REVIEW ARTICLE

# Alzheimer's Disease Treatment with Herbal Prospective

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## Abstract

Alzheimer's disease (AD) is a chronic, progressive, neurodegenerative disorder that places a substantial burden on patients, their families, and society. AD has no cure, but certain drugs are available, which can slow down the disease progression. During the past years, several agents have been approved that enhance cognition and global function of AD patients. The presently available drugs for the treatment of Alzheimer's disease are symptomatic only and produce adverse reactions in patients, thereby having limited scope for the treatment of patients of Alzheimer's syndrome. Herbal therapies for Alzheimer's disease have become more and more popular in recent years as herbal products have been found to be as effective as prescription drugs but also with fewer side effects. This review reveals that some plants and their part used having anti-Alzheimer's activity, which is helpful for the researcher to develop new herbal remedies in the treatment and management of Alzheimer's disease.

**Keywords:** Alzheimer's disease, Herbal remedies, Review

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## Introduction

Alzheimer's disease (AD) is a chronic, progressive, neurodegenerative disorder that places a substantial burden on patients, their families, and society. Alzheimer's disease (AD) is the sixth leading cause of all deaths in the United States and the fifth leading cause of death in Americans aged 65 and older.[1] It is estimated to affect 15-million people worldwide. AD is the cause of dementia in the elderly. AD is a progressive neurological disorder with a duration of around 8.5 years between the onset of clinical symptoms and death.[2] According to the free radical hypothesis, the aging process is associated with multisystem failure due to oxidative damage caused by an imbalance between reactive oxygen species production and antioxidant defenses. Cytopathological significances of oxidative damages are supported by findings of the upregulation of antioxidant enzymes like heme oxygenase$^{-1}$ and superoxide dismutase in neurons of AD. Furthermore, lipid peroxidation (LPO), a hallmark of oxidative tissue injury has been found to be elevated in AD brain.[3] 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 the names of close relatives. In stage six, "moderately severe" Alzheimer's, There is an inability to dress oneself and take care of personal needs. In stage seven, there is a loss of speech and incontinence. The eighth stage of Alzheimer'sdisease is death.[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 particular jobs, e.g., some are involved in thinking, learning, and remembering while others help us see, hear, and smell. Physically, Alzheimer's is characterized by a 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, the causative agent in AD, was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted among the 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 a highly changeable structure in a solution.[5] The presently available drugs for the treatment of Alzheimer's disease are symptomatic only and do not alter the course or progression of the underlying disease and produce adverse reactions in patients, thereby having limited scope for the treatment of patients of Alzheimer's syndrome.[6] Herbal medicine offers several options to modify the progress and symptoms of AD. There has been a new trend in the preparation and marketing of drugs based on medicinal plants, and their scientific and commercial significance appears to be gathering momentum in health-relevant areas. These plant-derived products are carefully standardized, and their efficacy and safety for a specific application have been demonstrated.[7]

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## AD Pathology

At the most basic level, AD results from cell death that can result from many different factors. Alzheimer's brains have low levels of acetylcholine (Ach), which can arise from the accumulation of beta-amyloid (βA) protein fragments that form hard plaques that can, in turn, interfere with the ability of Ach to affect synaptic transmission and initiate inflammatory processes that produce reactive oxygen species. Research suggests that βA opens channels in cell membranes, permitting calcium ions ($Ca^{2+}$) to enter the cell and triggering several processes leading to mitochondrial dysfunction, inflammation, and cell death. Some research suggests that, in the early stages of AD, βA has an antioxidant function so that efforts to reduce it might be counterproductive. Other research has found only a weak relationship between the amounts of βA and the severity of AD. βA may be the result of the destructive chain of events and hence more symptomatic than problematic. Another possible cause of cell death in AD is a chemical change

