**Mohamed Abdel Galil Hassan. *et al.* / *International Journal of Phytopharmacology*. 5(6), 2014, 454-462.**

e- ISSN 0975 – 9328
Print ISSN 2229 – 7472

**International Journal of Phytopharmacology**

Journal homepage: www.onlineijp.com

**IJP**

# ROLE OF MEDICINAL PLANTS IN NEURODEGENERATIVE DISEASES WITH SPECIAL EMPHASIS TO ALZHEIMER'S DISEASE

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**ABSTRACT**

Alzheimer's disease is an age-associated, irreversible, progressive neurodegenerative disease that is characterized by severe memory loss, unusual behavior, personality changes and a decline in memory function. It is the most common form of dementia and affects an estimated 10 million people worldwide. Alzheimer's disease demolishes the vital brain cells, causing trouble with memory, thinking and behavior, brutal enough to affect work, lifelong hobbies and social life. Recognized factors in Alzheimer's disease include acetylcholine deficiency, free radicals and inflammation of the brain tissue. There is no cure for Alzheimer's disease, but drugs designed to slow down the disease progression are available. Some herbs may help to improve brain function, but scientific evidence to prove that they can treat Alzheimer's disease. Medicinal plants have been the single most productive source of leads for the development of drugs, and over a hundred new products are already in clinical development. Indeed, several scientific studies have described the use of various medicinal plants and their constituents for treatment of Alzheimer's disease. This review gathers research on various medicinal plants that have shown promise in reversing the Alzheimer's disease pathology. The report summarizes information concerning applications of these various plants in order to provide sufficient baseline information that could be used in drug discovery campaigns and development process, thereby providing new functional leads for Alzheimer's disease.

**Key words:** Neurodegenerative disorders, Alzheimer′s disease, Brain disorder, Medicinal plants.

## INTRODUCTION

Alzheimer's disease (AD) is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906. AD is a progressive and neurodegenerative disease that primarily affects the elderly population of over 65 years of age, and is estimated to account for 50 - 60% of the dementia cases. The prevalence has been found to rise exponentially with age, ranging from 3.0% in patients aged 65 to 74 years to as much as 47.2% in those aged 85 years (Wernicke *et al*., 1994, Williams *et al*., 2003). This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. Although the etiology is unknown, genetic factors clearly play a role in 10% to 15% of cases (Anonymous, 2010; Francis *et al*., 1999)

The brain has 100 billion nerve cells (neurons). Each nerve cell connects with many others to form communication networks. Groups of nerve cells have special jobs. Some are involved in thinking, learning, and remembering. Others help us see, hear, and smell. To do their work, brain cells operate like tiny factories. They

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receive supplies, generate energy, construct equipment, and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen. The beta-amyloid peptide (BAP), with 39 - 42 amino acid residues plays a significant role in the development of AD. Although there is no cure for AD, it can be managed with the available drugs, to some degree. Several studies have revealed that natural antioxidants, such as vitamin E, vitamin C, and beta-carotene, may help in scavenging free radicals generated during the initiation and progression of this disease. The loss of memory is considered to be the result of a shortage of the nerve transmitter acetylcholine. It is possible to increase the level of this transmitter in the brain by inhibiting the activity of the enzyme acetylcholinesterase, which splits or breaks down the transmitter substance. Drugs that inhibit the breakdown of the messenger or transmitter acetylcholine delay the development of the disease (Jayaprakasam *et al*., 2010).

AD is the common form of dementia. It accounts for 60 to 70% of the cases of dementia. Other disorders that can cause memory loss, confusion and other symptoms associated with dementia include vascular dementia, often considered the second most common type of dementia. It refers to impairment caused by reduced blood flow to parts of the brain. One type may develop after a single major stroke blocks blood flow to a large area of brain tissue. Another kind, previously known as 'multi-infarct dementia,' can occur when a series of very small strokes block tiny arteries. Individually, these strokes are too minor to cause significant symptoms, but over time their combined effect becomes noticeable. Symptoms of vascular dementia can be similar to AD. The symptoms include problems with memory, confusion and difficulty following instructions. In some cases, the impairment associated with vascular dementia can occur in 'steps' rather than in a slow, steady decline, usually seen in AD. Mixed dementia is a condition in which AD and vascular dementia occur together. Some scientists believe that this combination is also common. Parkinson's disease affects the control of movement, resulting in tremors, stiffness and impaired speech. Many individuals with Parkinson's also develop dementia at a later stage of the disease.

