

Potential role of medicinal plants against Alzheimer's disease

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the brain which leads to a decline in memory and cognition. The Food and Drug Administration (FDA) approved medications provide only symptomatic relief and are often associated with adverse effects. Many natural products have shown their activities against AD. Bioactive compounds like polyphenols, tannins, alkaloids, flavonoids, terpenes, sterols, etc are present in various plants. These compounds have shown antioxidant, anti-inflammatory, anticholinesterase, and anti-amyloidogenic activities. This review article discusses the benefits of various plants against AD.

Keywords: alzheimer's disease, food and drug administration, glutamate excitotoxicity, cholinergic system

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Abbreviations: AD, Alzheimer's disease; FDA, food and drug administration; GPX, glutathione peroxidase; MO, moringa olifera; LPO, lipid peroxides; OGD, oxygen glucose deprivation

Introduction

Alzheimer's disease (AD) is a type of chronic neurodegenerative disease. It has many causes: accumulation of amyloid beta and neurofibrillary tangles, epigenetic changes, glutamate excitotoxicity, cholinergic system dysfunction, oxidative stress, and inflammation.^{1,2} AD leads to irreversible loss of synapses and neurons. Therefore, the two hallmarks are plaques of amyloid beta and neurofibrillary tangles. Hippocampus is the first site where the damage appears initially. Hippocampus is a crucial part of the brain, which forms memories. As time passes, more neurons die and the brain begins to shrink. In the final stage, the brain tissue has shrunk remarkably. It is responsible for about 60% of dementia cases. Every 1 in 8 people over the age of 65 while, nearly half over the age of 85 have AD.³

The initial stage of the disease shows changes in the brain but no symptoms. The mild cognitive impairment stage includes memory or other cognitive complaints. Dementia, the last stage, results in loss of memory, disorientation, increased anxiety, or aggregation. The FDA approved medications are cholinesterase inhibitors and glutamate modulators.⁴ These medications provide only symptomatic relief. Medicinal plants can delay the progression of the disease.

Natural products against AD

Recently natural products have gained importance because of fewer side effects as compared to synthetic products. Plants that have shown activity against Alzheimer's are *Ginkgo biloba*, *Withania somnifera*, *Huperzia serrata*, *Moringa olifera*, *Bacopa monnieri*, *Uncaria rhynchophylla*, *Galanthus woronowii*, *Curcuma longa*, *Panax ginseng*, *Centella asiatica*, *Glycyrrhiza glabra*, *Rosmarinus officinalis*, etc.

Ginkgo biloba

EGB 761 is a standardized extract of *Ginkgo biloba* leaves which contains approximately 24% flavone glycosides and 6% terpene lactones. The flavone glycosides consist of quercetin, kaempferol, and

isorhamnetin and terpene lactones consist of A, B, and C ginkgolides and bilobalide. In Germany, EGB 761 is approved for the treatment of dementia. It enhances SOD, catalase, and glutathione peroxidase (GPX) activities.⁵ EGB 761 offers protection against A β induced neurotoxicity by preventing neuronal apoptosis and by blocking ROS accumulation, glucose uptake, mitochondrial dysfunction, and activation of ERK and JNK pathways.⁶ Free circulating cholesterol can also affect APP processing and amyloidogenesis. Yao et al.⁷ have shown that the levels of circulating free cholesterol were lowered and that the production of brain β APP and A β peptides were inhibited in EGB 761 treated older rats.

Glycyrrhiza glabra

Glycyrrhiza glabra belongs to Fabaceae family and includes many compounds like saponin, flavonoids, isoflavonoids, stilbenoids, and coumarins. Glycyrrhizin is the bioactive molecule present in it. It inhibits ROS generation, cytotoxicity, and GSH downregulation. An aqueous extract of *Glycyrrhiza glabra* when administered in 1-month-old rats orally for 6 weeks improved memory and learning.⁸ Hence it can be helpful in AD.