in a protein (tau) that keeps microtubules stable. This causes a neuron's microtubules to pair with other tubules producing tau (neurofibrillary) tangles that result in tubule disintegration and block neurotransmitters, leading to cell death. Reactive oxygen speices (oxygen ions, peroxides, and free radicals) can result in cell death by initiating a chain reaction that leads to damage of cell membranes, mitochondria, lipids, and proteins. Damage from toxic excitotoxicity amino acid neurotransmitters, especially glutamate, can produce excitotoxicity and cell death. Excitotoxicity can occur even with normal glutamate levels if glutamate receptor sites become overstimulated. The receptor most involved in excitotoxicity is N-methyl-D-aspartic acid (NMDA). If NMDA sites are overactivated then high levels of $Ca^{2+}$ can enter the cell, causing a permanent depolarization of the postsynaptic neuron creating reactive oxygen species and other substances that may cause cell death. Potential mechanisms have also linked excitotoxicity to βA and tau tangles. Damage from toxins, chemicals, and trauma can produce inflammation, another factor in AD. Inflammation often results from persistent oxidative stress, but other determinants include βA, protease inhibitors, pentraxins, inflammatory cytokines, and prostaglandin-generating cyclooxygenases. Unhealthy neurons contain low levels of N-acetyl-aspartate (NAA), which may also be an issue. Exposure to pollutants can make the blood-brain barrier permeable to toxins, thus causing oxidative stress, inflammation, and βA accumulation.[8]

## Medicinal Plants to Treat Alzheimer

### *Ginkgo biloba* (Maidenhair tree)

*Family: Ginkgoaceae*

*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 brain activity, and to slow down the degenerative effects of Alzheimer's disease.[9] An extract of *Gingko 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 Tactrin, with minimal undesirable side effects. The ginkgolides 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. *Ginkgo Biloba* improves protection against Aβ protein-induced oxidative damages (degrading hydrogen peroxide, preventing lipids from oxidation, and trapping the reactive oxygen species).[5]

### *Galanthus nivalis* (snowdrop) (Alkaloid-Galantamine)

*Family: Liliacea*

The chief chemical constituent of the *Galanthus nivalis L*. (common snowdrop) is Galantamine, and this is an isoquinoline alkaloid. Acetylcholinesterase (AChE) inhibitors, that are also called 'anticholinesterase drugs', have been recently approved as a promising treatment approach for AD. Galanthamine has been found to be the long-acting and specific inhibitor of the AChE enzyme and to potentiate cholinergic nicotinic neurotransmission by allosterically modulating the nicotinic acetylcholine receptors, which may be of additional value in the treatment of AD.[10-11]

### *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 the central nervous system with both nicotinic and muscarinic binding properties.[5] The ethanolic extracts of *M. officinalis*, magnolol, and honokiol, are reported to have antioxidant activity *in vitro* and *in vivo*.[12]

### *Huperzia serrata* (firmosses)

*Family: Licopodiaceae*

*H. serrata* (Thunb. ex Murray) is one of the genera in the Huperziaceae family (Syn. Lycopodiaceae family). This genus has been used for its memory-enhancing effect since ages in the Traditional Chinese Medicinal system (TCM), and is known to contain a large group of alkaloids called 'Lycopodium alkaloids'. Huperzine A, a novel Lycopodium alkaloid extracted from Huperzia serrata, is well known as a reversible, potent, and selective AChE inhibitor. It is also known as 'Qian Ceng Ta' in China, and Huperzine A has been used as a therapeutic agent for AD from centuries. Research has also shown that Huperzine-A substantially reduces the abnormally high radical activity both in the brains of elderly animals as well as in the blood of Alzheimer's patients. An experimental study in monkeys has shown that it reverses scopolamine-induced amnesia, suggesting that it may benefit the cognitive problems in Alzheimer's patients or those with other cognitive disorders.[13]

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

*Family: Burseraceae*

It is a shrub or small tree, reaching a maximum height of 4 m, with thin papery bark. The active ingredient in the extract is the steroid guggulsterone, which acts as an antagonist of the farnesoid X receptor. The guggulipid shows potential cognitive enhancers for improving memory in scopolamine-induced memory deficits. The Commiphora whighittiacting on impairment in learning and memory and decreased choline acetyltransferase levels in the hippocampus.[14]

