# Alternative Medicine for Alzheimer's disease

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**Abstract**

*Alzheimer's disease (AD) is an age-related neurodegenerative disease which is recognized as one of the most important medical problems affecting the elderly. Extensive research in AD has substantially broadened the understanding of the pathogenetic mechanisms leading to neurodegeneration and dementia. AD is characterized at the microscopic level by the presence of large numbers of senile plaques and neurofibrillary tangles. Existing treatments like several cholinesterase inhibitors and memantine for AD provide short-lived symptomatic relief as they fail to address the underlying pathology of the disease. The situation is further worsened by the undesirable reactions produced by those drugs. Consequently, the progression of AD is unremitting, leading to a continual decrease in cognitive abilities. To overcome these limitations of current therapeutics for Alzheimer's disease, extensive ongoing investigations aim to identify drugs that are effective and free of undesirable side effects. Certain naturally occurring phytochemicals like curcumin, hupzerine, ginkgo and resveratrol have been suggested to be potential therapies due to their anti-amyloidogenic, anti-oxidative and anti-inflammatory properties. These protective effects are also related with the ability to regulation of expression of apoptotic proteins, mitochondrial protection, and interference with APP metabolism. The present review is an assortment of various herbs and concomitant investigations towards discovery of new chemical entities useful to prevent the onset and control the progression of AD.*

**Keywords:** Alzheimer's disease, curcumin, resveratrol, amyloid, neurodegeneration, resveratrol

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disease of the brain. The current estimate for people suffering from AD, the most common form of dementia, is close to 15–20 million people worldwide. AD is characterized at the microscopic level by the presence of large numbers of senile plaques and neurofibrillary tangles. These pathological changes are associated with neuroinflammation and neuronal cell loss.

Memory problems are typically one of the first signs of cognitive impairment related to AD. Some people with memory problems have a condition called mild cognitive impairment (MCI). In MCI, people have more memory problems than normal for their age, but their symptoms do not interfere with their everyday lives. Movement difficulties and problems with the sense of smell have also been linked to MCI. Older people with MCI are at greater risk for developing AD. The initial symptoms of AD are variable. In the early stages, the most commonly recognized symptom is inability to acquire new memories, such as difficulty in recalling recently observed facts [1] (Tabert et al, 2005). In addition to dementia, skills related to language, visuospatial ability, calculation, judgment are also impaired in many. Neuropsychiatric and social deficits develop resulting in depression, withdrawal, hallucinations,

delusions, agitation, insomnia, and disinhibition. Few AD patients develop the Capgras syndrome later in the course of the illness. The Capgras delusion is a delusional misidentification syndrome, which involves the misidentification of people, places, or objects.

## Pathophysiology

*Senile plaques and neurofibrillary tangles*

Alzheimer's diseased brains are predominantly characterized by the presence of senile plaques and neurofibrillary tangles (NFTs), usually found in the hippocampus, temporal cortex, and nucleus basalis of Meynert. Senile plaques are extracellular deposits, consisting predominantly of aggregates of insoluble amyloid peptides. These plaques are composed of deposits of β-amyloid (Aβ) peptide and play a central role in the inflammatory cascade [2]. β and γ secretase cleave the ubiquitously expressed amyloid precursor protein (APP)to generate the 39- to 43-residue Aβ peptide [3].

Neurofibrillary tangles are the other major histological feature of AD. Neurofibrillary tangles are neuronal inclusions composed mainly of paired helical filaments, resulting in a typical double helix. Paired helical filaments are chiefly composed of the microtubule-associated protein tau, which is in a hyperphosphorylated state in neurofibrillary tangles. Neurofibrillary tangles are found throughout the neocortex, but they are also found in the deep grey matter, including the nucelus basalis of Meynert, substantia nigra, locus coeruleus and the raphe nuclei of the brainstem [4]. Destabilization of microtubules leads to inappropriate protein metabolism, disruption in signaling and synaptic failure which contributes in communication failures within neurons.

*RAGE*

The formation of protein bound advanced glycation endproducts (AGEs) is a general phenomenon of aging [5]. AGEs result from the non-enzymatic glycation of proteins with reducing sugars and subsequent transition metal catalysed oxidation reactions\. AGEs accumulate on tau proteins and are found in high concentrations on senile plaques. Aβ peptide and AGEs can induce an inflammatory response by binding to the receptor for advanced glycation end products (RAGE) [6]. RAGE is a transmembrane, ubiquitous cell-surface receptor with affinity for multiple substrates and peculiarly demonstrates enhanced expression in an Aβ rich environment. Relevant preclinical models illustrate that the Aβ-RAGE interaction amplifies neuronal stress and the accumulation of Aβ, impairs memory and learning, and exaggerates neuroinflammation by augmenting the expression of a large number of proinflammatory cytokines through Nuclear Factor-κB (NF-κB) activation [7].

