

Effects of medicinal plants on Alzheimer's disease and memory deficits

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Abstract

Alzheimer's disease is an age-related neurodegenerative disorder characterized by memory deficits. Various studies have been carried out to find therapeutic approaches for Alzheimer's disease. However, the proper treatment option is still not available. There is no cure for Alzheimer's disease, but symptomatic treatment may improve the memory and other dementia related problems. Traditional medicine is practiced worldwide as memory enhancer since ancient times. Natural therapy including herbs and medicinal plants has been used in the treatment of memory deficits such as dementia, amnesia, as well as Alzheimer's disease since a long time. Medicinal plants have been used in different systems of medicine, particularly Unani system of medicines and exhibited their powerful roles in the management and cure of memory disorders. Most of herbs and plants have been chemically evaluated and their efficacy has also been proven in clinical trials. However, the underlying mechanisms of actions are still on the way. In this paper, we have reviewed the role of different medicinal plants that play an important role in the treatment of Alzheimer's disease and memory deficits using conventional herbal therapy.

Key Words: nerve regeneration; memory; Alzheimer's disease; medicinal plants; efficacy; literature review; neural regeneration

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease affecting older adults. In 1906, Alois Alzheimer, a German neuropathologist and psychiatrist discovered AD. About 24 million World population is suffering from dementia, in which majority of patients have AD (Ballard et al., 2011). AD is characterized by memory loss, behavior deterioration, performance impairment, and thought slowness. The condition is mimicked by severe depression (Squire, 1992). Cognitive and neural dysfunction occurs due to accumulation of oxidative damage to nucleic acid, protein and mitochondria in the brain. In Spain, survey was conducted on 1,637 people above 64 years of age regarding subjective memory complaints (SMC). SMC were reported in 524 persons (32.4%). Cognitive performance, mood, sex, education and age are associated with prevalence of SMC. SMC are reported in 24% of people between 65 and 69 years of age. SMC increase 57% in people up to 90 years or above group. SMC are 52.8% in people with anxiety and depression (Montejo et al., 2011). Severe psychological stress or drug use can cause amnesia. Various allopathic medicines are prescribed in AD but they exert side effects. Therefore, herbal medicine could be a good source of drugs for treatment of AD and memory deficit with fewer or no side effects. The present article reviews the medicinal plants that are proven for their efficacy to treat AD and memory deficits.

Pathogenesis

Two characteristic features are seen in the brain of patients with AD.

1. Senile plaques contain extracellular deposits of amyloid-beta ($A\beta$), a peptide synthesized by breakage of $A\beta$ precursors (genetic locus 21q21–22). Abnormal deposits of $A\beta$ are also found in blood vessels.

2. Neurofibrillary tangles, dense bundles of abnormal fibers in the cytoplasm of neurons which consist of an altered form of the microtubular-associated protein are found in patients with AD (Hoyer, 1992; Iqbal et al., 2005; Kuljis, 2007; Fernandez et al., 2008; Bamburg and Bloom, 2009).

Molecular Mechanism

The main features of AD are extracellular $A\beta$ pathology and neurofibrillary tau pathology (tangles and threads). For 25 years, most studies have been conducted on the $A\beta$ hypothesis of AD pathogenesis and progression (Pimplikar, 2009). But because of failure in clinical trials of $A\beta$ -targeted treatment and the new concept of prion like propagation of intracellular abnormal proteins, tau has come back into the spotlight as a candidate therapeutic target in management of Alzheimer's disease. Tau pathologies are found in a range of neurodegenerative disorders, but extensive analyses of pathological tau in diseased brains has indicated that the abnormal tau protein in each disease is structurally distinct

(Avila et al., 2004), supporting the concept that progression of the diverse but characteristic tau pathologies occur through prion like seed dependent aggregation. Therefore, intervention in the conversion of normal tau to abnormal forms and in cell-to-cell transmission of tau may be the key for development of disease modifying treatment of AD and other memory deficits (Hasegawa, 2016).

Drug Targets

The tau and amyloid hypothesis has led to focus on tau and amyloid as treatment targets. The current therapeutic goals are to decrease amyloid levels and prevent amyloid toxicity/aggregation and tau aggregation/phosphorylation. AD has a heterogeneous cause with a large percentage termed sporadic AD arising from unknown etiology and a smaller fraction of early onset familial AD caused by mutation in various genes, such as the presenilins (PS1, PS2) and β amyloid precursor protein (APP) (Tang, 2003; Bird, 2008). Other genes such as apolipoprotein E (*APOE*) are considered to be a risk factor for AD (Kim et al., 2009). Various proteins such as APOE, APP, BACE ($A\beta$ cleaving enzyme), PS1/2, secretases and tau play an important role in the pathogenesis of AD. Therefore, research is focused to develop new inhibitors for PS1, BACE and secretase for treatment of AD. There is also a significant advancement in understanding the cholinesterase function in the brain and the use of cholinesterase inhibitors in management of AD (Wilkinson et al., 2004; Yiannopoulou and Papageorgiou, 2013). The mechanism of new generation of acetyl and butyryl cholinesterase inhibitors is being studied and investigated in clinical trials for AD (Grossberg, 2003). Other strategies, such as hormone therapy, anti-oxidants, cholesterol lowering agents, anti-inflammatory agents and vaccinations are also being investigated for treating AD (Lahiri et al., 2002).