### *Panax ginseng* (Ginseng root)

*Family: Araliaceae*

*Panax Ginseng* (Ren-shen) contains saponins protopanaxadiol, protopantriol, and oleanolic acid saponins that are reported to have memory-enhancing action for the learning impairment induced by scopolamine. Ginseng grows in Northeastern Asia. The Ginseng root has been used in folk medicine in countries like China and Korea, for boosting *Qi* (energy), from ancient time. Ginseng has a history of medicinal use that goes back thousands of years. The ginseng extract has many uses, and claims to achieve and maintain both physical health and mental well-being. 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.[15]

### *Salvia officinalis* (Sage)

*Family: Lamiaceae*

S. officinalis has a very old reputation for improving memory. It is singularly good for the head and brain.[16] The potential pharmacological effects of the herb, which may be relevant to AD, include anti-inflammatory and antioxidant properties as well as weak AChE inhibitory effect. The leaves of S. officinalis L. (sage) are well known for their antioxidative properties.[17] Rosmarinic acid (the main active ingredient of S. officinalis) reduced a number of deleterious events induced by Aβ include reactive oxygen species formation, lipid peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation.[18]

### *Convolvulus pluricaulis Chois.* (Shahkpushpi)

*Family: Convolvulaceae*

*C. pluriculis*, commonly known as Shahkpushpi, is a fulvous hairy herb that has been prescribed by Ayurvedic practitioners for the treatment of nervous disorders and as an antiaging remedy.[19] The whole plant in the form of a decoction is used with milk and cumin to treat fever, disability, memory loss, syphilis, and scrofula.[20]

### *Centella asiatica* (Mandookparni/ Bramhi)

*Family: Umbelliferae*

*C. asiatica* is a slender perennial creeper that grows throughout the tropical regions in the world. The leaf, known locally as Gotu Kola, has been used in AM for revitalising and strengthening nervous function and memory. For example, an Ayurvedic formulation composed of 4 herbs, including C. asiatica is used as a restorative and for the prevention of dementia. In TCM, it is also used to combat physical and mental exhaustion. Aqueous leaf extracts modulated dopaminergic, serotonic, and adrenergic systems *in vivo* and improved learning and memory.[21]

### *Curcuma longa L.* (Turmeric, Harida)

*Family: Zingeberaceae*

Rhizomes of *C. longa*, commonly known as turmeric, have been used extensively for their culinary properties in Indian cooking and are used in AM as a remedy against aging. An aqueous extract of the rhizome demonstrated antidepressant activity in mice following oral administration, which was associated with inhibition of brain MAO type A. Antidepressant activity is of significant importance in the management of AD.[22]

### *Bacopa monnieri (Linn.) Weltst* (Nira Brahmi)

*Family: Scrophulariaceae*

Goswami *et al*. evaluate the effect of *Bacopa monnieri* (*Brahmi*), associated with the Ayurveda system of medicine, on the cognitive functions in Alzheimer's disease patients, and conclude that it could be beneficial in these patients, but more study is needed.[23]

### *Piper nigrum* and *Piper longum*(Black Pepper)

*Family: Piperaceae*

Piperine, a major alkaloid of black pepper (*Piper nigrum Linn.)* and long pepper (*Piper longumLinn.*), 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 noradrenaline and serotonin in the mouse brain, indicating its potential neurological benefits. Piperine could affect hippocampus neurogenesis in chronic mild stressed mice in which the level of brain-derived neurotrophic 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 acetylcholinesterase activity.[24-26]

### *Glycyrrhiza glabra* (The Licorice Root)

*Family: Fabaceae*

AD is characterized by neuronal loss and the presence of extracellular senile plaques, whose major constituent is an amyloid-β peptide (Aβ). In this study, we investigated the effects of a water extract of licorice (Yashti-madhuka) on Aβ25-35-induced apoptosis in PC12 cells. Results suggest that *Glycyrrhiza* 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 diseases like Alzheimer's and its associated symptoms.[27]

