Review Article

Role of Medicinal Plants in the Treatment of Alzheimer's Disease: A Review

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Abstract: Alzheimer's disease (AD) is an age related neuro degenerative disorder that is characterized by a progressive loss of memory and deterioration of higher cognitive functions. The brain of an individual with AD exhibits extracellular plaques of aggregated β-amyloid protein (Aβ), intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein and a profound loss of basal forebrain cholinergic neurons that innervate the hippocampus and the neocortex. There are several studies and alternative therapies which offer ways to slow the onset and progression of AD in some patients. Many synthetic drugs because of many unwanted but unavoidable side effects have poor patient compliance. Herbal remedies for AD have become more and more popular in the recent years and not without a reason that there is a possibility to slow down the brain's degeneration caused by Alzheimer's with natural treatments and it has drawn the attention of the scientific community. Therefore herbal treatment is being preferred over conventional treatments. This review covers a broad spectrum of natural drugs used in AD. This topic also discuss about active constituents and specific part of the plant being used.
Keywords : Alzheimer's disease, β-amyloid protein, cholinergic neurons, patient compliance, Herbal remedies.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of the dementia which occurs among older people above the age of 60 years. The Alzheimer's disease once considered a rare disorder and it is now seen as a major public health problem that is seriously affecting millions of older people and their family's world over. 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. According to the World Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide [1]. World Health Organization (WHO) has estimated that 35.6 million people are currently living with dementia worldwide which will be further increased to 65.7 million by 2030 and 115.4 million by 2050 [2].

It has been observed that there are seven stages found in Alzheimer's disease. Stage one is normal behavior. Stage two is minor memory lapse. In stage three, there is confusion and loss of names; this borderline condition which does not necessarily lead to Alzheimer's. Stage four or "mild" Alzheimer's is the inability to think rationally. In stage five, "moderate" Alzheimer's, the patient can't remember names of close relatives. In stage six, "moderately severe" Alzheimer's,

There is inability to dress oneself and take care of personal needs. In stage seven, there is loss of speech and incontinence. The eighth stage of Alzheimer's disease is death [3]. The disease can be diagnosed by post mortem, observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaques is a small, 40 or 42 amino acid peptide: amyloid beta (Aβ). Aβ, causative agent in Alzheimer's, was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted amongst scientific community. Uncovering the chemistry associated with Aβ is crucial to understanding Alzheimer's progression and may shed light on its cause or causes. Aβ is an elusive entity whose chemical and biological actions have been difficult to understand. It does not crystallize, is not very soluble and has a highly changeable structure in solution. On incubation, it does form ordered fibrils that can be analyzed by nuclear magnetic resonance (NMR) analysis. Whilst the structure of the toxic species has not been established, the peptide is known to be as it's most damaging in aggregates of two or more. Therefore, the fibril structures can provide clues about the nature of the toxic aggregates [4].

The studies have indicated that as Alzheimer's disease progresses neuro-fibrillary tangles spread throughout the brain and plaques also spread throughout the brain, starting in the neocortex. By the final stage damage is wide spread and brain tissue has shrunk significantly. The neuro chemical disturbances that arise in Alzheimer's disease have been studied intensively [5].

Herbal remedies for Alzheimer's disease have become more and more popular in the recent years and not without a reason that there is a possibility to slow down the brain's degeneration caused by Alzheimer's with natural treatments and it has drawn the attention of

the scientific community. Many natural herbal treatments have been researched and the benefits derived from using herbal treatments for Alzheimer's and Dementia have been very promising and the use of some medicinal herbs have been touted to extend beyond that of modern prescription drugs. With so many natural and healthy compounds, it's no wonder that these medicinal herbs may hold the key to the cure to this devastating disease. In addition, these herbs are inexpensive and can be easily obtained. Clinical research is being conducted world over to test the efficacy of herbal medicines in treating Alzheimer's or dementia patients. The results are promising, as herbal products have been found to be not only as effective as prescription drugs but also with fewer side effects. Herbal supplements may be used as a substitute for pharmaceutical drugs or can be used in conjunction with the latter. In the present review, attempts have been made to present state of art of studies made on the role of few herbal medicines in the treatment and management of Alzheimer's disease.