Drug Treatment

The demonstration of damage to the cholinergic pathways in the brain leads to great interest in drug development. Acetylcholinesterase inhibitors are usually prescribed to treat AD. These drugs help in enhancing cognitive functions such as memory and thoughts. These medicines are effective in patients with mild to moderate AD (Houghton and Howes, 2005). Tacrine (a cholinesterase inhibitor) at a high dose (160 mg/d) was reportedly used in the treatment of AD (Schneider, 2000). Tacrine was investigated in both clinical trials and neuropsychological test scores, in a 30 week randomized placebo controlled trial (Knapp et al., 1994). However, the use of tacrine is limited due to adverse effects such as hepatotoxicity (Watkins et al., 1994). Anti-oxidants are effective for AD because they aid in reducing the free radicals that damage the brain cells (Howes and Houghton, 2012).

Probiotics have been reported for their efficacy to enhance memory (Lyte, 2011). Probiotics are used as antidepressant in AD. It reduces anxiety like behavior and attenuates psychological stress. Neurochemicals are produced by microbes. Immunological and neurological effects are induced by

probiotics. Probiotics also have immunomodulating activity (Misra and Medhi, 2013). In Chinese and Ayurvedic medicines, medicinal plants are used to treat AD, neurodegenerative changes and cognitive diseases. Various western medicines being used in memory loss are derived from plants. Plant derived alkaloids such as anticholinesterase have been used to treat AD. In the United Kingdom, plant derived galantamine is also used in the treatment of neurodegenerative disorders. Five million Americans are suffering from AD and this number will increase up to 7.7 million in 2030. Symptoms of neurodegenerative disorders clearly appear after 60 years of age (Chengxuan et al., 2009). Etiology of neurodegenerative disorders is linked to genetic defect that is 10–15% of total cases. In AD, loss of neurons appears in subcortical structure, cortex and hippocampus. Various compounds have been identified by phytochemical studies such as alkaloids, sterols, triterpenes, polyphenols, tannins, flavonoids and lignins that have pharmacological activities including anti-cholinesterase and anti-amyloidogenic.

Medicinal plants are playing a significant role in the management of AD and memory deficit. The important traditional therapeutic methods are Ayurvedic, homeopathy, Unani and Sidha systems of medicine. Unani system of medicine offers traditionally a highly scientific health care therapy as a divine gift and as a result the global interest of the medical profession is focused on medicinal plants. Traditional system of medicine is fundamentally preventive, protective, nutritive and curative. Therefore, traditional medicines are safe and harmless which treat the patients with fewer or no side effects.

Herbal medicines have their origins in ancient cultures, including those of the Egyptian, Indians and Chinese. It involves the use of medicinal plants to treat AD and enhances general health and well beings. In fact, many pharmaceutical drugs are based on the synthesized adaptations of naturally occurring compounds found in plants. In recent years, interest in herbal medicine has increased, leading to a greater scientific interest in the medicinal use of plants in treating disease and improving health, often without any significant side effects. Herbal medicines and natural products are the oldest remedies known to mankind. Medicinal plants have been used by all cultures throughout the history. In present scenario, the demand for herbal products is growing, exponentially throughout the World.

In human body, the nervous system coordinates and regulates the various voluntary and involuntary activities of the body. The central nervous system and the autonomic nervous system are interlinked and some drugs affect the CNS producing reactions associated with the autonomic system (McCorry, 2007). Drugs involved with the CNS may have general stimulatory or depressant action with anti-convulsant and psychopharmacological activities. Memory deficit is a major global health problem. Current therapies are inadequate and have numerous adverse effects. There is an urgent need for possible alternative treatments for AD and memory deficit. Various medicinal plants are prescribed to enhance the memory. We have reviewed the literature on

