AYURVEDIC APPROACH WITH A PROSPECTIVE TO TREAT AND PREVENT ALZHEIMER’S AND OTHER COGNITIVE DISEASES: A REVIEW

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ABSTRACT
Alzheimer’s disease (AD) is the most common form of dementia which occurs among older people above the age of 60 years. Alzheimer’s disease is characterized by massive loss of neurons and disrupted signaling between cells in the brain. The cholinergic deficit in this disease is responsible for most of the short term memory which leads to progressive loss of memory, deterioration of all intellectual functions, increases apathy, decreases speech function, disorientation and gait irregularities. The currently available drugs for the treatment of Alzheimer’s disease are having a limited scope, symptomatic only and produce adverse reactions in the patients. The herbal remedies become more and more popular in the recent years and also provide very promising benefits to the patients suffering from AD. The current paper reviews the clinical effects of a few commonly used herbs for the treatment of Alzheimer’s disease.

Keywords: Alzheimer’s disease, herbal treatment, memory, cognitive disease, dementia.

INTRODUCTION
Rapid changes in life-style, environmental pollution and excessive use of fertilizers and hazardous toxic chemicals during the production of food materials, are seriously life threatening for human beings and causing health hazards. These toxic chemicals produce neurotoxins that affect the transmission of chemical signals between neurons resulting into
neurodegenerating disorders. Among different kind of neurodegenerating diseases, Alzheimer’s disease (AD) is the most common form of the dementia which occurs among the older people above the age of 60 years\[^1\].

Alzheimer’s disease is a progressive neurodegenerative brain disorder that is slow in onset but leads to dementia, unusual behavior, personality change and ultimately death\[^2\]. The prevalence has been found to rise exponentially with age, ranging from 3.0% in patient’s aged 65-74 years to as much as 47.2% in those aged 85 years\[^3\]. AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks. World Health organization (WHO) has estimated that 35.6 million people are currently living with dementia worldwide which will be further increase to 65.7 million by 2013 and 115.4 million by 2050\[^4\].

The brain has 100 billion nerve cells (neurons). Each nerve cell connects with many others to form communication networks. Groups of nerve cells have special jobs. Some are involved in thinking, learning and remembering. Others help us see, hear and smell. Physically, Alzheimer’s is characterized by massive loss of neurons and disrupted signaling between cells in the brain. The disease can be diagnosed postmortem by observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaque is a small, 40/42-amino acid peptide amyloid-beta (Aβ). Aβ, causative agent in AD, was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted among scientific community. Aβ is an elusive entity whose chemical and biological action has been difficult to understand. It is not very soluble, cannot crystallize and has highly changeable structure in a solution\[^5\].

The studies have indicated that as Alzheimer’s disease progresses, neurofibrillary tangles and also the plaques spread throughout the brain starting in the neocortex. By the final stage, damages widespread and brain tissue shrunks significantly. Studies have shown the involvement of neurotransmitter acetylcholine in Alzheimer’s disease resulting into disproportionate deficiency of acetylcholine. It has been documented that markers for cholinergic neurons, acetylcholine transferase and acetylcholine esterase are responsible for acetylcholine synthesis and its degradation decreases in the cortex and hippocampus area of the brain involved in cognition and memory\[^6\]. The study has demonstrated that the resultant decreased in acetylcholine dependant neurotransmission, is associated with the functional deficit of AD\[^7\].
The use of cholinesterase inhibitors in the treatment of patient with Alzheimer disease has been found to be better successful strategy\textsuperscript{[8,9]}. The tacrine, the acridine derivatives, was the first drug approved by food and drug administration (FDA), USA for general clinical use in Alzheimer’s disease. The other four new choline esterase inhibitors approved by FDA, USA to treat Alzheimer’s are Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Reminyl)\textsuperscript{[10-12]}.

The above mentioned drugs are used to treat mild to moderately severe Alzheimer’s. The new drug memantine (nemenda) approved by food and drug administration (FDA), USA in October 2003, is used for treatment of patient with Alzheimer’s at the moderate to severe stage of disease. Other drugs such as selegiline, vitamin E, estrogen and anti-inflammatory drugs have also been studied for treatment of Alzheimer’s, but their clinical use has not been clearly demonstrated\textsuperscript{[11,13]}.

The currently available drugs for the treatment of Alzheimer’s disease do not alter the condition and progression of the disease. They also produced adverse effects in the patients, there by cannot use them for prolong time. To alter the current conditions related to present dosage form, need to search alternative effective therapy, which will alter the present condition also retard the progression of the disease by preventing the formation or clearing of plaques.

