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# Multifarious role of medicinal plants in circumventing Alzheimer's disease: A review

Vinitha S. Babu and P. M. Radhamany\*

Plant Reproductive Biology Laboratory, Department of Botany, University of Kerala-695581 \*Corresponding author: radhamany\_m@rediffmail.com

#### Abstract

Alzheimer's disease (AD) is noticed to be a common age-related disorder in man. It is a multifactorial neurodegenerative disease characterized by changes in the brain tissue composition. Affected individuals exhibit a random deposition of betaamyloid proteins on the brain tissue, referred to as plagues. The disease is not yet known to have any preventive therapy. Drugs used for the treatment of AD have unpleasant side effects, and hence physicians are keen to find alternatives. Research has shown that phytochemicals can alleviate AD to a certain extent with little or no side effects. Though certain phytochemicals have been reported to offer promising effects, as is usual, there is a strict need to check the guality and efficacy of medicinal plants to be used as drugs against AD. The present review focuses on the pathophysiological features of AD and lists out some plants that can be effectively used against AD.

**Keywords:** Alzheimer's Disease, Medicinal Plants, Secondary metabolites

#### Introduction

In 1907, Alois Alzheimer, Physician delineated the brain of a 56-year-old woman, Augasta D with

dementia. She had a rapid progressive memory loss and hence, Alois conducted an autopsy of her brain and found two abnormalities due to this disease, of which, one was the presence of tangled clumps of nerve cells and the other, presence of patches of disintegrated nerve cells branched together called plaques.Plaques later came to be known as beta-amyloid. Even today, these conclusions made by Aloisare considered as the possible cause of Alzheimer's disease (AD). The disease is marked by memory lapse and confusion. AD is a heterogeneous neurodegenerative disorder which irreversibly hinders cognition, memory and also the ability to conduct day to day activities correctly. Even though, the etiology of AD has not been completely elucidated, different causative factors have been identified (Scheltens et al., 2016). Alzheimer's disease is the most common cause of dementias in western countries representing more than half of demented patients. Yet another factor governing AD, is age. It has been estimated that about 3% of individuals in the age group 65-74 and 17% of individuals in the age group 75-84 suffer from this disease. Scientific efforts to discover a cure for AD is expensive and disappointing with many drugs either addressing the symptoms of the disorder with limited effectiveness or the inability of the

drugs to manage the symptoms alongwith the severity of progression. In spite of the dreadful prevalence of AD, FDA has approved only very few drugs for its treatment. Some of which include, galantamine, rivastigmine, donepezil, memantine and a combination of donepezil and memantine. Nonetheless, as of now, aducanumab, a new drug has obtained accelerated approval.

#### Pathophysiology of Alzheimer's disease

The pathology of AD manifests itself atrophy of cerebral cortex with secondary enlargement of ventricular systems. Degeneration of neurons, along with loss of synapses in the cortex, hippocampus and sub cortical structures are observed. This neurodegeneration that may result from uncontrolled activation of microglia in brain may subsequently lead to the secretion of neurotoxins and inflammatory agents. Microscopic examination of the affected brain showed that the neurite plaque having betaamyloid got accumulated in arterial walls of cerebral blood vessels and further silver staining, showed neurofibrillary tangles (NFT) in neuronal cytoplasm. It is reported that the occurrence of beta-amyloid results in the abnormal appearance of small holes in neuronal tissues termed granulovacuole, that otherwise occur due to cell degeneration (Ghoshal et al., 1999). This may be associated with cytoskeletal changes attributed to hyperphosphorylation of microtubule associated 'tau' proteins, thereby resulting in brain atrophy. Neurodegeneration ultimatelyleads to gross atrophy in affected areas, thereby resulting in memory loss, inability to gain novel knowledge, executive dysfunction and inability to perform daily activities. Thus, apart from amyloid beta, abnormal accumulation of neurofibrillary 'tau' proteins can circumvent AD. Healthy neurons are supported internally by structures called microtubules that guide nutrients and molecules from the cell body of neuron to axon and dendrites. In healthy neurons, 'tau' binds and stabilizes microtubules, whereas in AD patients, 'tau' sticks to other 'tau' molecules, forming tangles inside neurons. These tangles block the neuron transport system, thereby harming synaptic communication between neurons. Research findings suggest that, brain changes in Alzheimer's patients might be due to the interplay between abnormal 'tau' and beta-amyloid proteins and several other factors. When the level of beta-amyloid reaches a tipping point, there occurs a rapid spread of 'tau' in the brain (Binder et al., 2005).

#### **Epidemiology**

Risk factors associated with AD in man are old age and genetic inheritance.

#### Age and AD

Increase in age has become the most common cause of dementia with nearly 10% of population > 65 years being affected. The frequency of AD increases with each decade of adult life reaching even up to 20 to 40% of the population in people over 85 years of age. A minor risk factor associated with AD is head trauma with concussion. Several environmental and biochemical factors such as aluminium, mercury and viruses have also been proposed as cause of AD but with little significance. On the other hand, potential risk factors of AD include elevated homocysteine, cholesterol levels and hypertension. (Sosa-Ortiz et al., 2012).