medicinal plants used in the treatment of AD and memory deficit (Xu et al., 2009). Several medicinal plants have been used for decades in different cultures to improve memory such as *Valeriana officinalis*, *Punica granatum* L., *Salvia officinalis*, *Myristica fragrans* *Bacopa monnieri* Linn, *Centella asiatica* Linn and *Evolvulus alsinoides* Linn. Elufioye et al. (2012) reported some plants used as anti-aging and memory enhancing activities in Sagamu, Nigeria that are *Bacopa floribunda*, *Angraecum eichlerianum*, *Parquet inanigrescens*, *Cleome gynandra*, *Dalbergia lacteal*, *Capsicum frutescens*, *Aframomum melegueta*, *Digitaria debilis*, *Musa sapientum*, *Bryophyllum pinnatum*, *Abrus precatorius*, *Ficus exasperate*, *Dioscorea mangenotiana*, *Jatropha curcas*, *Spondia smombin*, *Capsicum frutescens*, *Cola acuminata*, *Mirabilis jalapa*, *Elaies guineensis*, *Canna indica*, *Ipomoea mauritania*, *Bambusa vulgaris*, *Cordia millenii*, *Piper guineense*, *Dioclea sarmentosa*, *Cucumeropsis mannii*, *Eleusine indica*, *Ocimum basilicum*, *Khaya ivorensis*, *Carpolobia alba*, *Carapa procera*, *Entandrophragma utile*, *Xylopias thiopica*, *Garcinia kola*, *Theobroma cacao*, *Milicia excels*, *Blighia sapida*, *Baphia nitida*, *Peperomia pellucid*, *Vernonia amygdalina* and *Zea mays*. Jazayeri et al. (2014) reported some plants having anticholinesterase activity such as *Brassica alba*, *Brassica nigra*, *Camellia sinensis*, *Cinchona officinalis*, *Citrus aurantifolia*, *Citrus aurantium*, *Ferula assafoetida*, *Humulus lupulus*, *Juglans regia*, *Juniperus sabina*, *Myristica fragrans*, *Pelargonium graveolens*, *Pistacia vera*, *Punica granatum*, *Rheum officinale*, *Rosa damasceana*, *Salix alba* and *Zizyphus vulgaris*. Other plants having memory enhancing properties are *Juglans regia* (Haider et al., 2011), *Cuminum cyminum* (Koppula and Choi, 2011), *Ficus religiosa* (Kaur et al., 2010), *Melissa officinalis* (Kennedy and Scholey, 2006), *Rosmarinus officinalis* (Ozarowski et al., 2013), *Piper nigrum* (Hritcu et al., 2014), *Ginkgo biloba* (Tan et al., 2015), *Bacopa monnieri* (Roodenrys et al., 2002), *Desmodium gangeticum* (Mahajan et al., 2015) and *Embllica officinalis* Gaerth (Justin Thenmozhi et al., 2016). Herbal medicines have been used to treat various ailments in Unani system of medicine since ancient times. However, there is a lack of scientific data on the effectiveness and stability of bioactive chemical constituents in medicinal plants. In this review, we aimed at documenting the information on plants used as a memory enhancer in AD.

Withania somnifera

Withania somnifera belongs to the family Solanaceae. It (500 mg/d) exhibited calming effects on stress and reversed memory loss (Auddy et al., 2008). Cholinergic activity of *Withania somnifera* has been reported in a previous study (Schliebs et al., 1997). Memory enhancing activity and cognition improving property of *Withania somnifera* increase due to its ability to increase acetylcholine level in the brain. Neurotic outgrowth activity of *Withania somnifera* is reported already in human neuroblastoma cells that are time- and dose-dependent. *Withania somnifera* enhances dendrite and axon regeneration (Tomoharu et al., 2005). A molecular modeling study indicates that withanamides A and C bind to A β and inhibit fibril synthesis (Jayaprakasam et al., 2010).

Curcuma longa

Curcuma longa belongs to the family Zingiberaceae. In Southeast Asian countries, prevalence of AD is low due to consumption of turmeric. It has anti-inflammatory activity that is also associated with reduced risk of AD (Aggarwal and Harikumar, 2009). *Curcumin* reduces the plaque deposition in the brain. Turmeric decreases oxidative stress and amyloid pathology (Mishra and Palanivelu, 2008). In one study, administration of low doses of *curcumin* reduced A β level up to 40% in mice with AD as compared to control drug (Shytle et al., 2009). *Curcumin* at low doses caused 43% decrease in the plaque burden that these A β have on the brain of mice with AD (Mishra and Palanivelu, 2008). A previous study indicates that low doses of *curcumin* administered for long duration are more effective in the treatment of AD as compared to higher doses of *curcumin* (Yang et al., 2005). *Curcumin* has an ability to bind with A β and inhibits its self assembly (Reinke and Gestwicki, 2007). *Curcumin* has powerful anti-inflammatory and antioxidant effects (Fan et al., 2015); according to the researchers, these effects help in treating Alzheimer's symptoms caused by inflammation and oxidation (Frautschy and Hu, 2001). Hypercholesterolemia and hyperlipidemia increase amyloid plaques by intracellular accumulation of cholesterol esters (Tokuda et al., 2000). Scientists believe that *curcumin* might have therapeutic effects on AD by inhibiting cholesterol synthesis and reducing serum peroxides (Soni and Kuttan, 1992).