Dementia often starts with wide variations in attention and alertness. Individuals affected by this illness often experience visual hallucinations as well as muscle rigidity and tremors similar to those associated with Parkinson's disease. Physical injury to the brain caused by an automobile accident or other trauma can damage or destroy brain cells and cause symptoms of dementia, such as, behavioral changes, memory loss and other cognitive difficulties. Frontotemporal dementia or Pick's disease is another rare disorder that may sometimes be difficult to distinguish from AD. Personality changes and disorientation often occur before memory loss. Normal pressure hydrocephalus (NPH) is caused by a buildup of fluid in the brain. The cause of most cases is unknown. Symptoms include difficulty walking, memory loss and inability to control urine. NPH can sometimes be corrected with surgery to drain the excess brain fluid (Anonymous, 2010).

The cause of AD is being investigated in a number of areas. Several genes have been linked to the development of AD. Even as genetic factors may increase the likelihood that a person will develop AD, environmental factors are believed to have an important role as well. On the other hand, a number of environmental factors are found that have been associated with the development of AD, including long-term exposure to silicon or aluminium, chronic exposure to other toxins, free radical damage and traumatic head injury (Shin, 1997; Rosler *et al*., 1998).

The dysregulation of biometal (Cu, Zn, Fe) homeostasis and oxidative stress in the brain cells are major hallmarks in the pathogenesis of AD (Kastenholz, 2011). During the 1960s and 1970s, aluminum emerged as a possible suspect in causing AD. This suspicion led to concerns about everyday exposure to aluminum through sources such as cooking pots, foil, beverage cans, antacids, and antiperspirants. Since then, studies have failed to confirm any role for aluminum in causing AD, but few experts believe that continuous exposure to aluminum source may cause threat. According to a growing body of evidence, risk factors for vascular disease - including diabetes, high blood pressure, and high cholesterol may also be risk factors for AD and stroke-related dementia (Anonymous, 2010).

**Medicinal Plants to Treat Alzheimer**

A number of scientific researchers have been carried out on medicinal plants. Medicinal plants have anti-inflammatory and antioxidant activities that may be used in the treatment of AD. AD patients have an acetylcholine deficiency. Acetylcholine is a neurotransmitter that plays a key role in cognitive function and reasoning. The brains of those with mild-to-moderate AD, a progressive type of dementia, have abnormally low acetylcholine concentrations. This means that any compound that enhances the cholinergic system in the brain may be useful in treating AD and similar brain malfunctions. The herbs that inhibit Acetylcholinesterase (AchE) contain natural COX-2 inhibitors, also reported as medicinal plants for AD indication. Anti-inflammatory herbs like German chamomile, Ginseng, liquorice, turmeric, and white willow bark may reduce inflammation of the brain tissue in AD. The present review puts together research on various medicinal plants that have shown promise in

reversing the AD pathology. The report summarizes information concerning the phytochemical, biological and clinical applications of these various plants in order to provide sufficient basic information that could be used in drug discovery campaigns and development processes, thereby providing new functional leads for AD. Below we describe the various medicinal plants that are recommended for AD and their actions on the brain.

***Acorus calamus L.* (Araceae)**

The plant *A. calamus* commonly known as sweet flag is a perennial herb which grows mainly in swamps, marshes and river banks. In Ayurvedic medicine (AM), the rhizome has been used for the treatment of memory loss. Two rhizome extracts, ethanolic and hydroethanolic, exerted sedative and neuroprotective effects *in vivo* respectively (Vohora *et al*., 1990; Shukla *et al*., 2002).

***Bacopa monniera Wettst. (Scrophulariaceae)***

*B. monniera*, commonly known as water hyssop, is an annual plant found throughout the Indian subcontinent in wet, damp and marshy areas. In AM, the plant is used to improve memory and intellect. In India, this plant is locally known referred to as Brahmi or Jalanimab (Chopra *et al*. 1956). Ethanol extracts of aerial parts and rhizome from the plant possessed nootropic activity (Stough *et al*. 2001; Russo and Borrelli 2005; Kumar, 2006).

***Bertholettia excelsa* (Lecythidaceae)**

Although the name is Brazil Nuts, the most significant exporter of Brazil nuts is not Brazil, but Bolivia. In Brazil these nuts are called *castanhas-do-Para*. It has a high concentration of lecithin, which contains choline. Choline is a building block for acetylcholine. These building blocks enhance the concentration of acethylcholine in AD patients. Other plants that contain good amounts of lecithin are dandelion flowers, poppy seeds, soybeans, *mung* beans, horehound, ginseng, cowpeas, English peas, and lentils (Keyvan *et al*., 2007).