### *Withania somnifera* (Ashwagandha)

*Family: Solanaceae*

*Withania somnifera* (Ashwagandha) has been described as an anervine tonic in Ayurveda, and that is why it is a common ingredient of Ayurvedic tonic.[6] Active glyco with anolides of *Withania somnifera* (Ashawgandha) have a significant antioxidant function, which is accomplished by increasing the activities of superoxide dismutase, catalase, and glutathione peroxidase.[28]

### *Foeniculum vulgare* (Fennel)

*Family: Umbelliferae*

*Foeniculum vulgare* Linn. Extract used as a nootropic and anticholinesterase agent in mice. *F. vulgare* extract increased step-down latency and acetylcholinesterase inhibition in mice significantly. *F. Vulgare* is employed in the treatment of cognitive disorders such as dementia and Alzheimer's disease.[29]

### *Lepidium meyenii* (Maca)

*Family: Brassicaceae*

*Lipidium meyenni* (Brassicaceae), known commonly as maca, is an herbaceous biennial plant or annual plant native to the high Andes of Peru and Bolivia. It has shown beneficial improvement in memory and learning. Aqueous and hydroalcoholic extracts of Black Maca have significantly ameliorated the scopolamine-induced memory impairment in mice.[30] *Lipidium Meyanii* acting on cholinergic dysfunction, mainly neurotransmitter (ACh) related to memory and learning.[31] Black maca (0.5 and 2.0 g/kg) decreased brain malondialdehyde (MDA) levels marker of oxidative stress and acetylcholinesterase (Ache) levels in ovariectomized mice. In contrast, no differences were observed in monoamine oxidase (MAO) levels.[32]

### *Celastrus paniculatus* (Malkangni)

*Family: Celastraceae*

The plant *C.paniculatus*, commonly known as a black-oil tree, is a large woody climbing shrub. In India, it is known as Malkangni and has been mentioned in ancient Indian literature as an intelligence promoter. The seeds and seed oil have been used in AM as a memory enhancer, and it was reported that the seed oil reduces the levels of noradrenaline, dopamine, and 5-hydroxytryptamine (5-HT) *in vivo*.[21] Jothismati oil from seeds of *Celastrus paniculatus*