Convolvulus pluricaulis

Convolvulus pluricaulis belongs to the family Convolvulaceae. It is used as a memory enhancing agent. A previous study has shown that aqueous and ethyl acetate extract of *Convolvulus pluricaulis* increases memory functions and learning abilities (Bihaqi et al., 2011). In another study, a wide range of secondary metabolites such as steroids, anthocyanins, flavonol glycosides and triterpenoids have been isolated that are responsible for memory enhancing and nootropic properties (Malik et al., 2011). *Convolvulus pluricaulis* has been reported to calm the nerves by regulating the stress hormones synthesis (cortisol and adrenaline) in the body (Sethiya et al., 2009). The ethanolic extract of *Convolvulus pluricaulis* and its aqueous and ethyl acetate fractions significantly improved memory retention and learning abilities in rats (Nahata et al., 2008). Another study conducted by Bihaqi et al. (2011) indicated that extracts of *Convolvulus pluricaulis* enhance the memory in Wistar rats in a dose-dependent manner. Similarly, administration of *Convolvulus pluricaulis* for 1 week increased memory in aged mice (Sharma et al., 2010). Administration of *Convolvulus pluricaulis* increased the acetylcholinesterase activity in the hippocampal CA1 and CA3 regions associated with the memory function and learning abilities (Dubey et al., 1994).

Centella asiatica

Centella asiatica belongs to the family Apiaceae. It contains saponins, asiaticosides, madecassoside, madasiatic acid, brahmoside, brahminoside, sasiaticoside, sitosterol, tannins,

ascorbic acid, centoic acid, centellic acid, thankunside, brahmoside, brahminoside, siatic acid, thankunside, glycoside, triterpine, thankunic acid, vellarin, asiaticosides, thankunside, and isothankunside (Siddiqui et al., 2007). *Centella asiatica* is used in depression, rheumatism, mental weakness, abdominal pain, and epilepsy (Gohil et al., 2010). It is diuretic, anti-spasmodic, anti-convulsive, tonic, stimulant, emmenagogue, antioxidant and spermatogenic (Heidari et al., 2007). *Centella asiatica* reversed the A β pathology and reduced oxidative stress response (Amala et al., 2012).

Rao et al. (2007) reported that treatment with *Centella asiatica* (Linn) fresh leaf extract enhanced learning ability and memory retention power in Wistar rats. Adult rats of 2.5 months old were selected for this study. Three different doses (2, 4, and 6 mg/kg) of extracts were administered for 2, 4, and 6 weeks. Spatial learning (T-maze) and passive avoidance tests were performed after the treatment period. Results were compared with those of age matched control rats. Improvement in spatial learning was significant at the dose of 6 mL of extract. The use of *Centella asiatica* extract enhanced memory retention that was evident from passive avoidance test. This data showed that *Centella asiatica* enhances learning ability and memory retention power in adult rats. Veerendra and Gupta (2003) reported efficacy of *Centella asiatica* in AD. Its cognition enhancing activities and anti-oxidant effects have been reported. Aqueous extract of *Centella asiatica* (100, 200 and 300 mg/kg) was administered for 21 days in streptozotocin (STZ)-induced cognitive impairment and oxidative stress in rats. STZ at 3 mg/kg was intracerebroventricularly injected into male Wistar rats bilaterally on days 1 and 3. Cognitive behavior was assessed after 13, 14 and 21 days of treatment. Rats were sacrificed for assessment of oxidative stress after 21 days of treatment. Cognitive behaviors of rats treated with *Centella asiatica* extract improved significantly. The maximum response was observed after administration of extract at the doses of 200 and 300 mg/kg. Results from Veerendra and Gupta (2003) showed that *Centella asiatica* is effective in STZ-induced cognitive impairment in rats.

Celastrus paniculatus

Celastrus paniculatus belongs to the family Celastraceae. It prevented neuronal cell damage against hydrogen peroxide toxicity due to its antioxidant activity (Godkar et al., 2006). Administration of *Celastrus paniculatus* prevents neuronal cell damage caused by glutamine induced toxicity (Godkar et al., 2003). *Celastrus paniculatus* increases cholinergic activity that contributes its ability to improving memory performance (Bhanumathy et al., 2010). Aqueous extract of *Celastrus paniculatus* has antioxidant and cognition enhancing properties (Kumar and Gupta, 2002). *Celastrus paniculatus* extracts protected neuronal cells against hydrogen peroxide induced toxicity in part by virtue of their antioxidant and free radical scavenging activities (Katekhaye et al., 2011).

Nardostachys jatamansi

Nardostachys jatamansi belongs to the family Caprifoliace-

ae. It contains sesquiterpene valeranone that has been used for treatment of stress (Lyle et al., 2009). In a study, *Nardostachys jatamansi* exhibited memory retention and learning enhancing abilities in aged and young mice and reversed scopolamine and diazepam induced amnesia. *Nardostachys jatamansi* also reversed aging induced amnesia (Joshi and Parle, 2006). Karkada et al. (2012) reported efficacy of *Nardostachys jatamansi* in the prevention of stress induced memory deficit.