Ginkgo biloba

The Ginkgo tree is indigenous to Korea, Japan, and China, but can be found worldwide. It may grow to 40 m, and live for over 1,000 years. Fossils of the Ginkgo tree date back to 250 million years ago.10 Extracts from Ginkgo biloba have been used medicinally for thousands of years to treat circulatory problems, asthma, vertigo, fatigue and tinnitus, in addition to being used for cognitive disturbances. GbE is typically standardized to contain 24% ginkgo-flavones glycosides and 6% terpenoids, although concentrations and extraction methods vary. Numerous mechanisms have been proposed for GbE on the basis of animal studies which have suggested effects on cerebral blood flow, neurotransmitter systems, cellular redox state, nitric oxide levels, and antagonism of platelet activating factors [6, 7]. There have been several small clinical trials of Ginkgo. A 1998 meta-analysis of randomized placebo-controlled trials in patients diagnosed with Alzheimer disease identified four studies which met their established inclusion criteria and provided sufficient data for analysis, resulting in analyzable data for 212 patients treated with GbE and 212 with placebo. Dosage was either 120 mg or 240 mg of GbE per day in all four studies. This treatment with a standardized GbE provided a modest improvement in cognitive measures, with an effect size comparable to that reported in a meta-analysis of cholinesterase inhibitors [8, 9].

Ashwagandha

Withania somnifera (WS), also known as ashwagandha, Indian ginseng, and winter cherry, it has been an important herb in the Ayurvedic and indigenous medical systems for over 3000 years. The roots of the plant are categorised as rasayanas, which are reputed to promote health and longevity by augmenting defence against disease, arresting the ageing process,

revitalising the body in debilitated conditions, increasing the capability of the individual to resist adverse environmental factors and by creating a sense of mental wellbeing [10]. Chemical constituents of ashwagandha are always of an interest for the researchers. The biologically active chemical constituents are alkaloids (ashwagandhine, cuscohygrine, anahygrine, tropine etc), steroidal compounds, including ergostane type steroidallactones, withaferin A, withanolides A-y, withasomniferin-A, withasomidienone, withasomniferols A-C, withanone etc. Other constituents include saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides with a glucose at carbon 27 (sitoindoside IX and X) [11, 12]. Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of cultivated varieties of WS were studied on brain cholinergic, glutamatergic and GABAergic receptors in rats. The compounds slightly enhanced acetyl cholinesterase (AChE) activity in the lateral septum and globus pallidus, and decreased AChE activity in the vertical diagonal band. These changes were accompanied by enhanced M1-muscarinic-cholinergic receptor binding in lateral and medial septum as well as in frontal cortices, whereas the M2-muscarinic receptor-binding sites were increased in a number of cortical regions including cingulate, frontal, parietal, and retrospinal cortex. The data suggest the compounds preferentially affect events in the cortical and basal forebrain cholinergic-signal transduction cascade. The drug-induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognition enhancing and memory-improving effects of WS extracts in animals and in humans [13]. In a study by Zhao, Withanoside IV induced neurite outgrowth in cultured rat cortical neurons. Oral administration of withanoside IV significantly improved memory deficits in Abeta-injected mice and prevented loss of axons, dendrites, and synapses. Sominone, an aglycone of withanoside IV, was identified as the main metabolite after oral administration of withanoside IV. Sominone induced axonal and dendritic regeneration and synaptic reconstruction significantly in cultured rat cortical neurons damaged by Abeta. Withanoside IV may ameliorate neuronal dysfunction in Alzheimer's disease and that the active principle after metabolism is sominone. In another study reserpine treated animals also showed poor retention of memory in the elevated plus maze task paradigm. Chronic WS administration significantly reversed reserpine-induced retention deficits [14].