Moringa olifera (MO)

This plant belongs to the Moringaceae family. Bioactive compounds like alkaloids, tannins, flavonoids, isothiocyanates, and saponin are present in MO. It causes an increase in SOD and catalase and a reduction in lipid peroxides (LPO) levels. This antioxidant activity might be the reason for improved cognition.⁹ It restores the disturbed brain monoamines levels, enhances memory, and provides protection from neurodegeneration. MO also decreases tau hyperphosphorylation in hyperhomocysteinemia rats.¹⁰

Bacopa monnieri (Brahmi)

It is classified into Scrophulariaceae family and is found mostly in India and other Asian countries. It is used as a nootropic agent. Alkaloids and saponin are the chemical compounds present in Brahmi. Bacoside A is the active molecule in Brahmi. It prevents A β aggregation and formation of fibrils, prevents the reduction in SOD activity and decrease the LPO levels.¹¹

Centella asiatica

Centella asiatica belongs to the Umbelliferae family. It is mainly found in India, Sri Lanka, and Bangladesh. It contains asiatic acid, asiaticosides, triterpenes, sapogenins, glycosides, madecassic acid, etc. It shows antioxidant effect by causing an increase in SOD, GPX (glutathione peroxidase), and catalase enzymes.¹²

Panax ginseng

It belongs to the Araliaceae family and contains triterpenoid dammarane glycosides. It inhibits β - and γ -secretase activity, activates the nonamyloidogenic pathway, inhibits acetylcholinesterase activity and $A\beta$ -induced neurotoxicity, and decreases $A\beta$ -induced production of reactive oxygen species and neuroinflammatory reactions.¹³ Panax ginseng was administered for 12 weeks in an open label study. To monitor the cognitive performance, Mini-mental state examination (MMSE) and Alzheimer's disease assessment scale (ADAS) score were used. In this study, it was observed that supplementation of Panax ginseng powder improved cognition in AD patients.¹⁴

Rosmarinus officinalis

It belongs to the Lamiaceae family and possesses antioxidant properties. Carnosol and carnosic acid are the potent antioxidants present in rosemary leaves. Carnosic acid is involved in the synthesis of nerve growth factor (NGF). NGF is necessary for the growth and maintenance of nerve tissue. It maintains the levels of GPX and SOD activity.¹⁵

Galanthus woronowii

It belongs to the Amaryllidaceae family and consists of Galanthamine as the active compound. Galanthamine is a selective, reversible and competitive AChE inhibitor. It has shown improvement in memory and cognition in AD subjects. Currently, Galanthamine is the most widely approved AChE inhibitor approved by Food and Drug Administration (FDA) against AD.¹⁶

Uncaria rhynchophylla

It is a Chinese herbal drug that belongs to the Rubiaceae family. Aqueous extract of Uncaria rhynchophylla showed a significant reduction in $A\beta$ fibril formation. Oxindole and indole alkaloids present in *Uncaria rhynchophylla* might be responsible for this effect.¹⁷

Huperzia serrata

It belongs to the Lycopodiaceae family and is widely distributed as a nootropic agent. Huperzine A is the active constituent and an AChE inhibitor used in Schizophrenia. To develop neuronal ischemia, oxygen glucose deprivation (OGD) was induced in PC12 cells. This leads to cell death and increased lipid peroxidation and SOD levels. Cells treated with Huperzine A showed reduced oxidative damage and increased survival. Glutamate-induced neurotoxicity was also attenuated by Huperzine A.¹⁸ These studies show the potential of *Huperzia serrata* in the treatment of AD.

Withania somnifera (Ashwagandha)

It is a neuroprotective plant belonging to the Solanaceae family. It is used as a nerve tonic in Ayurveda. It has calming properties and reduces stress. In $A\beta$ (25–35) induced rats, oral administration of Withanoside IV attenuated axonal, dendritic, and synaptic loss and memory deficits. Enhancement of cholinergic activity by increasing the acetylcholine content and cholineacetyl transferase activity was

seen in rats after administration of aqueous extract of *W. somnifera*.¹⁹ In mice, methanol extract of *W. somnifera* reversed the amyloid induced memory deficit.²⁰

Curcuma longa (Curcumin)

It is classified into Zingiberaceae family. It has antioxidant, anti-inflammatory, and anti-amyloidogenic properties and hence it has the potential to be used in AD treatment. In vitro and in vivo studies show that curcumin prevents $A\beta$ aggregation and the formation of fibrils. There was a reduction in oxidative stress, inflammation, and cognitive deficits when $A\beta$ treated rats were given curcumin.²¹ In Tg2576 mice model of AD, the antioxidative and anti-inflammatory potential of curcumin is reported. The anti-inflammatory effect occurs due to inhibition of NF- κ B induced iNOS, COX (cyclooxygenase)-2, and inflammatory cytokine production.²²

Conclusion

Natural products are gaining popularity nowadays. Synthetic drugs show some serious side effects. This can be overcome by natural drugs that have low or no side effects. Medicinal plants can improve the quality of life of AD patients. Mechanism of actions of many medicinal plants is still not clear. Hence, trials involving larger populations are required to fully understand their role in Alzheimer's disease.

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Conflicts of interest

Declare if any conflict of interest exists.

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