Alzheimer's disease treatment: The share of herbal medicines

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A R T I C L E I N F O	**A B S T R A C T**
	One of the most frequent forms of dementia in neurological disorders is Alzheimer's disease (AD). It is a chronic neurodegenerative disease characterized by impaired learning and memory. Pathological symptoms as extracellular amyloid-beta (Aβ) plaques and intracellular accumulation of neurofibrillary tangles occur in AD. Due to the aging of the population and increased prevalence of AD, discovery of new therapeutic agents with the highest effectiveness and fewer side effect seems to be necessary. Numerous synthetic medicines such as tacrine, donepezil, galantamine, rivastigmine, memantine, glutathione, ascorbic acid, ubiquinone, ibuprofen, and ladostigil are routinely used for reduction of the symptoms and prevention of disease progression. Nowadays, herbal medicines have attracted popular attention for numerous beneficial effects with little side effects. *Lavandula angustifolia, Ginkgo biloba, Melissa officinalis, Crocus sativus, Ginseng, Salvia miltiorrhiza*, and *Magnolia officinalis* have been widely used for relief of symptoms of some neurological disorders. This paper reviews the therapeutic effects of phytomedicines with prominent effects against various factors implicated in the emergence and progression of AD.

Introduction

Alzheimer's disease (AD) is known as an epidemic problem throughout the world. It is one of the frequent forms of dementia disorder with progressive synaptic damage and neuronal degeneration (1, 2). There is a progressive increase in the prevalence of AD especially in ageing people such that about %4 of the populations have AD over the age of 65 and %47 after 85 years of age (3). The World Alzheimer Report in 2016 reported that about 47 million people are bearing physical, psychological, and behavioral problems related to AD, creating a heavy economic burden for both societies and healthcare providers (4).

AD is characterized by learning and memory deficits, causing severe mental deterioration with social and occupational problems (5). The data acquisition and collection from the environment are known as learning, while programmed neural connections in the CNS leading to encoding, storing, and recovering information create memory (6, 7). Both are associated with cognition that is impaired in AD people. The interactions between age, education, genetics, and environmental factors affect AD (8).

There are two main types of AD according to the age of occurrence; early-onset or familial form in the young and late-onset or sporadic form after 65 years. The early onset of AD, the autosomal dominant inherited form, is a rapid progression type of disease with shorter survival time compared to the sporadic form (9). Usually, the patients have a history of AD in their family and are frequently associated with genetic causes. Sporadic AD, as a highly polygenic disease, has slow progression with

a prevalence rate of > 95% in all AD cases (10). It occurs due to extracellular accumulation of the 42 amino acid peptide, called amyloid-beta (Aβ) plaque (see below), related to APP cleavage imperfection or deficit in Aβ clearance. Moreover, ε4 isoform of Apolipoprotein E (Apo E4) is another significant genetic risk factor for sporadic form of AD. Apo E4 inhibits proteolytic degradation of Aβ through neprilysin (NEP) and insulin-degrading enzyme (IDE) activity (11).

The main pathological features of AD are extracellular accumulation of Aβ plaques and intracellular formation of neurofibrillary tangles (NFT). In addition, glutamatergic and cholinergic dysfunction (12), oxidative stress (13), prion proteins (14), and inflammation (15) are implicated in the pathology of AD.

Today, herbal medicine has attracted the attention of researchers due to its more effective therapeutic aspects along with fewer side effects compared with synthetic drugs (16-18). Multifunctional effects have introduced them as a therapeutic strategy for the treatment of a wide range of diseases. In this study, we have focused on some medicinal herbs known to be suitable for the treatment of AD.

Etiology of AD
Amyloid-beta plaque

Extracellular accumulation of Aβ plaque is one of the main histopathological hallmarks of AD. It is normally produced in the brain and has an important role in cell signaling and synaptic plasticity (19). Sequential enzymatic action on the transmembrane amyloid precursor protein (APP) by β- and γ-secretases

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causes Aβ generation (20). During aging, because of mutation in APP or related cleavage enzymes, including secretases and presenilin family, there is an overproduction of Aβ as well as a deficiency in its clearance, resulting in peptide aggregation and plaque formation (21). Excessive amount of Aβ fibrils induces neurotoxicity and synaptotoxicity, dysfunction, and degeneration of neurons and ultimately neuronal death (20). It also induces some abnormalities in brain metabolic processes leading to neuroinflammation (22). There are several different ways including microglial and macrophage phagocytosis, transcytosis across the blood-brain barrier (BBB), autophagy, and proteolytic degradation to clear Aβ from the brain (23). The ability of some degrading enzymes such as metalloendopeptidase, NEP, and IDE in the clearance of Aβ has also been demonstrated (24).