Table 1: Herbs having anti-Alzheimer activity

| S.NO | Botanical name | Family | Parts used | Extract | References |
|---|---|---|---|---|---|
| 1 | *Acorus calamus L.* | Araceae | Rhizomes | ethanolic and hydroethanolic | 12 |
| 2 | *Abutilon indicum Linn.* | Malvaceae | Whole | Methanolic | 33 |
| 3 | *Abrus precatorius L.* | Fabaceae | Leaves | Petroleum ether and ethanolic | 34 |
| 4 | *Angelica archangelica L.* | Umbelliferae | Dried roots | Methanolic | 21 |
| 5 | *Bacopa monnieri* | Scrophulariaceae | arial parts and rhizomes | Ethanolic | 21 |
| 6 | Buxus sempervires Linn | Buxaceae | Whole | Chloroform: methanol (1:1) | 35 |
| 7 | *Boerhaavia diffusa* | Nyctaginaceae | Leaves | Ethanolic and methanolic | 4 |
| 8 | Carthamus tinctorius Linn. | Compositae | Flower | Methanolic | 36 |
| 9 | *Cassia fistula Linn* | Leguminosae | Roots | Methanolic | 36 |
| 10 | *Catharanthus roseus* | Apocynaceae | Dried root | | 37 |
| 11 | *Celastrus paniculata* Willd. | Celastraceae | Seeds | Aqueous | 6,21 |
| 12 | Clitoria ternatea L. | leguminosae | Rhizomes and arial parts | Ethanolic | 21 |
| 13 | *Centella asiatica* Linn | Umbelliferae | Whole Plant | Alcoholic and aqueous | 21 |
| 14 | *Convolvulus pluricaulis* | Convolvulaceae | whole plant | Ethanolic | 19,20 |
| 15 | *Crocus sativus L.* | Iridaceae | Pistils and stigmas | Alcoholic and hydroalcoholic | 12 |
| 16 | *Commiphora whighitti* | Burseraceae | Whole plant | - | 14 |
| 17 | Cyperus rotundus Linn. | Cyperaceae | Whole | Methanolic | 33 |
| 18 | Curcuma longa | Zingiberaceae | Rhizomes | Aqueous | 22 |
| 19 | *Dipsacus asper Wall.* | Dipsacaceae | Root | - | 38 |
| 20 | *Evolvulus alsinoides Linn* | Convolvulaceae | Whole Plant | Ethanolic, aqueous and ethyl acetate | 14 |
| 21 | *Emblica officinalis* | Euphorbiaceae | leaves | Methanolic | 40 |
| 22 | *Fumaria macrocarpa Boiss. Ex* | Fumariaceae | Whole | Chloroform: methanol (1:1) | 35 |
| 23 | *Galanthus nivalis* | Amaryllidaceae | Bulbs | - | 10,11 |
| 24 | *Ginkgo biloba* | Ginkgoaceae | Leaves | Ethanolic | 5,9,36 |
| 25 | *Glycyrrhiza glabra* | Fabaceae | Roots | Water | 27 |
| 26 | *Hypericum perforatum L.* | Hypericaceae | Arial parts | Hydroalcoholic extracts | 12 |
| 27 | *Ilex paraguariensis* Yebra. | Aquifoliaceae | Leaves | - | 14 |
| 28 | Lycopodium clavatum Linn. | Lycopodiaceae | Whole | Chloroform:methanol (1:1) | 36 |
| 29 | Lepidium meyenii | Brassicaceae | dried hypocotyls | aqueous and hydroalcoholic | 2 |
| 30 | *Magnolia officinalis* | Magnoliaceae | Stem | Ethanolic | 39 |
| 31 | *Matricaria recutita* | Asteraceae | Flower | - | 15 |
| 32 | *Melissa officinalis* | Lamiaceae | Leaves | Volatile oil | 5,12 |
| 33 | *Panax Ginseng* | Araliaceae | Roots | Aqueous | 15 |
| 34 | *Piper interruptum Opiz* | Piperaceae | Stems | Methanolic | 33 |
| 35 | *Piper nigrum Linn.* | Piperaceae | Seeds | Methanolic | 33 |
| 36 | *Rosmarinus officinalis* | Lamiaceae | Leaves | - | 5 |
| 37 | Rheum spp L. | Polygonaceae | Rhizomes | Methanolic etract | 21 |
| 38 | *Salvia officinalis* | Lamiaceae | Leaves | Ethanol 95%<br>Steam distilled oil | 16-18 |
| 39 | *Terminalia chebula* Linn. | Combretaceae | Rhizome | Methanolic | 12 |
| 40 | *Tinospora cordifolia* | Menispermaceae | | Alcoholic and aqueous | 15 |
| 41 | *Vicia faba Linn.* | Fabaceae | Whole | Chloroform:methanol (1:1) | 36 |
| 42 | *Withania somnifera* | Solanaceae | Roots | Methanolic | 6, 28 |

(CP) is used in the indigenous system of medicine for the treatment of brain-related disease. It has been described to promote memory and to posses various pharmacological activities.[6]

### *Tinospora Cordifolia* (Guduchi)

*Family: Menispermaceae*

*Tinospora Cordifolia (Guduchi)* 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 function.[15]

## Conclusion

During the past years, several agents have been approved that enhance cognition and global function of AD patients, and recent advances in understanding AD pathogenesis has led to the development of numerous compounds that might modify the disease process. Novel information gathered from the current data is important in preserving indigenous folk knowledge as well as in the discovery of novel potential compounds with promising Anti-Alzheimer's potential. Therefore, this review has been prepared to provide a new compilation of plants with specific use as anti-Alzheimer's drugs. Moreover, this review has incorporated the latest data on new plant species, which are not covered in previous reviews on AD.

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