 117(1): 51-57.

49. Kundan Singh Bora and Anupam Sharma. Neuroprotective effect of *Artemisia absinthium* on focal ischemia and reperfusion-induced cerebral injury. Journal of Ethnopharmacol, 2010; 129: 403-409.

50. Yamamotova M, Pometlova J, Harmatha H, Raskova and R. Rokyta. The selective effect of N-feruloyl serotonins isolated from *Leuzea carthamoides* on nociception and anxiety in rats. Journal of Ethnopharmacology, 2007; 112(2): 368-374.

51. Adriana L. da Silva, Angelo L. Piato, Juliana G. Ferreira, Barbara S. Martins, Domingos S. Nunes and Elaine Elisabetsky. Promnesic effects of *Ptychopetalum olacoides* in aversive and non-aversive learning paradigms. J. of Ethnopharm, 2007; 109(3): 449-457.

52. Luiz F. Lolli, Claudia M. Sato, Cassia V. Romanini, Larissa De Biaggi Villas-Boas, Cid A. Moraes Santos and Rubia M.W. de Oliveira. Possible involvement of GABA-A benzodiazepine receptor in the anxiolytic-like effect induced by *Passiflora ctinia* extracts in mice. Journal of Ethnopharmacology, 2007; 111(2): 308-314.

53. Thakur VD and Mengi SA. Neuropharmacological profile of *Eclipta alba* (Linn.) Hassk Journal of Ethnopharmacology, 2005; 102(1): 23-31.

54. Kim DI, Lee SH, Hong JH, Lillehoj HS, Park HJ, Rhie SG, Lee GS. The butanol fraction of *Eclipta prostrata* (Linn) increases the formation of brain acetylcholine and decreases oxidative stress in the brain and serum of cesarean-derived rats. Nutrition Research, 2010; 30(8): 579-84.

55. Kaur H, Singh D, Singh B, Goel RK. Anti-amnesic effect of *Ficus religiosa* in scopolamine-induced anterograde and retrograde amnesia, Pharmaceutical Biology, 2010; 48(2): 234-40.

56. Xue W, Hu JF, Yuan YH, Sun JD, Li BY, Zhang DM, Li CJ, Chen NH. Polygalasaponin XXXII from *Polygala tenuifolia* root improves hippocampal-dependent learning and memory. Acta Pharmacologica Sinica, 2009; 30(9): 1211-9.

57. Akhondzadeh S, Noroozian M. Alzheimer's disease: Pathophysiology and pharmacotherapy. Drugs, 2002; 4: 1167- 1172.

58. Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NS. Medicinal plants and Alzheimer's disease: from ethno botany to phytotherapy. Medical Research Council, Newcastle General Hospital, Newcastle upon Tyne. J Pharm Pharmacol, 1999; 51(5): 527-34.

59. Mahadevan S, Park Y. Multifaceted Therapeutic Benefits of *Ginkgo biloba*; Chemistry, Efficacy, Safety, and Uses. Journal of Food Science, 2008; 73(1): 14-19.

60. Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia: Intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. Pharmacopsychiatry, 2003; 36: 297-303.

61. Schulz V. Ginkgo extract or cholinesterase inhibitors in patients with dementia: What clinical trials and guidelines fail to consider. Phytomedicine, 2003; 10: 14-14: 74-79.

62. Kurz A, Van Baelen B. *Ginkgo biloba* compared with cholinesterase inhibitors in the treatment of dementia: A review based on meta-analyses by the Cochrane collaboration. Dementia Geriatr Cogn Disord, 2004; 18: 217-226.

63. Woodruff-Pak D S, Vogel R W, Wenk G L. Galantamine: effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning. Proceedings of the National Academy of Sciences of the United States of America, 2001; 98(4): 2089-2094.

64. Raskind MA, Peskind ER,Wessel T. Galantamine in AD: A six month randomized placebo-controlled trial with a six month extension. Neurology, 2000; 54: 2261-2268.

65. Raves ML, Harel M, Pang YP, Silman I, Kozikowski AP, Sussman JL. Structure of acetylcholinesterase complexed with the nootropic alkaloid. huperzine A. Natural Struct Biol, 1997; 4: 57-63.

66. Zhang Z, Wang X, Chen Q. Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease: A placebo-controlled, double-blind, randomized trial. Zhonghua Yi XueZaZhi, 2002; 82: 941-944.