*Oxidative stress*

There is a great deal of evidence indicating that damage in neuronal tissue in AD patients is accelerated due to oxidative stress during the course of the disease. Since oxidative stress is characterized by an imbalance in production of reactive oxygen species (ROS) and antioxidative defense, both are considered to have a major role in the process of age-related neurodegeneration and cognitive decline. Oxidative stress results in oxidation of lipids, proteins and DNA [8].

## Phytochemicals for the prevention of Alzheimer's disease

The phytochemicals for Alzheimer's disease have been isolated from different plants as some indexed in table 1.

***Huperzine***

Huperzine A, is a naturally occurring sesquiterpene alkaloid compound found in the plant *Huperzia serrata.* Huperzine A is an acetylcholinesterase inhibititor and NMDA receptor antagonist [9]. Compared with tacrine, donepezil, and rivastigmine, HupA has better penetration through the blood-brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action. In mammalian brain, the bulk of AChE occurs as a tetrameric, G4 form and HupA preferentially inhibits G4 AChE form. Huperzine A has been examined for its potential to antagonize the deleterious neurochemical cognitive effects of infusing Aβ into the cerebral ventricles of rats. Daily intraperitoneal administration of huperzine A for 12 consecutive days produced significant reversals of the Aβ induced deficit in learning a water maze task along with reduction in Aβ induced neuronal degeneration. Additionally, huperzine A inhibited the down-regulation of anti-apoptotic Bcl-2 and the up-regulation of pro-apoptotic Bax and P53 proteins, caspase-3 and reduced the apoptosis that normally followed Aβ injection [10]. Huperzine A was also found to improve cognitive deficits caused by chronic cerebral hypoperfusion in rats indicating its beneficial effect on the oxygen free radical system and energy metabolism [11]. Huperzine A has been found to protect mitochondria, upregulate nerve growth factor and its receptors, and interfere with APP metabolism which could contribute to its neuroprotective mechanism. Antagonizing effects of HupA on NMDA receptors and potassium currents may also contribute to its neuroprotection as well. Huperzine A was evaluated for its ability to reverse the deficits in spatial memory produced by scopolamine in young adult monkeys or those that are naturally occurring in aged monkeys using a delayed-response task. Huperzine A provided long lasting beneficial effects on delayed-response performance task [12].

A phase IV clinical trial in China have demonstrated the effects of HupA in AD patients. HupA significantly improved memory deficits in elderly people and patients with AD and vascular dementia [13]. In a placebo-controlled, double-blind, randomized trial 202 patients with AD were administered either huperzine A 400 μg/day for 12 weeks or placebo. Huperzine A remarkably improved the cognition, behavior, activity of daily life and mood of AD patients [14].

**Table 1:** Herbs with protective effects in Alzheimer's disease

| **Plant** | **Family** | **References** |
|---|---|---|
| *Salvia officinalis* | Lamiaceae | [32] |
| *Clitoria ternatea* | Fabaceae | [33-34] |
| *Centella asiatica* | Apiaceae | [35-36] ; |
| *Bacopa monniera* | Scrophulariaceae | [37-38]; |
| *Salvia miltiorrhiza* | Labiatae | [39-40]; |
| *Cajanus cajan* | Fabaceae | [41] |
| *Uncaria rhynchophylla* | Rubiaceae | [42] |

***Curcumin***

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae). The curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin exists in

at least two tautomeric forms, keto and enol. Curcumin has pleiotropic beneficial effects on the neurons such as decreased Aβ plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation and thus has been extensively studied with the objective of being a therapeutic option in AD [15]. The protective effect of curcumin against colchicine-induced cognitive impairment and oxidative stress in rats has been investigated. Chronic treatment with curcumin significantly improved the colchicine-induced cognitive impairment. Curcumin significantly reduced the elevated lipid peroxidation, restored the decreased reduced glutathione level and acetylcholinesterase activity, and attenuated the raised colchicine-nduced elevated nitrite levels indicating protective role of curcumin in cognitive impairment and associated oxidative stress [16]. The beneficial effects of curcumin have been found to inhibit the memory impairment caused by intracerebral streptozotocin administration along with increasing cerebral blood flow and reducing oxidative stress and cholinergic dysfunction [17]. Curcumin reverses existing amyloid pathology and associated neurotoxicity in a mouse model of AD [18]. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid *in vivo* [19]. Recent *in vivo* studies indicate that curcumin is able to reduce Aβ related pathology in transgenic AD mouse models. The effects of curcumin on Aβ levels and APP processing in various cell lines and mouse primary cortical neurons were investigated. Curcumin potently lowers Aβ levels by attenuating the maturation of APP in the secretory pathway [20]. Curcumin stimulates multiple signaling pathways survival pathways such as those regulated by NF-κB, Akt, and growth factors; cytoprotective pathways dependent on Nrf2.