***Celastrus paniculatus Willd. (Celastraceae)***

The plant *C. paniculatus*, commonly known as 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 (Nalini *et al*. 1995; Gattu *et al*. 1997). The seeds and seed oil have been used in AM as a memory enhancer (Nadkarni, 1976). Nalini *et al*. (1995) reported that the seed oil reduced the levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) *in vivo*. In another study, the seed oil reversed scopolamine-induced task deficit (Gattu *et al*. 1997). Nalini *et al*. (1986) reported that treatment of mentally retarded children with the oil produced an improvement in their IQ scores. An aqueous seed extract showed antioxidant effect in rat brain, which may be contribute to cognitive enhancing activity observed *in vivo* (Kumar and Gupta 2002a) Ahmad *et al*. (1994) reported that a methanol extract of the inflorescences showed anti-inflammatory effect which may be relevant to AD therapy. A methanol extract was assessed for N-methyl-D-aspartate (NMDA) and Gama aminobutyric acid (GABA) binding activities and nerve growth factor (NGF) effects but did not show any response (Dev, 1997). A possible explanation may be that the extraction solvent was polar and the seed oil and hydrophobic constituent may be responsible for the cognitive enhancing effects of *C. paniculatus*.

***Centella asiatica L. (Umbelliferae)***

*C. asiatica* is a slender perennial creeper which grows throughout the tropical regions in the world. The leaf, known locally as Gotu Kola, has been used in AM for revitalizing 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 (Manyam, 1999). In TCM, it is also used to combat physical and mental exhaustion (Duke and Ayensu, 1985; Brinkhaus *et al*. 2000).

An alcoholic extract of the plant possessed tranquilising and potentially cholinomimetic activities *in vivo*, which may be due to the presence of the triterpenoid brahminoside (Sakina and Dandiya 1990). Aqueous extract of the whole plant enhanced cognitive function in rats, which was associated with the *in vivo* anti-oxidant activity of the extract (Kumar and Gupta, 2002b). Aqueous leaves extract modulated dopaminergic, serotonic and adrenergic systems *in vivo* and improved learning and memory (Nalini *et al*. 1992). The essential oil from the plant is reported to contain monoterpenes (Brinkhaus *et al*. 2000), which have demonstrated AchE inhibitory activity, though not as potent as the standard reference substance (Perry *et al*. 2000).

***Clitoria ternatea L. (Leguminosae)***

*C. ternatea*, commonly known as butterfly-pea, is a persistence herbacous perennial legume. The rhizome has been used in AM as a brain tonic and is reputed to promote memory and intellect (Misra, 1998). In a study carried out by Taranalli and Cheeramkuzhy (2000), ethanol extracts of the rhizome and aerial parts exerted memory enhancing effects *in vivo*. These effects were associated with increased levels of ChAT and ACh *in vivo*. However, there was no associated increased in AChE inhibitory activity. In another study, an aqueous rhizome extract increased the level of ACh in rat hippocampus, which has been proposed to be due to an increase in ChAT (Rai *et al*. 2002). An ethanol extract

obtained from the stem, flowers, leaves and fruits of the plant were reported to be sedative in mice (Kulkarni *et al*. 1988).

***Commiphora whighitti* (Burseraceae)**

*C. whighitti* (*Guggulu*), a plant resin, contains the major constituent of guggulipid, which is guggulsterone. The guggulipid has been seen to be a potential cognitive enhancer for improvement of memory in scopolamine-induced memory deficits. *Commiphora whighitti* acts on impairment in learning and memory and decreased choline actyl transferase levels in hippocampus. However, *Commiphora whighitti* shows maximum effects on memory functions and the potential for dementia disorder (Rubio *et al*., 2008; Lannert and Hoyer, 1998).

***Convolvulus pluricaulis Chois. (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 antiaging remedy (Kumar, 2006). The whole plant in the form of a decoction is used with milk and cumin to treat fever, disability, memory loss, syphilis, and scrofula (Ganju *et al*. 2003).