Herbal medicine treatment for Alzheimer’s disease becomes very popular now a day because of their activities against AD and slowing down the progression of it. Many herbal medicines have been researched and the benefits derived from using these medicines for AD and dementias are promising. Also, these herbs are inexpensive and can be easily available. The results observed form the treatment with herbal medicines are promising also with fewer adverse effects. Instead of using synthetic drugs with more side effects, herbals supplements can be used as their substitutes. In the present review article, we tried our best to present some of herbal drugs which are using now a day for the treatment of AD. Also, some current research work going on them to prove their mechanism for slowing down the progression of AD. Following herbal plants or their parts are used for treatment for AD.
**Curcuma longa L. (Turmeric, Haridra)**

Family: Zingiberaceae

*Curcuma Longa L.* is an herbal medicine being used in India. It is cultivated in almost all the state of India. It has curcuminoids (~6%), the yellow coloring principles, of which curcumin (diferuloylmethane), constitutes 50-60%\[^{14}\]. Studies have proved that curcumin has anti-inflammatory and antioxidant activities, and it also helps in combating Alzheimer’s disease (AD). Regular consumption of this herb helps in keeping the mind balanced\[^{15}\]. The dose of curcumin can be reduced by making colon targeting\[^{16}\]. Crude drug is used in doses of 3-9 g daily\[^{17}\].

**Bacopa monnieri (Linn.) Welst (Nira Brahmi)**

Family: Scrophulariaceae

It has been used in the ayurvedic system of medicine for centuries. Traditionally, it has been used as a brain tonic to enhance memory development, learning, and concentration\[^{18}\]. Also, it provides relief to patients with anxiety or epileptic disorders\[^{19}\]. In ancient Indian literature, *Bacopa* has been described as one of the most popular medhya drug (Noo-tropic agent). Several studies have revealed that this medicinal herb is advocated as a nervine and mental tonic and may be used for the treatment of neurological and mental disorders\[^{20-24}\]. The constituents which are responsible for *Bacopa*’s cognitive effects are bacosides A and B\[^{25}\]. The triterpenoid saponins and their bacosides are responsible for *Bacopa*’s ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission. Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer’s disease. *Bacopa* has been shown to decrease whole brain AChE activity which reflects that *Bacopa* might prove to be an useful memory restorative agent in the treatment of Alzheimer’s and dementia\[^{26}\]. A clinical study on human subjects demonstrated the potential of *Bacopa monnieri* in the treatment of neuritis\[^{27}\]. Dosage of powdered drug is 5-10 g and infusion 8-16 ml\[^{28}\].
**Centella asiatica** (Mandookparni/ Brahmi)

Family: Apiaceae

It has been demonstrated to possess neuro protective property[29]. Extract from the leaves of *Centella asiatica* has been used as an alternative medicine for memory improvement in the Indian ayurvedic system of medicine for a long time[30]. Recent study conducted on transgenic animal model to evaluate the efficacy of *Centella asiatica* extract (CaE) in the management of AD, has shown that CaE can impact the amyloid cascade altering amyloid β pathology in the brains of PSAPP (presenilin ‘Swedish’ amyloid precursor protein) mice and modulating components of the oxidative stress response that has been implicated in the neurodegenerative changes occurring in AD[31].

**Ginko biloba** (maidenhair tree)

Family: Ginkgoaceae

*Ginkgo biloba* is a 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[32,33]. The broad therapeutic spectrum of *Ginkgo* may be explainable in part by the fact that it influences two fundamental aspects of human physiology: 1) it improves blood flow to the brain and other tissues and 2) it enhances cellular metabolism. Because these functions are essential for good health, it is not unreasonable to consider the possibility that *Ginkgo* might have a broad spectrum of clinical applications. An extract of *Ginkgo biloba* has been found in several studies to improve the symptoms and slow the progression of Alzheimer’s disease (AD) similar to prescription drugs such as Donepezil or Tacitrin, with minimal undesirable side effects. The ginkolides present in *Ginkgo biloba* possess activities pertinent to the disease mechanisms in Alzheimer’s such as antioxidant, neuroprotective and cholinergic activities according to the studies conducted by Medical Research Council of New castle General Hospital[34]. *Ginkgo biloba* improves protection against Aβ protein-induced oxidative damages (degrading hydrogen peroxide, preventing lipids from oxidation, and trapping the reactive oxygen species)[35]. *Ginkgo* leaf extract contains terpenoids (bilobalides and ginkgolides) and flavonoid glycosides. Flavones can reduce the fragility of capillaries, and protect the body...
from blood loss through damaged capillaries, particularly in the brain. The ginkgolides, particularly ginkgolide B, inhibit the platelet-activating factor and so increase the fluidity of the blood that improves circulation, again particularly in the micro-capillaries of the brain. This is also why it is believed to reduce the incidence of cerebral thrombosis and resultant strokes[36]. Various clinical studies have indicated that 3- to 6-month treatment with 120-240mg of *G. biloba* has produced significant effect in Alzheimer’s patients and this herbal drug has shown no significant adverse effect except few case reports of bleeding complications, gastrointestinal discomfort, nausea, vomiting, diarrhoea, headache, dizziness, heart palpitations and restlessness[37-40].