Neurofibrillary tangles

Neurofibrillary tangles are another fundamental neuropathological hallmark of AD. They are generated by hyperphosphorylation of the cytoskeletal microtubules associated protein called tau protein (25). Normally, tau proteins stabilize microtubules in neuronal pathways, however, in AD patients, hyperphosphorylation of tau proteins leads to formation of paired helical NFT filaments that stimulate host neuronal cell death (26). It is revealed that Aβ stimulates phosphorylation of tau and, therefore, provokes formation of NFT (27). Formation of NFT correlates with functional impairment, cognitive decline, and neurodegeneration especially in AD (28).

Neurotransmission dysfunction
Glutamatergic system

Glutamate is the most important excitatory neurotransmitter in the brain which is involved in different mechanisms of synaptic plasticity, the necessary process for encoding learning and memory phenomena (29). Dysfunction of the ionotropic N-methyl-D-aspartate (NMDA) glutamate receptor is importantly implicated in the neuronal excitotoxicity in AD (30). In late onset AD, Aβ can directly bind to the NMDA receptors, leading to increased extracellular glutamate concentration and excessive activation of the receptor (31). Overactivity of NMDA receptors itself disrupts Ca^{2+} influx leading to un-regulated intracellular signaling and neurotoxicity; a pathological mechanism recognized in some neurodegenerative disorders, including AD (32). It is also shown that Aβ oligomers have a toxic impact on glucose metabolism via AMP-activated kinase (AMPK). An impaired AMPK destroys synaptic plasticity through NMDA receptors which (33). In an Aβ independent manner, Apo E4 can occupy the NMDA receptors and impair synaptic plasticity in AD (34).

Cholinergic system

Acetylcholine (ACh) abundantly occurs in the brain synapses and is essential for brain processing and memory formation. It is synthesized and degraded by choline acetyltransferase and acetylcholinesterase enzymes, respectively (35). The level of ACh is shown to be declined in the cognition and memory relevant areas of the brain such as the cortex and hippocampus (36). Also, documents indicate that dysfunction of the cholinergic system is responsible for short-term memory deficit in AD (37). Importantly, in the latest stages of AD, due to decreased synthesis and increased degradation of ACh, the levels of the neurotransmitters decline by up to 85%.

Cholinesterase enzymes that hydrolyze ACh exist in both neuronal and non-neuronal tissues; they are classified as acetylcholinesterase (AChE) and butyrylcholinesterase (BchE). Overactivity of AChE and BChE reduces ACh and disrupts the cholinergic system (38). Clinical evidence also shows that AChE can promote production and deposition of Aβ in AD patients (39). BchE, known as pseudocholinesterase, is a nonspecific cholinesterase enzyme involved in hydrolyzing of different types of choline esters. It is primarily associated with glial cells and endothelial cells in the brain with a minor role in regulation of brain ACh levels (40).

Oxidative stress

Oxidative stress is another mechanism through which the possibility of AD occurrence will be increased. Oxidative stressors cause damage to DNA, proteins, and other macromolecules (41). They cause mitochondrial dysfunction leading to excessive production of oxidative agents such as reactive oxygen species (ROS) and free radicals, leading to neurotoxic events (42) and autophagic degradation of mitochondria in AD people (43). Oxidative stress stimulates lipid peroxidation, a process that leads to formation of some reactive aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal. They are known as major bioactive markers of lipid peroxidation and act as ROS. It is proven that the lipid peroxidation by-products play an important role in AD pathogenesis (44, 45). Plenty of studies have shown that many of the pathological symptoms of AD occur due to oxidative stress, which promotes the initiation and progression of AD (46-48). Indeed, a category of the proposed drugs treating AD are anti-oxidants which scavenge free radicals and prevent cells from damage (49).

Prion proteins

Another effective mechanism involved in AD is prion (PrPc). This cell surface glycoprotein is found in neurons especially in the spinal cord (50). The normal function of PrPc is enigmatic but it seems that the PrPc acts as an anti-apoptotic and anti-oxidant protein (51). The expression of PrPc is regulated by the amyloid intracellular domain. PrPc reduces beta-secretase (BACE1) activity and prevents overproduction of the Aβ peptide. In AD patients, this interaction is disrupted, resulting in overactivity of BACE1, which in turn, leads to extra production of Aβ peptide (52). On the other hand, by binding to the ends of growing polymers, PrPc has an inhibitory effect on fibril elongation of Aβ. Interaction of Aβ oligomers with mutated PrPc plays a destructive effect on synaptic transmission (53) and inhibits memory consolidation (54).

Neuroinflammation

Immunopathological investigations have proven that inflammatory mediators are increased in AD. High levels

of complement proteins and acute phase reactants are detected in the brain of AD patients. Also transforming growth factor ß (TGF-ß), an anti-inflammatory cytokine that also regulates brain inflammatory mediators, is up-regulated in AD (55).