Coriandrum sativum

Coriandrum sativum belongs to the family Apiaceae. In one study, *Coriandrum sativum* was given for 45 days for its efficacy on cognitive function in male Wistar rats. This study was conducted in comparison with aging, scopolamine and diazepam induced amnesia. *Coriandrum sativum* exhibited memory enhancing effects due to its antioxidant, anti-inflammatory and cholesterol lowering activities (Vasudevan and Milind, 2009).

Ficus carica

Ficus carica belongs to the family Moraceae. It was investigated for its effect in retrieval, retention and acquisition of spatial recognition. *Ficus carica* contains quercetin that plays an important role in memory deficit and AD due to its antioxidant activity. For this study, mice with memory deficit and normal mice were used. Rectangular maze model and Y-maze were used to assess efficacy of *Ficus carica* on cognitive functions. Hexane extract (100 and 200 mg/kg) was administered to adult swiss Wistar albino mice. In this study, Bacopa monniera and scopolamine were used as standard drug and amnesic agent respectively. *Ficus carica* 200 mg/kg exhibited maximum nootropic response that is near to response exhibited by a standard drug Bacopa monniera. In conclusion, *Ficus carica* at lower doses exhibits mild memory enhancing effect and higher doses evoke better learning ability and alter behavior (Saxena et al., 2013).

Ginkgo biloba

Ginkgo biloba belongs to the family Ginkgoaceae. It contains bilobalide that has a neuroprotective activity (Chandrasekaran et al., 2001). *Ginkgo biloba* decreases free radical and improves memory in patients with AD (Shi et al., 2010). It contains flavonoids that are involved in memory enhancement (Bastianetto et al., 2000). *Ginkgo biloba* prevents neurodegeneration and GABA inhibitory neurotransmission induced by hippocampal corticosterone (Walesiuk and Braszko, 2009). Administration of *Ginkgo biloba* significantly improved memory and learning performance in albino rats (Nalini et al., 1992).

Ilex paraguariensis

Ilex paraguariensis belongs to the family Aquifoliaceae. It has a memory enhancing property. It contains vitamin B12, B1 and C. *Ilex paraguariensis* is being used as an anti-dementia agent (Bastos et al. 2007). Its memory enhancing property was investigated in different rat models (Colpo et al., 2007).

Ilex paraguariensis has been shown to improve short and long term memory (Rui et al., 2008). There is evidence that *Ilex paraguariensis* for treatment of vascular dementia improves memory (Heck et al., 2007). Literature review indicates that *Ilex paraguariensis* is effective in the treatment of neurodegenerative disorders such as AD (Muzzafera, 1997).

Commiphora whighitti

Commiphora whighitti belongs to the family Burseraceae. It is a potent cognition enhancer for memory improvement in scopolamine induced memory deficits (Gujran et al., 2007). Another study shows that brain pathology develops in cholesterol fed rabbits similar to AD (Ghribi, 2008), which is supported by clinical trials in human, showing that statin treatment decreases the risk of AD (Raja and Hoyer, 2004). Memory enhancing and anti-dementia activity of *Commiphora whighitti* has been reported that is due to reduction in acetylcholinesterase contents in the hippocampus (Lannert and Hoyer, 1998).

Glycyrrhiza glabra

Glycyrrhiza glabra belongs to the family Fabaceae. It contains pentanol, hexanol, linalool oxide, tetramethyl pyrazine, terpinen, terpinol, geraniol, propionic acid, benzoic acid, ethyl linolenate, methyl ethyl ketone, butanediol, feuferaldehyde, furfuryl formate, trimethylpyrazine, maltol, glycyrrhizin, tannin, and glycyrrhizic acid (Rekha and Parvathi, 2012). *Glycyrrhiza glabra* is used in gastric ulcer, lung congestion, hoarseness and throat problems (Dastagir and Rizvi, 2016). Memory enhancing activity of *Glycyrrhiza glabra* was reported in scopolamine induced dementia (Ambawade et al., 1998). Dhingra et al. (2004) reported the memory enhancing activity of *Glycyrrhiza glabra* in mice. Three dose levels (75, 150, 300 mg/kg, p.o.) of *Glycyrrhiza glabra* extracts were administered to mice in 7 successive days. *Glycyrrhiza glabra* at 150 mg/kg was found effective in memory enhancement.

Lepidium meyenii

Lepidium meyenii belongs to family Brassicaceae. It is known as Maca which shows improvement in learning abilities and memory function (Julio et al., 2007). *Lepidium meyenii* exhibited memory enhancing activity in patients with AD. It enhances memory by increasing level of acetylcholine (Wang et al., 2006). It improves experimental memory impairment induced by ovariectomy, due in part to its acetylcholinesterase inhibitory and antioxidant effects. Results showed that *Lepidium meyenii* can enhance memory retention and learning abilities in ovariectomized mice and this activity might be related, at least in part, to its ability to decrease lipid peroxidation and acetylcholinesterase in ovariectomized mice (Rubio et al., 2011).