*Salvia officinalis* (Sage)

Family: Lamiaceae

The extract of *Salvia officinalis* (sage) has been found to produce significant benefits in cognition to the patients with mild to moderate AD after 16 weeks of treatment with *S. officinalis*[41]. It contains the antioxidants carnosic acid and rosmarinic acid. These compounds are thought to protect the brain from oxidative damage[42]. The studies have demonstrated that the side effect associated with *S. officinalis* where similar to those observed with cholinesterase inhibitor[43]. However, frequency of agitation appeared to be higher in placebo group which may indicate an additional advantage in the management of patient with Alzheimer’s disease.

*Rosmarinus officinalis* (Satapatrika)

Family: Lamiaceae

It contains the following natural COX-2 inhibitors: Apigenin, carvacrol, eugenol, oleanolic acid, thymol and ursolic acid. In addition, *Rosemary* contains antioxidants and anti-inflammatory compounds. Some of the strongest antioxidants in the herb are carsonic acid and ferulic acid, which have even greater reported antioxidant activity than the widely common synthetic antioxidants Butylated hydroxytoluene (BHT) and Butylated hydroxyanisole (BHA)[44]. The findings of the study indicate that the olfactory properties of this essential oil can produce objective effects on cognitive performance, as well as subjective effects on mood[45]. It has been evaluated using different in vitro and in vivo models to prove their efficiency in the
management of Alzheimer’s disease patient. The studies have demonstrated that extract from plants of the lamiaceae family are active not only in the inhibition of AchE or β-amyloid deposits inhibition 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[46].

*Melissa officinalis* (Lemon Balm)
Family: Lamiaceae

*Melissa officinalis* was believed to sharpen memory. *Melissa officinalis* has shown to improve cognitive function and to reduce agitation in patients with mild to moderate AD. Studies have demonstrated *M. officinalis* causes ACh receptor activity in central nervous system with both nicotinic and muscarinic binding properties[47-48]. This plant has also been reported to modulate mood and cognitive performance when administered to young and healthy volunteer[49]. So, concluded that *M. officinalis* one of several plants that may be useful in the prevention and treatment of Alzheimer’s disease due to its ability to inhibit acetylcholinesterase and its antioxidant activity.

*Glycyrrhiza glabra* (Licorice Root)
Family: Fubaceae

Alzheimer’s disease is characterized by neuronal loss and the presence of the extracellular senile plaque, whose major constitute is amyloid-β peptide (Aβ). In that study, it was investigated the effect of water extract of licorice on Aβ 25-35- induced apoptosis in PC12 cells. Results suggest that GWE exerts a protective effect against apoptotic neuronal cell death induced by Aβ fragments. Extract from the licorice root is reported to treat or even prevent brain cell death in disease like Alzheimer’s and its associated symptoms[50]. Recent studies have shown that the dose of 150 mg /kg of the aqueous extract of licorice significantly improved learning and memory of mice[51].
**Galanthus nivalis** (snowdrop) (Alkaloid-Galantamine)

Family: Liliaceae

The chief chemical constituent of the *Galanthus nivalis* is galantamine, and this is an isoquinoline alkaloid. Clinical studies on the efficacy of galantamine have demonstrated its use in the treatment of mild to moderate AD and other memory impairments. This drug has been found to be a competitive and selective acetylcholinesterase inhibitor. It is hypothesized that this action might relieve some of the symptoms of AD. This drug has also been shown to modulate allosterically nicotine Ach receptors on cholinergic neurons to increase acetylcholine release, which can be beneficial for the treatment of AD\textsuperscript{52}.

**Huperzia serrata** (firmosses)

Family: Licopodiaceae

*Huperzia serrata* contains a large group of alkaloids called ‘licopodium alkaloids’. Huperzin A, a novel licopodium alkaloid extracted from *Huperzia serrata*, is well known as a reversible, potent and selective AChE inhibitor and improves memory and mental functioning in patient with alzheimer’s and other severe conditions\textsuperscript{52-54}. This drug has been shown to possess antioxidant and neuroprotective properties suggesting thereby its potential in the treatment of Alzheimer’s disease\textsuperscript{55,56}.