Cyclooxygenase (COX) is a key enzyme responsible for brain inflammation in AD patients. It is shown that non-steroidal anti-inflammatory (NSAIDs) drugs play their anti-inflammatory role by inhibition of COX ll. Also, in AD patients, the amount of C-reactive protein and IL-6, as inflammation biomarkers, is considerably higher than in normal people, particularly in the early stages of the disease (56).

Another important progressive biomarker of AD is the serum amyloid P component (SAP) which is produced in the liver and localized in the brain. SAP is a neurotoxic agent that, through binding to fibrils, protects Aβ from proteolysis. With disease progression, more cytokines and acute-phase proteins are released and, thus, more Aβ fibrils will be deposited (57, 58).

Current therapeutic methods

Obviously, there are no absolute medications to reverse neuronal and synaptic destruction in AD (59), and currently approved drugs only alleviate clinical symptoms. The routine drugs for AD are cholinesterase inhibitors (60), NMDA receptor antagonists (61), and anti-oxidant and anti-inflammatory agents (62). These chemical synthetic drugs have various adverse effects such as nausea, diarrhea, bradycardia, and hepatotoxicity (63). Cholinesterase inhibitors such as tacrine, donepezil, galantamine, and rivastigmine are able to inhibit AChE, increase ACh concentration, and improve cognitive function (64, 65). Memantine, as a glutamate receptor antagonist, reduces Aβ deposition and disaggregates Aβ fibrils and thus, prevents neurotoxic effects. It also reduces neuronal cell death via Ca^{2+} influx regulation (66). Anti-oxidant agents such as glutathione, ascorbic acid, and ubiquinone scavenge free radicals and chelate metal ions, as well as preventing cell damage by ROS neutralization (67, 68). NSAIDs such as ibuprofen have a protective effect against the incidence of AD (69). Also, ladostigil is a chemical neuroprotective, anti-inflammatory, and neurogenesis inducing agent that is able to slow down the progression of mild cognitive impairment to AD (70, 71). Interestingly, in addition to synthetic drugs, current knowledge recommends the use of micronutrients (69, 70), supplements (73-71), and herbal medicines to relieve AD symptoms.

Traditional phytomedicine

In parallel to increasing concerns about the side effects of synthetic drugs, the tendency to use herbal medicines is growing. Although popularity of traditional treatment varies in different countries, the therapeutic role of herbs is under consideration worldwide (16, 18, 72). It is for a long time that herbal medicines have been used for the relief of brain disorders including AD (17, 73). In this context, albeit scant, attempts have been made to examine if herbal medicines have a considerable role in the treatment of AD. Here, we review recent findings from animal and clinical research about protective and therapeutic effects of several herbal medicines on

AD. Behavioral, biochemical, cellular, and molecular aspects of investigations are considered. Henceforth, we evaluate the characteristics of some available and routinely used herbal medicines and their role in the treatment of AD.

Lavandula angustifolia Mill.

Lavandula angustifolia (lavender) is a native aromatic shrub in the Mediterranean region that belongs to the *Lamiaceae* family (74, 75). Different extract forms of this plant including essential oil, aqueous extract, alcoholic extract, hydroalcoholic extract, and phenolic extract have been used in traditional treatment. While the main constituents of the essential oil of lavender are linalool and linalyl acetate, aqueous extract of lavender primarily consists of caffeic acid and luteolin (Figure 1) (76, 77). Our study indicated that the aqueous extract of lavender has no toxic effect on the Hep G2 cell line (75).

Numerous characteristics of herbal drugs such as anti-inflammatory (78) and anti-oxidant activities (79), inhibition of glutamate-induced neurotoxicity (80), prevention of Aβ polymerization (73), anti-oxidant properties (77), and AChE inhibitory effect (80) have encouraged researchers to focus on lavender as a candidate medicine for the treatment of AD.

It is reported that treatment of rat pups' cerebellar granular cell culture with aqueous extract of lavender diminishes glutamate-induced neurotoxicity (76). It is shown that, via scavenging free radicals, lavender aqueous extract displays a potent anti-oxidant effect (77).

In the level of neuronal activity, administration of aqueous extract of lavender in the Aβ injected rats restored deteriorated plasticity of hippocampal glutamatergic

Caffeic acid

Luteolin

Linalool   linalyl acetate
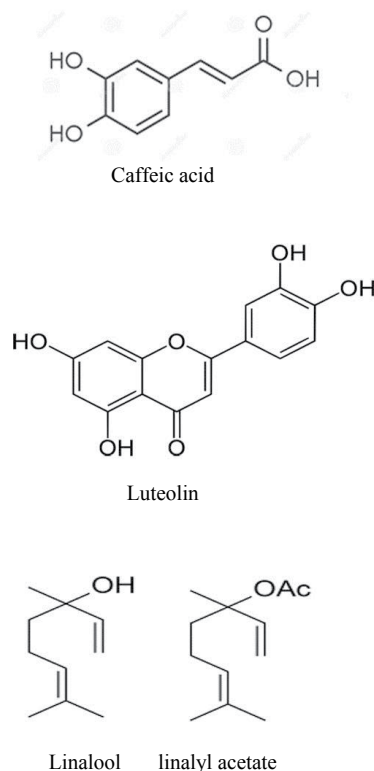
Figure 1. Chemical structure of caffeic acid, luteolin, linalool, and linalyl acetate (77, 85)