**Ginklolides**

*Ginkgo biloba* extracts are now prescribed in several countries for their reported health benefits, particularly for medicinal properties in the brain. The standardized Ginkgo extract, EGb761, has been reported to protect neurons. The *Ginkgo biloba* extract EGb 761 has shown biological activities relevant to the treatment of cognitive dysfunction. The efficacy of EGB 761 in prevention and treatment of the post-stress memory dysfunctions has been investigated. Results indicate that EGB 761 diminishes stress-induced memory deficits in rats [21]. EGB 761 normalized cognitive deficits seen in rats treated with an s.c., 5mg/kg corticosterone [21]. The neuroprotective role of EGb 761 has been studied in ischemic models involving permanent and transient focal cerebral ischemia. EGb 761 prevented decrease of Bcl-2 and Bcl-X(L) levels, while on the contrary increased Bax expression [22].

The effects of EGb761 and two of its constituents, quercetin and ginkgolide B, on the cytotoxic action of Aβ (1-42) were tested with human neuroblastoma SH-SY5Y cells where EGb761 was able to block Aβ induced cell apoptosis. Additionally, ROS accumulation, mitochondrial dysfunction and activation of c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt signaling pathways were inhibited indicating its neuroprotective role [23]. Treatment with EGb 761 (10-100 μg/mL) protected hippocampal neurons against toxicity induced by Aβ fragments in a concentration dependent manner [24].

The efficacy of EGb 761 in the treatment of dementia of AD has been studied in 10 randomised, controlled, double-blind clinical trials. EGb 761 was significantly superior to placebo in restoration

of cognitive performance [25]. The efficacy of EGb 761 in comparison to donepezil in treatment of AD was studied in a 24-week randomized, placebo-controlled, double-blind study. Patients suffering from dementia were treated with 160 mg/day EGb 761 and donepezil. Results suggest that the clinical efficacy of EGb 761 in the treating dementia of AD was significant and was comparable with donepezil [26].

**Resveratrol**

Resveratrol (3, 4', 5-trihydroxy stilbene) is a phytoalexin found in the skin and seeds of grapes, which has been reported to possess anti-inflammatory, anticarcinogenic, and antioxidant activities. The effect of resveratrol was investigated on (intracerebroventricular) ICV streptozotocin induced cognitive impairment. resveratrol treatment significantly prevented ICV streptozotocin induced cognitive impairment demonstrating effectiveness of resveratrol in preventing the cognitive deficits [27]. Resveratrol was found to be effective in prevention of colchicine-induced cognitive impairment and oxidative stress in rats as it reduced the elevated MDA and nitrite levels and restored the depleted GSH and acetylcholinesterase activity. Results indicate neuroprotective role of resveratrol against colchicine-induced cognitive impairment and associated oxidative stress [28].

Efficacy of beneficial effects of resveratrol in traumatic brain injury (TBI) has been investigated employing the controlled cortical impact (CCI) model which produces cognitive and motor deficits. 100 mg/kg intraperitoneal resveratrol administered after injury provided significant protection against cognitive and motor defects [29]. Resveratrol has been found to significantly lower the levels of Aβ peptides. Resveratrol has been found to promote intracellular degradation of Aβ by a proteasome mediated mechanism which was inhibited by proteasome inhibitors [30]. Resveratrol is also a direct activator of sirtuin 1 (SIRT1), related to increased lifespan in various species similar to calorie restriction, thereby providing significant neuroprotective benefits. Recent studies in a variety of species including mammals showed that resveratrol treatment and caloric restriction increased silent information regulator 2/sirtuin 1 activity, which mediated increase in life span/cell survival. The protective effects of resveratrol are mediated by Akt and mitogen-activated protein kinases. Resveratrol activates the sirtuins' family member SIRT1. SIRT1 also has been shown to upregulate the expression of α secretase, which in turn suppresses Aβ production [31].

**Conclusion**

The treatment of AD remains a challenge in the modern day medicine and none of the current therapeutic options inhibit the progression of AD at an early stage. Thus, there is the perpetual need to carry out extensive studies in order to search for new active extracts or components derived from various herbal sources for the treatment of AD. some bioactive extracts or phytoconstituents are highly potent and present great deal of hope for the treatment of AD. The need of the hour is to elucidate the underlying molecular mechanisms. There have been encouraging signs in the preclinical and clinical trials and with persistent efforts novel therapeutic options could be found out.

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