67. Lorincz C, Szász K, Kisfaludy L. The synthesis of ethyl apovincaminate. Arzneimittelforschung, 1976; 26(10a): 1907.

68. Szilágyi G, Nagy Z, Balkay L, Boros I, Emri M, Lehel S, Márián T, Molnár T, Szakáll S, Trón L, Bereczki D, Csiba L, Fekete I, Kerényi L, Galuska L, Varga J, Bönöczk P, Vas A, Gulyás B. Effects of vinpocetine on the redistribution of cerebral blood flow and glucose metabolism in chronic ischemic stroke patients: a PET study. J Neurol Sci, 2005; 229-230: 275-84.

69. Dézsi L, Kis-Varga I, Nagy J, Komlódi Z, Kárpáti E. Neuroprotective effects of vinpocetine *in vivo* and *in vitro*. Apovincaminic acid derivatives as potential therapeutic tools in ischemic stroke. Acta Pharmaceutica Hungarica, 2002; 72(2): 84-91.

70. Monograph. Vinpocetine. Alternative Medicine Review, 2002; 7(3): 240–3.

71. Perry EK, Pickering AT, Wang WW, Houghton P, Perry NS. Medicinal plants and Alzheimer's disease: Integrating ethnobotanical and contemporary scientific evidence. J Altern Complement Med, 1998; 4(4): 419-428.

72. Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes Kakennedy. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). Pharmacol Biochem Behav, 2002; 72: 953-964.

73. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomised, placebo controlled trial. J. Neurol Neurosurg Psychiatry, 2003; 74: 863-866.

74. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomized and placebo-controlled trial. J Clin Pharm Ther, 2003; 28: 53-59.

75. Wake G, Court J, Pickering A, Lewis R, Wilkins R, Perry E. CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. J Ethnopharmacol, 2000; 69: 105-114.

76. Moss M, Cook J, Wesnes K, Duckett P. Aromas of rosemary and lavender essential oils differentially affects cognition and mood in healthy adults. Int J

Neurosci, 2003; 113: 15-38.

77. Ożarowski M, Mikołajczak P Ł, Bobkiewlcz-Kozłowska T, Kujawski R, Mrozikiewicz P M. Neuroactive compounds from medicinal plants of the *Lamiaceae* family showing potentially beneficial activity in treatment of Alzheimer's disease. Herba Polonica, 2009; 55(4): 148-163.

78. Winston D, Maimes S. Adaptogens. Herbs for Strength, Stamina, and Stress Relief, Healing. Arts Press, 2007; 22: 146-156.

79. Mukherjee B. Traditional Medicine. In the Proceedings of an Int Seminar, Nov. 7-9, 1992, pg 308-319. Hotel Taj Bengal, Calcutta India. Oxford & IBH Publishing, New Delhi, 1992; 308-319.

80. Schliebs R, Liebmann A, Bhattacharya SK, Kumar A, Ghosal S, Bigl V. Systemic administration of defined extracts from *Withania somnifera* (Indian Ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain. Neurochem Int, 1997; 30(2): 181-90.

81. Frotan MH, Acharya SB. Pharmacological studies of shilajit. Ind. J. Pharmacology 1984; 16: 45.

82. Giri RK, Rajagopal V, Kalra VK. Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor. J Neurochem, 2004; 91: 1199–210.

83. Jiang J, Wang W, Sun YJ, Hu M, Li F, Zhu DY. Neuroprotective effect of curcumin on focal cerebral ischemic rats by preventing blood-brain barrier damage. Eur J Pharmacol, 2007; 30: 54–62.

84. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem, 2005; 280(7): 5892–901.

85. Frautschy SA, Hu W. Phenolic, anti inflammatory antioxidant reversal of induced cognitive deficits and neuropathology. Neurobiol Aging, 2001; 22: 993–1005.

86. Bala K, Tripathy BC, Sharma D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. Biogerontology, 2006; 7: 81–89.

87. Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology *in vivo* disrupts existing plaques and partially restores distorted neurites in an Alzheimer mouse model. J Neurochem, 2007; 102: 1095–104.

88. Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, Sayre J, Zhang L, Zaghi J, Dejbakhsh S, Chiang B, Hui J, Mahanian M, Baghaee A, Hong P, Cashman J. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimers patients are improved by bisdemethoxy curcumin. Proc Natl Acad Sci, 2007; 104: 12849–12854.