synaptic transmission (1). Also, intracerebroventricular injection of Aβ altered hippocampal protein expression in the hippocampus (81). Importantly, in an *in vitro* study using an atomic force microscope, we found that aqueous extract of lavender dose-dependently inhibits polymerization of Aβ monomer and prevents thickening of the Aβ fibrils (77). Further, histological assessment proved that lavender aqueous extract substantially clears brain Aβ plaques in the rat model of AD (82). In our previous study, using a Morris water maze task, we showed that aqueous extract of lavender improves impaired spatial learning and memory in an animal model of AD (5). A clinical trial, reported that lavender significantly reduced physical non-aggressive behaviors in patients with the dementia disorder (83). Metabolomic analysis of serum collected from the AD model of rats, receiving aqueous extract of lavender, showed that the extract restores metabolic profile of AD treated animals to normal status (84).

Despite behavioral, electrophysiological, and histological evaluations confirming the favorable effect of lavender on the treatment of AD, due to different constituents of oil based, alcoholic, and aqueous extracts of lavender, caution must be exercised in using the herbal medicine. For instance, while the aqueous extract of lavender inhibits polymerization of the Aβ monomer, its essential oil promotes the formation of Aβ fibrils (73).

Ginkgo biloba

Ginkgo biloba, or ginkgo, is a large tree with an angular crown and long erratic branches. This well-known traditional Chinese therapeutic herb has multi-functional effects. It has been used for thousands of years in folk medicine to treat a wide range of diseases (86). Several clinical investigations on AD patients validated the improving effect of *G. biloba* on cognitive impairment and disease progression especially in the early stages (87-89). It is shown that *G. biloba* can normalize ACh receptors in the hippocampus and stimulate the neurotransmitter activity leading to improvement of learning and memory in AD (90). A study showed the strong AChE inhibitory activity of *G. biloba* (91). The *G. biloba* extract protects brain cells against toxicity related to Aβ plaques (92) and affects some Aβ-induced events including ROS generation and accumulation, mitochondrial dysfunction, and apoptosis (92-94). Herbal medicine also inhibits free cholesterol circulation and interferes with Aβ synthesis (95). Consistently, research found that extract of the plant prevents *in vitro* Aβ oligomerization and fibril formation (93). Some evidence indicates that *G. biloba* can inhibit Aβ production by stimulation of the gamma-secretase pathway in the APP cleavage process (96). Moreover, *G. biloba* can protect astrocytes of rat hippocampus (97) and displays a neuroprotective effect through regulation of tau phosphorylation, elimination of amyloid plaques (98), induction of growth factors synthesis, and calcium homeostasis (99).

The free radical scavenging effect of *G. biloba* has been proven by numerous *in vitro* and *in vivo* studies (94, 100-103). The medicinal plant increases the activity of anti-oxidant enzymes such as superoxide dismutase (SOD) and catalase (101).

Glutathione (GSH) is a critical anti-oxidant agent in humans, animals, plants, fungi, and some bacteria and archaea. It is produced by the reduction of glutathione disulfide to sulfhydryl form of GSH enhanced by glutathione reductase. GSH is capable of preventing oxidative stress damage to cellular components. It is proven that *G. biloba* enhances the activity of glutathione reductase and stimulates generation of GSH (104, 105). Another important mechanism implicated in various neurodegenerative diseases is the apoptotic pathway. It is reported that, through maintenance of mitochondrial membrane integrity and inhibition of cytochrome c releasing, *G. biloba* appears as an anti-apoptotic agent (101, 102, 106). It prevents formation of the pre-apoptotic complexes and related caspase cascade.

Plentiful evidence indicated that ginkgolide (Figure 2) and flavonoids, as biological terpenic lactone components of this herb, display very specific and potent anti-inflammatory effects through antagonist activity on platelet-activating factor, a regulator of pro-inflammatory cytokines synthesis (107).

Some other neuroprotective effects of *G. biloba* are protection against H_2O_2, NO, glutamate-induced toxicity, and hypoxia, as demonstrated in cultured neurons (108).

Melissa officinalis

Melissa officinalis, also called lemon balm, belongs to the *Lamiaceae* family. This plant has small white flowers during summer and leaves with a mild lemon scent. This phytomedicine is used to ameliorate motivation and behavior in patients with dementia disorder (107). Anti-oxidant (110, 111), anti-depressant (112), anxiolytic (112), and anti-inflammatory (113) activities are attributed to this plant. The therapeutic effects of this herbal medicine are due to its main active constituents: triterpenes, phenolic acids, and flavonoids (114).