Bacopa monneri

In the ancient Indian system of medicine, viz., Ayurved, *B. monnieri* has been classified under medicinal plants rejuvenating intellect and memory. Therefore, this plant has been investigated in several laboratories in India for its various neuropharmacological [15, 16]. *B. monnieri* in the

treatment of dementia disorders, effects of these plants on acetyl cholinesterase (AChE) enzyme has not been investigated. Knowing the fact that the inhibition of AChE, the metabolizing enzyme of acetylcholine is presently the most accepted and recognized therapeutic marker for development of cognitive enhancers, it becomes more pertinent to study the anticholinesterase activities of this plant [17, 18]. The saponins bacoside A and B have been claimed to be the active principles regarding enhancement of cognitive function [19]. They, apart from facilitating learning and memory in normal rats, inhibited the amnesic effects of scopolamine, electroshock and immobilization stress. Furthermore, *Bacopa monnieri* has been shown to enhance protein kinase activity in the hippocampus, which could also contribute to its nootropic action. When *Bacopa monnieri* was administered along with phenytoin for 2 weeks, it significantly reversed phenytoin-induced impairment in rats [20]. *Bacopa monnieri*, administered for 2 weeks, reversed the depletion of acetylcholine. Further, it reduced the choline acetylase activity and decreased muscarinic, cholinergic receptor binding in the frontal cortex and hippocampus, induced by neurotoxins, such as colchicines [21].

Centella asiatica

Centella asiatica (L.) Urban, family Apiaceae (CA) is known as *Mandookaparni* or *Brahmi* in Ayurvedic medicine. It is highly regarded as a "rasayana" or rejuvenating herb and is reputed to increase intelligence and memory. The dried herb has enjoyed growing popularity in the USA and other Western countries, where it is sold as the dietary supplement "gotu kola" [22]. Cognitive effects of the aqueous extract of CA (100– 300 mg/kg/day) have been evaluated in several rodent studies using standard tests including shuttle box, step-through paradigm, elevated plus maze, and passive avoidance tests. CA extract markedly improved learning and memory of wild-type rats [23], rats subjected to CNS toxicity intracerebroventricular streptozotocin [24], and pentylenetetrazole (PTZ) kindled rats [25].When administered to neonatal mice from day 15 to 30 postpartum, the extract caused significant enhancement in learning efficiency and spatial memory with no effects on loco motor function . Direct neurotropic effects of CA have also been reported. CA aqueous extract caused significant increases in dendritic arborization of apical and basal dendrites in hippocampus neurons of neonatal mice and both adult and neonatal rats [26, 27, 28]. These studies, performed in diverse settings, show that CA water extract has biological effects of relevance to memory, learning, and aging, and potentially to disease progression in Alzheimer's disease (AD).

Ocimum sanctum Linn

Ocimum sanctum Linn (OS) (Labiatae), a popular indigenous plant in India, and is commonly grown in households here. In Ayurveda, it is described as 'Rasayana' [29]. It has earlier been proved to possess cognition enhancing and antioxidant attributes in other models of cerebrodegenerative disorders. As AD is also associated with cognitive deficits and increased oxidative stress, the effect of OS in Alzheimer's disease was evaluated in well-validated models, using neurotoxins like ibotenic acid and colchicine. Ibotenic acid is a structural analogue of glutamate and causes neuronal necrosis by excitotoxicity stimulating glutamate receptors. Injections of ibotenic acid into the medial septum in rats lead to a profound deficit in spatial learning and memory in the Morris water maze test, a model that represents the advanced stage of AD. It has been reported that intradentate infusion of colchicine induces memory deficits, by destroying granule cells in the dentate gyrus of the hippocampus [30].

Emblica officinalis

Emblica officinalis (Euphorbiaceae) is a native plant with rasayana properties and the main ingredient in this preparation for a disease-free life with long lasting youth, great vigour and no dementia. Another traditional recipe made is prepared with 1000 fruits of *Emblica officinalis* (Euphorbiaceae) and 1000 fruits of *Piper longum* (Piperaceae). They are dipped in alkalinewater prepared from a *Butea monosperma* (Fabaceae) tree, and then powdered. The powder is mixed four times its weight with honey and ghee, and one-fourth of sugar and stored underground for 6 months. The preparation should be taken life-long from new moon to full moon starting later in youth or middle age. The dose is based on the person's individual digestive ability. This remedy is optimistically recommended for a lifespan of 100 years with full vigour, cognitive function and to preserve youth [31].

Curcuma longa

Curcuma longa is a member of the ginger family indigenous to South and Southeast Asia, where it is grown commercially. Turmeric is derived from the rhizome (root) of the plant, whose most important commercial application is curry. Eleven clinical trials are currently recruiting participants, including two in Alzheimer disease. Experimental evidence has suggested several possible mechanisms of action relevant to AD. *In vitro* and *in vivo* evidence suggests anti-oxidant and anti-inflammatory properties as well as a direct effect against β-amyloid aggregation. *In vivo* data has demonstrated curcumin passes the blood-brain barrier, and that it possesses cholesterol-lowering properties. Several animal studies suggest that this agent may reduce of oxidative damage and amyloid pathology in Alzheimer transgenic mice and may modulate of amyloid-induced cytopathology or macrophage processing of amyloid [32, 33, 34].