**Commiphora wighitti** (Guggul or Mukul myrrh tree)

Family: Burseraceae

*Commiphora wighitti*, a plant resin contains a major of guggulipid, which is guggulusterone Z and E. The guggulipid has been seen to be a potential cognitive enhancer for improvement of memory in scopolamine induced memory deficits\textsuperscript{57}. *Commiphora wighitti* acts on impairment in learning and memory and decreases choline acetyl transferase levels in hippocampus. However it shows maximum effect on memory functions and the potential for dementia disorder\textsuperscript{58}.
Panax ginseng (Ginseng root)
Family: Araliaceae
Panax ginseng contains saponins protopanaxadiol, protopantriol and oleanolic acid. Saponins that are reported to have memory enhancing action for the learning impairment induced by scopolamine\(^5\). Ginseng has been shown to exhibit protective and tropic effect in memory functions of alzheimer’s disease. Clinical study conducted on group of AD patients has demonstrated that Panax ginseng is clinically effective in the cognitive performance of AD patients\(^5\)\(^9\). In addition, the studies conducted to evaluate the efficiency of Panax ginseng in the treatment of alzheimer’s disease patients have demonstrated significant effect in the favor of ginseng on the Mini-Mental Status Examination, and on the alzheimer’s disease assessment scale (ADAS)-cognitive\(^6\)\(^0\). Research has also suggested that ginseng is able to enhance the psychomotor and cognitive performance, and can benefit AD by improving the brain cholinergic function, reducing the level of AD and repairing the damaged neuronal networks\(^6\)\(^1\).

Tinospora cordifolia (Guduchi)
Family: Menispermaceae
Tinospora cordifolia possesses a memory enhancing property for learning and memory in normal and memory deficits animals. Tinospora cordifolia’s mechanism for cognitive enhancement is by immunostimulation and synthesis of acetylcholine, this supplementation of choline enhances the cognitive functions\(^5\)\(^7\).

Withania somnifera (Ashwagandha)
Family: Solanaceae
Withania somnifera has been described as a nervine tonic\(^6\)\(^2\)\(^,\)\(^6\)\(^3\) in ayurveda and that is why it is a common ingredient of ayurvedic tonics, rejuvenators and vitalizer appear to ally disease and induced immunity and longivity in the users\(^6\)\(^4\)\(^-\)\(^6\)\(^6\). The assessment of cholinesterase inhibition was carried out using a colorimetric method based on Ellman’s reaction and demonstrated
that the W. Somnifera extract significantly inhibited AChE in a concentration dependent manner[67]. Withania somnifera has been shown to slow, stop reverse and remove neuritic atrophy and synaptic loss, which is the main cause for neurodegenerative disorders including Alzheimer’s and dementia as confirmed by several clinical studies. Therefore, this herb can be used for the treatment and management of patient with AD. It improves growth of new dendrites of neurons. Glycowithanolides withaferin – A and sitoindosides VII-X isolated from the roots of Withania somnifera have been shown to significantly reverse the ibotenic acid induced cognitive defects in AD model[68].

*Catharanthus roseus* (Alkaloid-Vinpocetine)

Family: Apocynaceae

Vinpocetine is a chemical derived from vincamine, a constituent found in the leaves of *Catharanthus roseus*, as well as the seed of various American plants[69]. Vinpocetine is described as a specific inhibitor of basal and calmodulin-activated phosphodeesterase 1 (PDE1). This effect leads to an increase of cAMP over cGMP[70]. Vinpocetine has been shown to facilitate long term potential, enhance the structural dynamics of dendritic spines improve memory retrieval[71], and enhance performance on cognitive test in humans[72]. Vinpocetine is found to dilate the cerebral vascular, promote the redistribution of blood flow and favor the aerobic glycolysis towards damaged areas[73]. Because of this it’s showing neuro protective effects[74]. It is used as a drug in Eastern Europe for the treatment of cerebrovascular disorders and age related memory impairment[75]. Several double –blind studies have evaluated vinpocetine for the treatment of AD and related conditions[76]. It increases level of neuro transmitters like cholinergic, nor-adrenaline and dopamine associated with spatial working memory tasks[77] and enhances cognition and memory[78]. Vinpocetine decreases the disrupting effect of scopolamine on acquisition and prevent the memory loss. It also has been reported that vinpocetine improves memory and reduce oxidative stress and cholinergic deficit in experimental model of Alzheimer’s disease[77].