#### **Genetic Inheritance in AD**

It has been noticed that, the immediate relatives of affected individuals have an increased risk of Alzheimer's disease. The beta amyloid protein involved in AD is formed from the breakdown of the amyloid precursor protein (APP). Human chromosome 21 is known to carry this gene for APP. Abnormal levels of this protein clump together and any mutationstherein can also result in AD. This finding is consistent with the pathology of the autopsy of Alzheimer's patients. Several other genes associated with the early onset of AD are Presenilin I (PS-I) on chromosome 14 and Presenilin-D2 (PS-2) on chromosome 1. Also, mutations in Apo E4 (an allele of APOE), a plasma protein involved in cholesterol and triglyceride transport, located on chromosome 19 increase the risk for AD upto 45-60%. Generally, 5-10 % of familial AD is associated with genetic factors and the remaining 90-95 % is sporadic. Moreover, the homozygosity or heterozygosity of the ApoE4 has elevated the risk of AD development (Uddin et al., 2019).In addition, chromosomes 10 and 12 aredetected to harbour other alleles with polymorphic effects that increase susceptibility to late onset of AD (Tanzi and Bertram, 2001).

# Medicinal Plants against Alzheimer's disease

Since inception, human beings have experimented with plants as herbal remedies. Yet, a minimal scientific attention is gained in the usage of these traditional medicines. It has been opined that bioactive constituents present in traditional herbs help to alleviate different symptoms of AD such as poor cognition and memory loss, thereby proving their role in neuroprotection and improved memory (Hassan et al., 2022). Medications like Ayurveda, Homeopathy, Sidha and Unani systems of medicine play a significant role in the management of AD. The traditional systems of medicine thatprimarily originated in parts of Egypt, India and China, are considered to be fundamentally primitive.Basically, the traditional systems of medicine, involve the usage of medicinal plants to treat AD, but are directed mostly towards the enhancement of general health and well-being.However,more advanced forms of medication should replace these generalized medicines. In par with this, many pharmaceutical drugs are formulated using naturally occurring compounds that have been isolated in their pure form. The recent, interest in herbal medicine and their application in disease managementis possibly due to their usage without any side effects (Durairajan et al., 2022).

It is well-known that the nervous system coordinates and regulates various voluntary and involuntary activities in the human body. The components of the central nervous system and autonomous nervous system are interlinked and therefore it is likely that certain drugs affect the reactions of central nervous system associated with autonomous nervous system. Care should be taken in drug use and dosage. Drugs involved in central nervous system may have a stimulatory or depressant action along with anticonvulsant and psychopharmacological action on the autonomous nervous system. Thus, it is evident that thecurrent therapies for AD are inadequate and have several adverse effects. Hence, there is an urgent need for alternatives for the treatment of AD and memory defects. Some of the medicinal plants used in the treatment of AD are shown in Table 1.

Table 1	
Selected medicinal plants used for the treatment of Alzheimer's D	isease

SI. No	Name of the Plant	Family	Part Used	References
1.	Acanthus ebracteatus	Acanthaceae	Aerial	Ingkaninan et al., 2003
2.	Andrographis paniculata	Acanthaceae	Aerial	Mukherjee et al., 2007
3.	Acanthopanax henryi	Araliaceae	Leaf	Zhang et al., 2014
4.	Arnica chamissonis	Asteraceae	Flower	Wszelaki et al., 2010
5.	Artemisia annua	Asteraceae	Leaf, Twig	Chougouo et al., 2016
6.	Atriplex laciniata	Chenopodiaceae	Whole Plant	Kamal et al., 2015
7.	Alchornialaxiflora	Euphorbiaceae	Leaf	Elufioye et al., 2010
8.	Acacia nilotica	Fabaceae	Root	Crowch and Okello (2009)
9.	Acacia raddiana	Fabaceae	Bark	Benamar et al., 2017
10.	Albizia adianthifolia	Fabaceae	Leaf	Sonibare et al., 2017
11.	Albizia procera	Fabaceae	Bark	Ingkaninan et al., 2003
12.	Butea superba	Leguminosae	Root, Bark	Ingkaninan et al., 2003
13.	Bacopa monniera	Scrophulariaceae	Whole Plant	Limpeanchob et al., 2008
14.	Crinum jagus	Amaryllidaceae	Leaf	Fawole et al., 2010
15.	Crinum moorei	Amaryllidaceae	Bulb	Fawole et al., 2010
16.	Cassia obtusifolia	Fabaceae	Seed	Jung et al., 2016
17.	Cyclotrichiumniveum	Lamiaceae	Whole Plant	Orhan et al., 2004
18.	Cassia fistula	Fabaceae	Seed	Tappayuthpijarn et al., 2011
19.	Corydalis intermedia	Papaveraceae	Whole Plant, Tuber	Uddin et al., 2015