***Crocus sativus L. (Iridaceae)***

*C. sativus*, commonly known as saffron, is small bulbous perennial that has been cultivated throughout the world for its culinary properties. The plant is used in TCM for treating disorders of the nervous system. An alcohol extract of pistils of *C. sativus* and the component crocin improved ethanol-induced impaired learning and behaviour in mice (Sugiura *et al*. 1995a; Abe and Saito, 2000). This may have been achieved by the inhibiting the impairment of hippocampal synaptic plasticity (Sugiura *et al*. 1995a, 1995b). A hydroalcoholic extract of dried stigmas inhibited fibrillogenesis and exerted antioxidant effect *in vitro* (Papandreou *et al*. 2006).

***Curcuma longa L. (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 (Yu *et al*. 2002). Antidepressant activity is of significant importance in the management of AD.

***Galanthus nivalis L.* (Amaryllidaceae)**

The chief chemical constituent of the *G. nivalis L*. (Common snowdrop) is Galanthamine, and this is an isoquinoline alkaloid. Acetylcholinesterase (AChE) inhibitors, which 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 (Bores *et al*., 1996; lkay *et al*., 2010).

***Ginkgo biloba L. (Ginkgoaceae)***

*G. biloba* is dioecious perennial tree that is indigenous to East Asia, which has been used in TCM for the improvement of memory loss associated with abnormalities in the blood circulation (Samuelsson 2004). Administration of plant extracts to AD and non-AD patients in various randomised, double-blind, placebo controlled, and multicentre trials resulted in improvement of cognitive functions (Hofferberth 1994; Kanowski *et al*. 1997; Rigney *et al*. 1999). Since early pharmacological studies revealed that the flavonoids from G. biloba modulated contractile motion of vascular smooth muscles, attempts were made to prepare a standardised extract rich in flavonoids, the outcome of which is EGb 761 (Kumar, 2006). EGb 761 showed cognitive enhancing activity in number of clinical studies (Hofferberth, 1994; Maurer *et al*. 1997; Kanowski *et al*. 1997). The extract showed neuroprotective effect against A and nitric oxide (NO) induced toxicity in the neuronal cell culture (Bastianetto *et al*. 2000a, 2000b) and could reduce apoptosis both *in vitro* and *in vivo* (Schindowski *et al*. 2001; Yao *et al*. 2001). EGb 761 showed protective effect against ischaemia-induced neurotoxicity (Chandrasekaran *et al*. 2001). The extract also demonstrated *in vitro* and *in vivo* antioxidant activities (Barth *et al*. 1991; Marcocci *et al*. 1994; Topic *et al*. 2002). The extract improved blood supply to the brain, thereby ensuring its efficient functioning and enhanced cognitive performance (Heiss and Zeiler 1978; Loffler *et al*. 2001). Modulation of muscarinic cholinergic system enhanced performance of spatial task (Kristofiková *et al*. 1992).

***Glycyrrhiza glabra* (Fabaceae)**

AD is characterized by neuronal loss and the presence of extracellular senile plaques, whose major constituent is 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 (Bilge and Ilkay, 2005).

***Huperzia serrata* (Lycopodiaceae)**

*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 (Yalla Reddy *et al*., 2010).

***Hypericum perforatum L. (Hypericaceae)***

*H. perforatum* commonly known as St. John's Wort is an herbaceous perennial plant that has been used in Portuguese and Turkinsh folklore medicine for the treatment of neurological disorders (Ross, 2001). The dried crude herb standardized to hypericins improved memory and learning dysfunction (Widy-Tyszkiewicz *et al*. 2002; Trofimiuk *et al*. 2005). Lu *et al*. (2001) reported that a standard extract of *H. perforatum* (hypericin) possessed neuroprotective activity. It is reported that extracts of *H. perforatum*, which have been standardized to hypericin and hyperforin respectively, showed *in vitro* antioxidant activity (Hunt *et al*. 2001; Zheng and Wang 2001), *in vivo* anti-inflammatory effects (Kumar *et al*. 2000). Hydroalcoholic extracts of aerial parts of *H. perforatum*, demonstrated nootropic activity *in vivo*, which may due to adrenergic and serotonergic (5HT1A) antagonistic activity (Khalifa 2001; Kumar *et al*. 2002, 2000). Re *et al*. (2003) suggested that a hydroalcoholic extract of the plant could reduce the rate of degradation of ACh.

***Lipidium Meyenii Walp* (Brassicaceae)**

*L. Meyenii* is known as Maca which shows beneficial improvement in memory and learning. Black maca improves experimental memory impairment, induced by ovariectomy, due in part, to its antioxidant and AChE inhibitory activities. Results demonstrated that black maca can enhance learning and memory in OVX (ovariectomized) mice and this effect might be related, at least in part, to its ability to reduce LPO (Lipid peroxidation) and AChE in OVX mice (Rubio *et al*., 2008).