A Study by Lopez *et al.* confirmed that the aqueous and methanol extracts of *M. officinalis* diminish intracellular ROS generation (115). A study showed that some derivatives of *M. officinalis* such as flavonoids, caffeic acid, and rosmaric acid have anti-oxidant
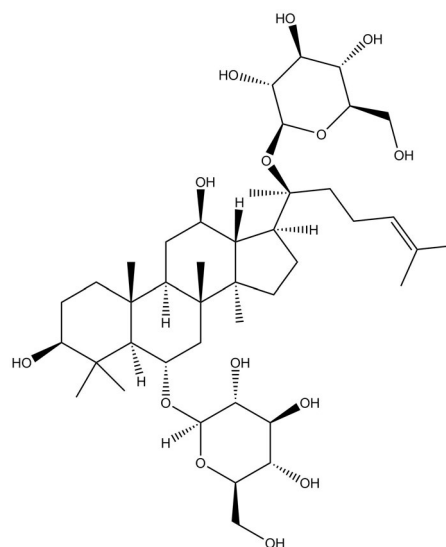
Figure 2. Chemical structure of ginkgolide (109)
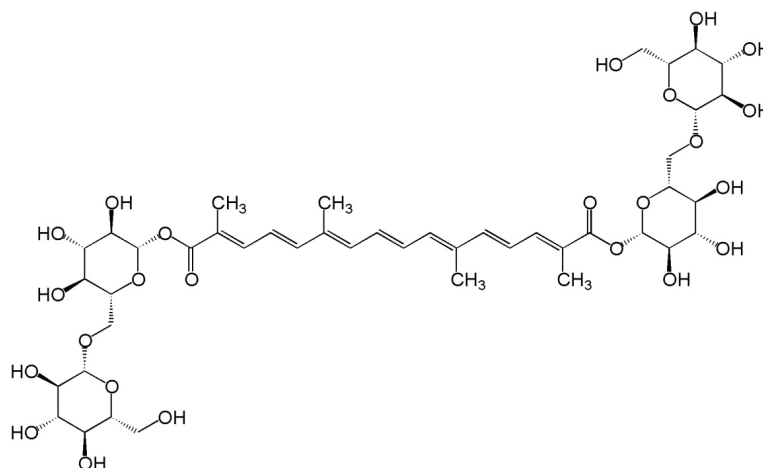
Figure 3. Chemical structure of crocin (131)

properties (116). It is demonstrated that medicine plays a potent anti-oxidant role through decreasing MDA (117), increasing GSH (118), and Paraoxonase 1, as critical enzymes in detoxifying oxidative stress mediators (117). It also displays anti-oxidant activity by scavenging free radicals, inhibiting lipid peroxidation, and protecting against H_2O_2 (119).

It is reported that *M. officinalis* diminishes agitation and physical non-aggressive behavior in aged people (120) and modulates cognitive performance in healthy young volunteers (121). Soodi *et al.* demonstrated that the ethanol extract of *M. officinalis* enhances improvement of learning and memory in the scopolamine model of dementia. They attributed this cognitive supporting action to its inhibitory effect on AChE activity (122). *M. officinalis* alleviates neuronal excitability and improves cognitive dysfunction in AD patients (123). Research indicates that through affecting the serotonergic system and ligand-gated and ion channels, *M. officinalis* improves some symptoms in AD people (120, 124). Research proved that gallic acid, as an important constituent of *M. officinalis*, can reduce matrix metalloproteinase-2 activity that is involved in AD (125). The medicinal plant also shows a neuroprotective effect through reduction of Aβ induced neurotoxicity (126).

Taken together, different pharmaceutical effects of *M. officinalis* especially anti-cholinesterase, anti-oxidant, and anti-neurotoxicity activities have made herbal medicine an appropriate candidate for relieving symptoms of neurodegenerative diseases such as AD.

Crocus sativus

Crocus sativus, a species of *Iridaceae* family that is called saffron as well, has been widely used in traditional medicine. Anti-inflammatory (127), radical scavenging (128), and neuroprotective effects (129) are attributed to this herbal plant. The main sources of anti-oxidant activity of saffron are phenolic and carotenoids compounds (130). Most saffron effects, in fact, belong to one of the main active phytochemical ingredients called crocin (Figure 3) (131). Crocin plays multi pharmacological activities such as anti-oxidant (129), inhibition of peroxidized lipids formation (132), SOD activity restoration (133), neuronal protection (134),

and neuron morphology preservation (135). This low stability compound is able to remove ROS powerfully (136). Experimental evidence proves the positive effect of crocin on memory and cognition improvement (137, 138), as well as plasticity of synaptic transmission in the neural circuits (139), a neural mechanism involved in learning and memory phenomena. This stemless flowering plant is shown to be effective in the treatment of mild to moderate depression (140) and mental illnesses (139).