Panax ginseng

Panax ginseng belongs to the family Araliaceae. A previous study has shown that learning ability increases in animals by consumptions of *Panax ginseng*. Recent studies have shown the efficacy of *Panax ginseng* powder, extract and various

ginsenosides on AD using *in vivo* and *in vitro* models (Heo et al., 2008; Cho, 2012; Hee et al. 2013). Patients receiving Korean white ginseng powder (4.5 g/d) or Korean red ginseng powder (9 g/d) showed significant improvement in Clinical Dementia Rating, Mini-Mental State Examination scores and the Alzheimer's Disease Assessment Scale after 12 weeks of ginseng treatment in comparison with those in the control group (Heo et al., 2008; Lee et al., 2008).

Embllica officinalis

Embllica officinalis belongs to the family Euphorbiaceae. It exhibited significant improvement in memory retention of young and aged rats in a dose-dependent manner. It reversed the diazepam and scopolamine induced amnesia. As a memory enhancer and reversal of memory deficits, *Embllica officinalis* plays an important role in the treatment of memory deficits and AD (Mani et al., 2007). A study was conducted to investigate the memory enhancing effect of piracetam when used together with *Embllica officinalis* and *curcuma longa* against aluminium-induced cognitive dysfunction and oxidative damage in rats. Aluminium chloride at 100 mg/kg was given orally to rats for 6 weeks. *Embllica officinalis* (100 mg/kg, p.o.), *curcumin* (100 mg/kg, p.o.) and piracetam (200 mg/kg, i.p.) were concomitantly administered to rats daily for 6 weeks. Elevated plus maze task paradigms and Morris water maze tests were used to evaluate memory on days 21 and 42 of treatment. On day 43 of treatment, rats were sacrificed to evaluate the extent of oxidative stress. Oxidative stress was significantly reduced and memory was significantly improved in rats treated with *Embllica officinalis* (100 mg/kg, p.o.), *curcumin* (100 mg/kg, p.o.) and piracetam (200 mg/kg, i.p.) than the rats treated only with piracetam (200 mg/kg, i.p.). As antioxidant and memory enhancer agent, *Embllica officinalis* could be used to treat memory loss and AD (Ramachandran et al., 2013).

Magnolia officinalis

Magnolia officinalis belongs to the family Magnoliaceae. It improves the scopolamine induced memory deficits (Lee et al., 2009). *Magnolia officinalis* inhibits acetyl cholinesterase activity (Jae et al., 2009). Ethanolic extract of *Magnolia officinalis* containing honokiol and magnolol has been reported to possess antioxidant effects (Lo et al., 1994; Chiu et al., 1997; Kong et al., 2000). *In vitro* antioxidant activities of various Soxhlet and supercritical fluid extracts have been reported, with the ethyl acetate Soxhlet extract being the most active (Li and Weng, 2005). Biphenolic lignins (magnolol (29) and honokiol (28) derived from *Magnolia officinalis*, have the ability to enhance the choline acetyltransferase effects and inhibit the acetylcholine cleavage and have also been shown to release acetylcholine from the hippocampus (Hou et al., 2000). Both compounds exhibited *in vivo* antioxidant effects (Lo et al., 1994). Magnolol showed *in vitro* neuroprotective activity (Lee et al., 2000). The compound also exhibited anti-inflammatory effect *in vivo* and *in vitro* (Wang et al., 1992, 1995). Honokiol exhibits anti-inflammatory activity by inhibiting reactive oxygen species synthesis (Dikalov et al., 2008). As

an anti-inflammatory and antioxidant agent, *Magnolia officinalis* plays an important role in the management of AD and memory deficits (Jie et al., 2000; Chen et al., 2001; Liou et al., 2003).

Zingiber officinale

Zingiber officinale belongs to the family Zingiberaceae. It is used for treatment of headache, rheumatism and stomach trouble (Malhotra and Singh, 2003). It improves memory impairment induced by scopolamine via inhibition of acetylcholinesterase activity (Hanumanthacar et al., 2006). As a booster of antioxidant and a reducer of free radical, *Zingiber officinale* plays an important role in the treatment of AD and memory deficits (Masuda et al., 1997). In another study, male rats (250–300 g) were divided into treatment and control groups. The treatment group was further divided into three subgroups. Plant mixed in food at a ratio of 6.25% was administered in the first group. Plant extract at 50 mg/kg and 100 mg/kg (intraperitoneal) was administered to the second and third subgroups, respectively. Shuttle box test and Y maze test were used to investigate acquisition-recalling and spatial recognition behaviors. Significant improving effects on recall, retention and acquisition were observed in male rats after intraperitoneal and oral administration of *Zingiber officinale* (Gharibi et al., 2013).

Tinospora cordifolia

Tinospora cordifolia belongs to the family Menispermaceae. Pharmacological activities include anti-fertility, antioxidant and immunomodulating activities (Reddy and Rajasekhar, 2015). *Tinospora cordifolia* possesses a memory improving effect in animals with memory deficits (Malve et al., 2014). The mechanism by which *Tinospora cordifolia* improves memory is the synthesis of acetylcholine and immunostimulation (Asuthosh et al., 2000). Administration of *Tinospora cordifolia* increases the cognitive function in patients with AD (Lannert and Hoyer, 1998).