20.	Eugenia dysenterica	Myrtaceae	Leaf	Gasca et al., 2017
21.	Embeliaribes	Myrsinaceae	Root	Vinutha et al., 2007
22.	Fumaria asepala	Fumariaceae	Whole Plant	Chlebek et al., 2016
23.	Ficus religiosa	Moraceae	Stem, Bark	Vinutha et al., 2007
24.	Hyssopus officinials	Lamiaceae	Whole Plant	Wszelaki et al., 2010
25.	Hypericum amblysepalum	Hypericaceae	Flower, Fruit, Seed	Béjaoui et al., 2017
26.	Harpephyllumcaffrum	Anacardiaceae	Leaf, Stem, Bark	Moyo et al., 2010
27.	Jatropha gossypifolia	Ericaceae	Stem, Bark, Roots	Saleem et al., 2016
28.	Kaempfera parviflora	Zingiberaceae	Rhizome	Tappayuthpijarn et al., 2011
29.	Mimosa pudica	Fabaceae	Whole	Ingkaninan et al., 2003
30.	Paeonia lactiflora	Paeoniaceae	Root	Fujiwara et al., 2009
31.	Ruta graveolens	Rutaceae	Whole Plant	Wszelaki et al., 2010
32.	Streblus asper	Moraceae	Seed	Ingkaninan et al., 2003
33.	Tinospora cordifolia	Menispermaceae	Stem	Vinutha et al., 2007
34.	Vanda roxburghii	Orchidaceae	Root	Uddin et al., 2015
35.	Withaniasomnifera	Solanaceae	Root	Jayaprakasam et al., 2010

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## Secondary metabolites responsible for neuroprotectivity

The curative power of herbal plants has grabbed the attention of researchers all over the world. Among the diverse groups of plant secondary metabolites, Polyphenols present in fruits, vegetables, legumes, cereals, and beverages like tea, coffee, and wine have potential medicinal properties. Although phenolic compounds are mainly derived from the shikimic acid and acetate pathways, other biosynthetic routes such as the terpenoids and alkaloids can also go through extensive aromatization and oxidation reactions to give rise to polyphenolic compounds. One of the most common classes of polyphenols are the C6-C1 structural group of hydroxybenzoic acid derivatives such as protocatechuic and gallic acid. Other diverse groups of shikimic acid products of phenolics include, the C6-C3 metabolites (phenylpropanoids) such as cinnamic, p-hydroxy cinnamic, and caffeic and ferulic acids which are again abundant in many vegetables, fruits, and seeds. The other major classes of polyphenolic compounds are flavonoids having the C6-C3-C6 structural configuration which are frequently found in cereals and legumes. Flavonoids are again divided into several classes such as flavones, flavanols, flavanones, isoflavones, anthocyanidins, and chalcones. These polyphenolic compounds upon esterification with each other or with sugars, form polymeric macromolecules such as tannins.

certain plants Research on and their phytochemicals has progressed more than in others. For eq.The rhizomes of turmeric (Curcuma longa L., Zingiberaceae) and related species have long been known as spices. Their characteristic vellow colour is attributed to the principal pharmacologically active principle, curcumin. Curcumin has been shown to have neuroprotective effect in a 6-OHDA (6-hydroxydopamine)induced hemi parkinsonian mice model. It also ameliorated that, a neuronal specific marker, A53T α-synuclein-induced human neuroblastoma, SH-SY5Y to cell death and decreased  $\alpha$ -synucleininduced intracellular ROS generation and inhibited caspase-3 activation. This might be due to the presence of active neuroprotective component in them (He et al., 2022).

Alkaloids are yet another class of compounds inducing neuroprotectivity. Galantamine, an alkaloid originally isolated from *Galanthus woronowii* (Amaryllidaceae) and a related species, *G. caucasicus* is are reported to show neuroprotectivity. Rivastigmine (trade name Exelon, 31) is another approved drug of natural origin for the treatment of AD. It is a semisynthetic derivative of physostigmine obtained from *Physostigmavenenosum* (Fabaceae).Berberine, an isoquinoline alkaloid of the protoberberine type isolated from numerous plants have multiple therapeutic implications. It shows neuroprotective effect in various animal models of CNS-related disorders (Kulkarni and Dhir,2010).

A rather simple compound, indole-3-propionic acid obtained by the deamination of tryptophan, is an example of neuroprotective natural products that can be obtained through a simple biosynthetic route (Negatu et al., 2020). Different terpenoids have shown to possess neuroprotective function. The triterpenoid, Ginsenosides obtained from the roots and rhizomes of *P. ginseng* and *P. notoginseng* (Araliaceae) has been evaluated for their neuroprotectivity in SH-SY5Y cells (González-Burgos et al., 2015). Based on the studies conducted, it is evident that, components obtained from medicinal plants have the potential to alleviate several neurological disorders.

#### Conclusion

Plant derived compounds have immense potential in the treatment of several ailments, including memory related disorders such as Alzheimer's possibly due to their low toxicity and high bioavailability. Even though, the cause of this disease is unclear, it is evident that natural products have several advantages over the synthetic drugs and have an upper hand in managing multifarious disorders especially due their multiple activities. Natural products alone (with multiple activities) or in combination with other neuroprotective drugs may enhance memory and improve cognitive dysfunction. Hence, it is imperative to screen plants and their chemicals for the desired activities.

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