Salvia species

Tabernaemontanus (1687) recommended sage, *Salvia* sp., from various regional provenances for the treatment of a 'weak brain'. Flowers should be crushed and mixed with sugar. Or the plant can be extracted in strong wine in the sun for a day before distilling. The remedies help those who shiver and suffer the effects stroke and strengthen weak minds and memories [35]. Since Perry recently provided a review, summarizing available literature on the use of *Salvia* species in dementia therapy, this plant will only be treated briefly [36]. Besides the cholinergic activity, there has already been a wider range of activities reported for the genus *Salvia*, which may be relevant for CNS disorders. It assessed the efficacy and safety of *Salvia officinalis* extract in patients with mild to moderate AD. The participants experienced statistically significant benefits in cognition after 16 weeks of treatment. Despite the limitations of this study, a small number of patients and a relatively short period of follow-up, this initial oil and extracts, may have potential for treatment of AD and memory related disorders [37].

Melissa officinalis

"Aerial parts of lemon balm, *Melissa officinalis* (Lamiaceae) are finely cut and covered in good wine over night in a clean dish, before being distilled. Taken on an empty stomach a spoonful quickens the senses, brightens the mind and improves memory. It aides shaking limbs caused by stroke, and helps retrieve the lost ability to speak". The remainder of this historic citation is a romantic description of clever bees sucking at the flowers. Essential oil of *Melissa officinalis*, which contains monoterpenes such as citral and citronella, shows a dose-dependent inhibitory effect on the enzyme AChE [38, 39].

Boerhavia diffusa

Boerhaavia diffusa, belonging to the family of the Nyctaginaceae, is mainly a diffused perennial herbaceous creeping weed of India (known also under its traditional name as *Punarnava.* Ethanol and methanol extracts were prepared and screened for in-vitro antioxidant activities using Ferric reducing power and Hydrogen peroxide scavenging activity. The activity was compared to standard antioxidant like ascorbic acid. Both the extract showed strong antioxidant activity in both the methods. Between these two extracts, ethanolic extract has shown better antioxidant activity as compared to methanolic extract in both the activities[40]. Aqueous extract of each plant part was tested against DPPH radical, one reactive oxygen species and one reactive nitrogen species (NO). Moreover, activity against acetyl cholinesterase, an enzyme with a well-known role in several physiopathological processes, was assayed. When possible, the relation between the chemistry and activity displayed was established. Leaves revealed stronger antioxidant activity than roots, and acetyl cholinesterase inhibition was not found in neither plant part [41].

Piper nigrum and Piper longum

Piperine, a major alkaloid of black pepper (*Piper nigrum Linn.*) and long pepper (*Piper longum Linn.*), has been used in folk medicine for the treatment of various diseases. Pharmacological studies have shown that piperine possesses various activities including anti-inflammatory and analgesic, anticonvulsant, anti-ulcer, anti-depressant, cytoprotection, antioxidant and cognitive enhancing effect. It inhibits monoamine oxidase (MAO) activity and increases the level of nor adrenaline and serotonin in mouse brain, indicating its potential neurological benefits. Piperine could affect hippocampus neurogenesis in chronic mild stressed mice in which the level of brain-derived neurotropic factor decreased. At a dose between 5 - 20mg/kg body weight given to cholinergic-deficient rats, induced by AF64A, piperine could attenuate the increase in lipid peroxidation and acetyl cholinesterase activity [42, 43, 44].

CONCLUSION

Herbal medicines are considered as big chemical libraries have been developed for the treatment of AD. To date the pathophysiology of AD is not yet nearly clarified. Further research will provide better understanding of the molecular pathways involved and hereby lead to the development of additional pharmacological test systems, in which activities may yet be observed. Also, some traditional medical systems such as Ayurveda emphasize health maintenance and disease prevention over curative treatments. Hence, preclinical and clinical research into protective and preventive effects of herbals drugs should be carried out in the future.

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