Via suppression of inflammatory cytokines, *C. sativus* demonstrates anti-inflammatory properties. The attenuating effect of saffron extract on the production and deposition of Aβ in the hippocampus has been verified (141). It enhances up-regulation of lipoprotein receptor-related protein 1 and NEP enzymes. It can stimulate Aβ clearance by decreasing the tightness of BBB. It is found that, through anti-amyloidogenic activity (142) and anti-Aβ fibrilization (143), saffron plays an important role in the prevention of Aβ plaque formation in AD.

Panax ginseng

Panax Ginseng is the root of a plant in the *Panax* genus that belongs to the *Araliaceae* family. It occupies a special place in ancient medicinal treatment (144). This hand-picked herb grows naturally in mountains and contains triterpene glycosides (Ginsenosides, Figure 4) responsible for main pharmacological activities (145).

Aqueous extract of *ginseng* with polyphenol contents exhibits anti-oxidant activity (146). The herbal medicine scavenges free radicals such as superoxide anions and hydroxyl radicals and enhances the activity of the SOD enzyme (147).

Choi *et al.* demonstrated that *ginseng* extract inhibits neuronal death and neuro-inflammation. With inhibition of hyperphosphorylation of tau protein, *ginseng* prevents formation of the neurofibrillary tangle. Further, it is able to inhibit the BACE1 enzyme and, therefore, reduce the level of Aβ (148). Ginsenosides increase hippocampal expression of brain-derived nerve factor (BDNF) (149), a key neuromodulator in learning and memory processing. Consistently, biochemical and behavioral evaluations have demonstrated that *ginseng* can improve stress-induced learning and memory
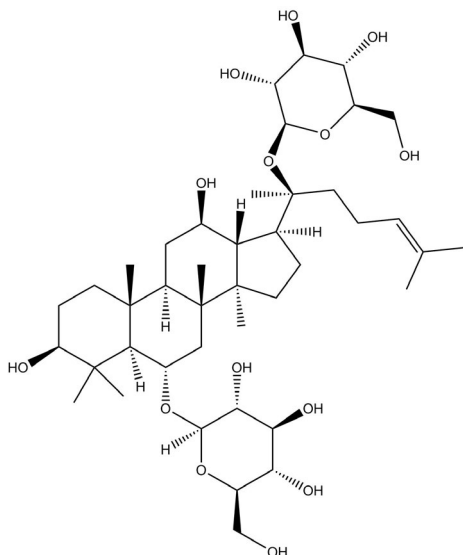
Figure 4. Chemical structure of ginsenosides (161)

impairment (150-152). Hence, it is proposed that the phytomedicine can play a distinct positive role in attenuation of memory impairment in AD (148).

It has been reported that ginsenoside inhibits activity of AChE and BchE in cultured PC12 cell line resulting in increased amount of ACh content (153). In parallel, it restores choline acetyltransferase activity in an animal model of AD (154). It also shows neuroprotective ability where it suppresses the glutamate-induced toxicity in AD (155, 156).

In vivo and in vitro studies have indicated that *ginseng* has anti-inflammatory activity through attenuating expression of inflammatory mediators such as TNFα, NF-κB, IL1β, and IL6 (157-159). It also decreases the level of the COX-2 enzyme, a key mediator in the inflammatory process (160).

Salvia miltiorrhiza

Salvia miltiorrhiza is another member of *the Lamiaceae* family with branching stems and widely spaced leaves. It has been broadly used for treatment of various diseases (162-164).

Cryptotanshinone (Figure 5), as the main active ingredient of *S. miltiorrhiza*, possesses many pharmaceutical functions including anti-AChE (165), anti-neurotoxicity (166), anti-inflammatory (167), anti-oxidative (168), and anti-apoptotic activities (169). Cryptotanshinone is reported to reduce Aβ deposition and improve spatial learning impairment (170). By affecting the gamma-secretase pathway, it prevents Aβ plaque formation and inhibits glutamate-induced neuronal toxicity (166). It is reported that cryptotanshinone ameliorates cognitive disturbance and significantly affect amnesia (165).

Salvianolic acid is another polyphenolic derivative of *S. miltiorrhiza* that displays anti-inflammatory and anti-oxidant activity (171) and influences AD symptoms (172, 173). It dose-dependently prevents self-aggregation of Aβ and further disaggregates Aβ fibrils and protects cells against Aβ fibrils neurotoxic effect (174). Zhang *et al.* demonstrated that salvianolic acid increases BDNF expression and stimulates neuronal differentiation (175). Salvianolic acid protects the PC12 cell line
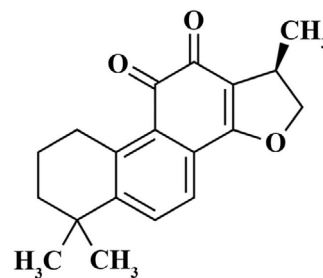

Figure 5. Chemical structure of Cryptotanshinone (185)

against neurotoxicity induced by H_2O_2 and reduces lipid peroxidation and perseveres anti-oxidant enzymes, intracellular ca2+ level, and caspase-3 enzyme in the normal activity state (176). Zhang *et al.* demonstrated that salvianolic acid decreases leakage of lactate dehydrogenase and, hence, protects neuronal cells against H_2O_2 damage (177).