***Magnolia officinalis* (Magnoliaceae)**

The bark of *M. officinalis* (*Talauma*) is used as a traditional memory enhancing agent in Chinese medicine for the treatment of neurosis, anxiety, stroke, and dementia. *Magnolia Officinalis* inhibits the memory impairment induced by scopolamine through the inhibition of AChE. The ethanolic extracts of *M. officinalis*, magnolol and honokiol, are reported to have antioxidant activity *in vitro* and *in vivo* (Lannert and Hoyer, 1998).

***Terminalia chebula L. (Combretaceae)***

The ripe fruit of *T.chebula* is reputed to enhance memory and to promote longevity (Misra, 1998; Manyam, 1999). However, there is no hard data substantiating the reputed effects of this plant in the AM. A methanol extract is reported to bind NMDA and GABA receptors, but did not show any cholinesterase inhibitory activity (Dev 1997).

***Tinospora cordifolia* (Menispermaceae)**

*T. 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 (Lannert and Hoyer, 1998).

***Urtica dioica L. (Clusiaceae)***

Stinging Nettle has been used for centuries to treat allergy symptoms, particularly hay fever, which is the most common allergy problem. It contains biologically active compounds that reduce inflammation. It contains the mineral boron that is reported to enhance the levels of estrogen, which is a hormone in the body, which can be beneficial in short-term memory. Stinging nettle has also been shown to elevate the mood in some Alzheimer's patients (Keyvan *et al*., 2007).

***Withania somnifera L. (Solonaceae)***

The root of the plant *W. somnifera* known by the name Ashwagandha is one of the most valuable herbs used in AM. It is used rejuvenative tonics ('Rasyanas'), and enhancement of memory and intellect in AM (Upton, 2000). Administration of the standardised root extracts improved cognitive dysfunction *in vivo* (Dhuley 2001; Naidu *et al*. 2006). A hydroalcoholic extract of the roots standardised for withanolides and withanoles showed neuroprotective effect *in vivo* (Jain *et al*. 2001). Hydroalcoholic and ethanolic root extracts demonstrated *in vitro* and *in vivo* antioxidant and anti-inflammatory properties (Dhuley, 1997; Chaurasia *et al*. 2000; Gacche and Dhole, 2006). A methanol root extract promoted the formation of dendrites in a culture of human neuroblastoma cells (Tohda *et al*. 2000). Bhatnagar *et al*.

(2005) reported that the methanolic extract possessed *in vivo* antioxidant properties. *W. somnifera* root powder demonstrated *in vivo* antioxidant and anti-inflammatory effects (Rasool and Varalakshmi, 2007).

## CONCLUSION

The pharmaceutical industry is facing serious challenges to finding a lead molecule for neurodegenerative diseases is becoming extremely expensive, riskier, and critically inefficient. A significant shift from a single-target to a multi-target drug approach, especially for chronic and complex disease syndromes, is being witnessed. Approaches based on reverse pharmacology (from the clinic to the bedside) also offer efficient development platforms for herbal formulations. The Indian system of medicine has gained increasing recognition in recent years with regard to diet and treatment options. Early development of medicinal plant supplements required only anecdotal or epidemiologic information (or both) without an understanding of the mode of action. The natural products industry has come a long way from when it was considered unnecessary to test medicinal plants and their chemical components prior to use, to several randomized, double-blind, controlled studies and to the introduction of good manufacturing practice guidelines for the industry. It has taken a more rigorous scientific and quality enhanced approach to provide 'proof of concept' and a 'mode of action'. It might be worth pointing out that, while medicinal plants and their products has been prescribed for centuries for neurodegenerative diseases (including dementias), only recently have there been Western, mechanistic studies on AD; however, these mechanistic studies point to the same mechanisms addressed by the Indian system of medicine (for example, increase in nerve growth factors and neurotrophic factors and reduction in inflammation and oxidative damage), providing strong support for herbal therapy for AD. It is hoped that the strong knowledge base of medicinal plants and natural products coupled with combinatorial sciences and high-throughput screening techniques will improve the ease with which medicinal plant products and formulations can be used in drug discovery programmes and development process, thereby providing new functional leads for AD and other age associated neurodegenerative diseases.

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