Punica granatum

Punica granatum belongs to the family Punicaceae. It contains corilagin, granatin, puniacortin A, pedunculagin and punicafolin. *Punica granatum* is used in diarrhea and dysentery (Das et al., 1999). It is anthelmintic and astringent. Cambay et al. (2011) reported the efficacy of *Punica granatum* flower in learning and memory performance impaired by diabetes mellitus in rats. In this study, rats were divided into five groups ($n = 12$): control, streptozocin, streptozocin + pomegranate flowers at 300, 400 and 500 mg/kg/d. Results showed that rats in the streptozocin group showed memory impairment than those in the control group. Administration of pomegranate flower powder led to improvement in learning abilities and memory retention in diabetic rats. Pomegranate flower powder supplementation decreased oxidative stress and alleviated learning and memory impairment as compared to streptozocin induced diabetic rats. Therefore, *Punica granatum* flower plays an important role in the treatment of neurological deficits in patients with diabetes mellitus.

Crocus sativus

Crocus sativus belongs to the family Iridaceae. There is an increasing trend to prescribe the *Crocus sativus* in the treatment of AD and memory deficits. In clinical trials, efficacy of *Crocus sativus* was investigated in 54 patients aged 55 years during a 22-week study period. Patients were randomly assigned to receive donepezil 10 mg/d or capsule saffron 30 mg/d. *Crocus sativus* at 30 mg/d was found to be effective similar to donepezil in patients with mild to moderate AD after 22 weeks of treatment. Adverse effects occurred at similar frequencies between donepezil-treated and saffron-treated patients, with the exception of vomiting which occurred more in donepezil-treated patients (Akhondzadeh et al., 2010). Another similar study was conducted to investigate the effects of saffron extract versus memantine in decreasing cognitive deterioration of patients with moderate to severe AD. In this clinical trial, 68 patients received saffron extract (30 mg/d) or memantine (20 mg/d) for 1 year. Functional Assessment Staging and Severe Cognitive Impairment Rating Scale were used to evaluate patients every month and possible adverse effects were recorded. *Crocus sativus* at 30 mg/d was found to be effective similar to memantine in patients with moderate to severe AD after 1 year of treatment. There was no significant difference in frequency of adverse effects in both treatment groups (Farokhnia et al., 2014).

Cissampelos pareira

Cissampelos pareira belongs to the family Menispermaceae. It was investigated for its effect on memory and learning in mice. Memory and learning was tested via passive avoidance paradigm and elevated plus maze. Hydroalcoholic extract of *Cissampelos pareira* was given orally at 100, 200 and 400 mg/kg for 7 days. Memory and learning significantly improved after administration of *Cissampelos pareira* at 400 mg/kg in mice. *Cissampelos pareira* extract at 400 mg/kg reversed the scopolamine induced amnesia. Nootropic effect of *Cissampelos pareira* was observed that may be due to decreased activity of acetylcholinesterase enzyme and increased antioxidant and anti-inflammatory activities (Prasad et al., 2011).

Mellisa officinalis

Mellisa officinalis belongs to the family Lamiaceae. It is anxiolytic, anti-inflammatory and antidepressant (Taiwo et al., 2012). In a randomized clinical trial conducted by Kennedy et al. (2002), 20 young participants received a single dose of 300, 600 and 900 mg of *Mellisa officinalis* or a matching placebo at 7 day intervals. *Mellisa officinalis* at 600 mg significantly improved memory and cognitive performance. Akhondzadeh et al. (2003a) conducted a study to investigate the efficacy and safety of *Mellisa officinalis* (60 drops/day) in the treatment of AD. Patients were randomly divided into test and placebo groups. *Mellisa officinalis* extract was administered to patients between 65 and 80 years of age for 4 months. At 4 months of treatment, *Mellisa officinalis* extract exhibited a significant effect on cognitive function as com-

pared to the placebo group. There were no significant side effects observed in both treatment groups except agitation in the placebo group.

Moringa oleifera

Moringa oleifera belongs to the family Moringaceae. *Moringa oleifera* leaf extract contains Vitamin C and E that are anti-oxidant and are involved in enhancing memory in AD (Pakade et al., 2013). It has nootropic activity and combat stress in AD (Mohan et al., 2005). *Moringa oleifera* alters monoamines that are involved in memory process (Ganguly and Guha, 2008). A study conducted in rats indicated that *Moringa oleifera* ameliorates the colchicines-induced AD by modifying levels of monoamines such as nor epinephrine, dopamine and serotonin (Obulesu and Rao, 2011).