*Euphorbia royleana* boiss (source of Shilajit)

Family: Euphorbiaceae

Shilajit is a dark, thick, viscous, sticky, unctuous, complex substance having a number of organic and inorganic
compounds flowing out from the rocks occurring in the north western belt of lower Himalayan hills from Nepal to Kashmir and is known as bitumen or mineral resin\textsuperscript{[79]}. Shilajit is used in Ayurveda, the traditional Indian system of medicine. It is a rasayan material which has adaptogenic, antistress and immunomodulatory activities\textsuperscript{[80]}. Studies have demonstrated the potential of shilajit in the treatment of AD disease\textsuperscript{[81]}. The studies to assess its effectiveness in the management of AD demonstrate that shilajit affects some events in cortical and basal forebrain cholinergic signal transduction cascade in rat brain. Studies have been conducted on drugs that enhance cholinergic activity as potential therapeutic agent in the treatment of AD. Further, it has also been seen that systemic administration of defined extracts from the \textit{Withania somnifera} (Indian ginseng) in combination with shilajit differentially affects preferentially events in the cortical and basal forebrain cholinergic signal transduction cascade\textsuperscript{[82]}.

\textbf{Crocus Sativus (Saffron)}

Family: Iridaceae

Studies suggest that \textit{Crocus Sativus} stigmas extract may have antioxidant and antiamyloidogenic activity, thus reinforcing ethnopharmacological observation that saffron has a positive effect on cognitive function\textsuperscript{[83]}. The main carotinoid constituent, trans-crocin-4, the digentibiosyl ester of crocetin inhibited Aβ fibrillogenosis formed by the oxidation amyloid β-peptide in AD\textsuperscript{[84]}. \textit{Crocin} demonstrated cognitive enhancing activity in mice\textsuperscript{[85]}.

\textbf{Eclipta alba (Bhringaraj)}

Family: Asteraceae

\textit{Eclipta alba} leaf extract contains luteolins, which may be responsible for minimizing cognitive deficit due to cholinergic disfunctioning. Their profound free radical scavenging action could insulate neuronal tissues from degeneration probably by preserving these areas from stress perturbations. Protection of neuronal tissues may be possibly due to the immune modulatory actions of \textit{Eclipta alba}. Therefore, \textit{Eclipta alba} can serve as a potential memory modulator\textsuperscript{[86]}. \textit{Eclipta alba} has been found to activate Na\textsuperscript{+} K\textsuperscript{+} ATPase which produces an elevation in the intracellular concentration of Ca\textsuperscript{+2}. Stimulation of the Ca\textsuperscript{+2} receptor induces
the release of 5-hydroxytryptamine. The enhanced turnover of 5-HT can cause blunting of aggression and could be of plausible reason for the antiaggressive property of *Eclipta alba*. In conclusion, the total aqueous extract of *Eclipta alba* was found to be efficacious in producing serenity and masking the constellation of behavioral changes encountered during aggressive bouts making it a promising naturally derived product\[87\].

Some others medicinal plants effects in the treatment of Alzheimer’s disease (AD) and are: *Maticaria recutita* (Asteraceae), *Lipidium meyetti walp* (Brassicaceae), *Acorus ralamus* (Araceae), *Angelica archangelica* (Umbelliferae), *Colliuronia canadensis* (Lamiaceae), *Bentholattia excels* (Lecythidaceae), *Celastrus peniculatus* (Celastraceae), *Urtica dioica* (Clusiaceae), etc.

**CONCLUSION**

The present treatment strategies for the management of patients with Alzheimer’s disease available in allopathic drugs are approved by Food and Drug Administration (FDA), USA. These treatment strategies are not satisfactory and not able to cure the disease completely. Moreover, these drugs are symptomatic and do not alter the current conditions or progression of the underlined disease. Also they produce various side effects. Therefore, further exploration can be done for the better treatment with least side effects for Alzheimer’s disease.

Herbs have a low toxicity compare to allopathic drugs approved by FDA,USA which play a important role in the early stages of the disease and other conditions involving poor memory and dementia. The herbal drugs can be used along with the other drugs as supplementary. For the patients having the history of AD in the family may start taking these supplements to delay or to reduce the further advancement of the disease. This review is to highlight the possible role of many herbs which have shown their effectiveness in Alzheimer’s or any other memory related disorders. The plants mentioned in this article helpful in treating and managing the disease due to their anti-oxidant, anti-inflammatory, neuroprotective, procholinergic and anti-acetylcholinesterase properties. Further, large scale studies are required to determine effectiveness of these herbs in the treatment and management of AD. Until then, this review will provide some facts regarding the benefit of the herbs mentioned in the article.
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