Salvia officinalis

Salvia officinalis belongs to the family Lamiaceae. It enhances memory retention by interacting with muscarinic and cholinergic pathways that are involved in memory retention process (Eidi et al., 2006). A study was conducted to investigate the efficacy of *Salvia officinalis* in 42 patients (18 female and 24 male, age between 65 and 80 years) with AD living in Tehran, Iran. After 4 months of treatment, significant efficacy was observed in *Salvia officinalis* treated patients than in the placebo-treated patients. The findings indicate the effectiveness of *Salvia officinalis* in the treatment of AD and memory deficits (Akhondzadeh et al., 2003b).

Myristica fragrans

Myristica fragrans belongs to the family Myristicaceae. It contains camphene, b-pinene, sabinene, cymene, garaniol, d-borneol, linolool, terpineol, safrol, elemicin, myristicins, phenylpropane derivatives, lauric acid, myristic acid, pentadecanoic acid, palmitic acid, heptadecanoic acid, stearic acid, oleic acid and b-sitosterol (Maeda et al., 2008). *Myristica fragrans* is used in nervous disorders, digestive disorders, leukemia, bodyache, vomiting, tachycardia, dizziness and memory disturbances (Asgarpanah and Kazemivash, 2012). It is hypolipidemic, antidepressant, antioxidant and antibacterial (Narasimhan and Dhake, 2006). N-hexane extract of *Myristica fragrans* at three dose levels (5, 10 and 20 mg/kg p.o.) was administered orally to young and aged mice for 3 successive days. This drug was found effective at 5 mg/kg in reversing scopolamine and diazepam induced impairment in learning and memory. This study validated use of *Myristica fragrans* in the management of AD and memory deficits (Parle et al., 2004).

Bacopa monnieri

Bacopa monnieri belongs to family Scrophulariaceae. It contains sterols, saponins, alkaloids, monnierin, hersaponin acid A, herpestine and brahmine (Singh, 2012). Traditional healers use *Bacopa monnieri* in combination with *Centella asiatica* and *Evolvulus alsinoides* to treat memory disorders and AD (Russo and Borrelli, 2005). *Bacopa monnieri* enhances memory in patients with AD. It is adaptogenic, neuropro-

TECTIVE, antimicrobial and memory enhancer (Aguiar and Borowski, 2013). Carlo et al. (2008) reported the efficacy of *Bacopa monnieri* on cognitive performance, anxiety, and depression in the elderly and found effective in enhancing cognitive functions in the elderly. This study justifies its use as a memory enhancer. Another study demonstrated that *Bacopa monnieri* inhibits cholinergic degeneration and exhibits cognition enhancing activity in a rat model of AD (Uabundit et al., 2010).

Evolvulus alsinoides

Evolvulus alsinoides belongs to the family Convolvulaceae. Nahata et al. (2010) reported the efficacy of *Evolvulus alsinoides* in learning behavior and memory enhancement activity in rodents. Ethanol extracts of *Evolvulus alsinoides* and its ethyl acetate and aqueous fractions were investigated for memory enhancing activities in rats. Extracts at 100 mg/kg and 200 mg/kg were administered orally. All extracts significantly enhanced learning ability and memory retention in rats. Furthermore, these extracts (0.3 mg/kg, i.p) significantly reversed scopolamine induced amnesia in rats. Nootropic activity of extracts was compared with piracetam as the standard drug. Extract showed significant memory enhancing activity in the step-down and shuttle-box avoidance paradigms.

Ficus racemosa

Ficus racemosa belongs to the family Moraceae. Faiyaz et al. (2011) reported the memory enhancing activity of *Ficus racemosa* bark in rats and found that *Ficus racemosa* (250 and 500 mg/kg) significantly increased acetylcholine level in the hippocampus of rats. This study suggests its potential to treat memory deficits in patients with AD.

Ginkgo ginseng

Ginkgo ginseng belongs to the family Ginkgoaceae. Wesnes et al. (2000) reported the memory enhancing effect of *Ginkgo ginseng* in 256 healthy middle-aged volunteers through a 14-week study period. A questionnaire including sleep, mood, and quality of life was filled before and during the treatment period. Assessment was done at weeks 0, 4, 8, and 14 of the treatment. *Ginkgo ginseng* powder was found effective in improving memory deficits.

Conclusion

In this paper, we have reviewed more detail about the management of AD and the medicinal plants with potential therapeutic values. Despite the bulk of knowledge regarding this complex disease, there is no complete cure except symptomatic treatment. So, the herbal therapy is now anticipated to control AD progression and help to relieve the symptoms related to AD. Herbal therapy can improve the life quality of patients with AD and memory deficits. Worldwide research is being done to find effective treatment of AD. This review reveals that herbal therapy is an encouraging choice as alternative to treat AD. Medicinal plants used in different systems of medicine particularly

Unani system of medicines exhibit their powerful role in the management and cure of memory disorders. Most of herbs and plants have been chemically evaluated and some of them are in the clinical trial stage. The results are magnificent and considerable. However, the underlying mechanisms of action are still on the way. As reviewed in this paper, future clinical trials involving larger sample sizes are needed to investigate the role of different medicinal plants and the underlying mechanisms.

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