Another constituent of *S. miltiorrhiza*, tanshinone, displays anti-oxidant activity. It can chelate metal ions that stimulate Aβ plaque formation and also inhibits ROS formation (178, 179). Tanshinone suppresses expression of inducible nitric oxide synthase (iNOS) and NO, and inhibits expression of inflammatory mediators (167, 180).

It is reported that tanshinone has a strong preventive activity on the AChE enzyme (165) and significantly improves the amnesic activity in behavioral examination (181). Moreover, a study showed that tanshinone restores learning and memory deficit induced by scopolamine (182). Anti-apoptotic activity of tanshinone is shown to be due to down-regulation of caspase-3 expression or up-regulation of Bcl-2 expression (183). Tanshinone can activate the Bcl-xL pathway and, thus, through that, suppresses Aβ induced apoptosis (184).

Magnolia officinalis

Magnolia officinalis is a deciduous tree with thick and brown aromatic bark and fragrant flowers used as a rich source of biologically active compounds (186). This curative herb displays some medicinal aspects including anti-inflammatory (187), anti-oxidative (188), and neuroprotective activities (189). *M. officinalis* reduces the expression of inflammatory agents especially those stimulating NOS and inhibits activation of astrocytes and microglia (190). The multifunctional activity of *M. officinalis* is due to some ingredients such as magnolol (Figure 6), 4-O-methylhonokiol, honokiol, obovatol, and magnolol (191-193). It is reported that magnolia, as a major bioactive component of *M. officinalis*, positively impacts different oxidative agents and inflammatory
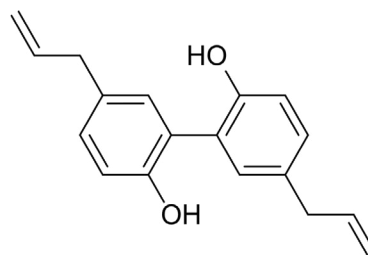

Figure 6. Chemical structure of magnolol (202)

cytokines, including ROS, iNOS, NF-κB, TNF-α, TGF-β, IL-1β, COX2, and MAP kinases family (191). It also up-regulates some proteins effective in anti-inflammatory activities such as Ras and Raf proteins (194). Honokiol, magnolol and 4-O-methylhonokiol display some neuroprotective effects through prevention of Aβ induced cell death, reduction of ROS generation, suppression of intracellular calcium elevation, and inhibition of caspase-3 activity (190, 195).

It is shown that the ethanol extract of *M. officinalis* has a preventive effect on Aβ accumulation in the mouse brain (196). It also inhibits the expression of BACE1 and therefore prevents Aβ production and has a hampering effect on memorial perturbation induced by Aβ plaque (196, 197). It was shown that 4-O-methylhonokiol prevents apoptosis induced by Aβ, resulting in cell survival, and down-regulates β-secretase expression and, thus, prevents Aβ formation. It also inhibits ROS generation and plays inhibitory action on H_2O_2 induced neurotoxicity (198, 199). Magnolol and honokiol inhibit AChE activity and stimulate release of ACh in the brain particularly in the hippocampus (200, 201).

It is documented that the ethanol extract of *M. officinalis* prevents memory deficit in an animal model of AD (190). Evidence indicates that ethanol extract of this medicinal herb reduces the level and activity of AChE in the cortex and hippocampus of mice treated with scopolamine (192). Table 1 summarizes the biochemical, histopathological, and behavioral effects of the herbal medicines in *in vivo* and *in vitro* studies.

Conclusion

Taken together, extracellular Aβ plaque formation and intracellular accumulation of NFT are the main pathological features of AD. These structural abnormalities lead finally to neuronal death and synaptic loss which, in turn, result in violent neurobehavioral damages, mainly recent memory impairments. Oxidative agents, inflammatory factors, glutamate, or Aβ induced neurotoxicity, and cholinergic transmission deficit also promote occurrence of the diseases. Anti-oxidative, anti-inflammatory, and anti-neurotoxicity properties, as well as Aβ formation inhibitory and cholinergic excitatory activities of the herbal medicines are promising for the prevention and treatment of AD. As reviewed in this paper numerous herbal plants have potential therapeutic effects on AD associated symptoms. Despite abundant preclinical studies on the effectiveness of medicinal plants for neurodegenerative diseases including AD, clinical research is also required to warrant the use of herbal medicine in alleviating AD symptoms.

Coflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Soheili M, Tavirani MR, Salami M. *Lavandula angustifolia* extract improves deteriorated synaptic plasticity in an animal model of Alzheimer's disease. Iran J Basic Med Sci 2015; 18:1147-1152.
2. Salami M, Alinaghipour A, Daneshvar R, Hamidi GA, Agahi A, Soheili M, *et al*. Adapted MMSE and TYM cognitive tests: how much powerful in screening for Alzheimer's disease in Iranian people. Aging Ment Health 2020; 24:1010-1017.
3. World Health Organization. Neurological disorders: public health challenges. Switzerland: World Health Organization. 2006:204-207.
4. Alzheimer's Disease International. World Alzheimer Report 2016, Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future, https://www.alz.co.uk/research/world-report-2016.
5. Kashani MS, Tavirani MR, Talaei SA, Salami M. Aqueous extract of lavender (*Lavandula angustifolia*) improves the spatial performance of a rat model of Alzheimer's disease. Neurosci Bull 2011; 27:99-106.
6. Blaisdell AP. Mental imagery in animals: Learning, memory, and decision-making in the face of missing information. Learn Behav 2019; 47:193-216.
7. Ritvo VJH, Turk-Browne NB, Norman KA. Nonmonotonic plasticity: How memory retrieval drives learning. Trends Cogn Sci 2019; 23:726-742.
8. Rowland HA, Hooper NM, Kellett KAB. Modelling sporadic Alzheimer's disease using induced pluripotent stem cells. Neurochem Res 2018; 43:2179-2198.
9. Israel MA, Yuan SH, Bardy C, Reyna SM, Mu Y, Herrera C, *et al*. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. Nature 2012; 482:216-220.
10. Kondo T, Asai M, Tsukita K, Kutoku Y, Ohsawa Y, Sunada Y, *et al*. Modeling Alzheimer's disease with iPSCs reveals stress phenotypes associated with intracellular Abeta and differential drug responsiveness. Cell Stem Cell 2013; 12:487-496.
11. Mulder SD, Nielsen HM, Blankenstein MA, Eikelenboom P, Veerhuis R. Apolipoproteins E and J interfere with amyloid-beta uptake by primary human astrocytes and microglia *in vitro*. Glia 2014; 62:493-503.
12. Howes MJ, Houghton PJ. Ethnobotanical treatment strategies against Alzheimer's disease. Curr Alzheimer Res 2012; 9:67-85.
13. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol 2018; 14:450-464.
14. Westergard L, Christensen HM, Harris DA. The cellular prion protein (PrP(C)): its physiological function and role in disease. Biochim Biophys Acta 2007; 1772:629-644.
15. Latta CH, Brothers HM, Wilcock DM. Neuroinflammation in Alzheimer's disease; A source of heterogeneity and target for personalized therapy. Neuroscience 2015; 302:103-111.
16. Akhondzadeh S, Abbasi SH. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimers Dis Other Demen 2006; 21:113-118.
17. Shi J, Ni J, Lu T, Zhang X, Wei M, Li T, *et al*. Adding Chinese herbal medicine to conventional therapy brings cognitive benefits to patients with Alzheimer's disease: a retrospective analysis. BMC Complement Altern Med 2017; 17:533-539.
18. Wu JG, Wang YY, Zhang ZL, Yu B. Herbal medicine in the treatment of Alzheimer's disease. Chin J Integr Med 2015; 21:102-107.
19. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, *et al*. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 2010; 330:1774-1777.
20. Steiner H, Fukumori A, Tagami S, Okochi M. Making the final cut: pathogenic amyloid-beta peptide generation by gamma-secretase. Cell Stress 2018; 2:292-310.

21. Bergstrom P, Agholme L, Nazir FH, Satir TM, Toombs J, Wellington H, *et al*. Amyloid precursor protein expression and processing are differentially regulated during cortical neuron differentiation. Sci Rep 2016; 6:29200-29213.

22. Sato N, Morishita R. The roles of lipid and glucose metabolism in modulation of beta-amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. Front Aging Neurosci 2015; 7:199-207.

23. Arbel-Ornath M, Hudry E, Eikermann-Haerter K, Hou S, Gregory JL, Zhao L, *et al*. Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer's disease mouse models. Acta Neuropathol 2013; 126:353-364.

24. Saido T, Leissring MA. Proteolytic degradation of amyloid beta-protein. Cold Spring Harb Perspect Med 2012; 2:1-18.

25. Metaxas A, Kempf SJ. Neurofibrillary tangles in Alzheimer's disease: elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. Neural Regen Res 2016; 11:1579-1581.

26. Lasagna-Reeves CA, Castillo-Carranza DL, Sengupta U, Sarmiento J, Troncoso J, Jackson GR, *et al*. Identification of oligomers at early stages of tau aggregation in Alzheimer's disease. Faseb j 2012; 26:1946-1959.

27. Stancu IC, Vasconcelos B, Terwel D, Dewachter I. Models of beta-amyloid induced Tau-pathology: the long and "folded" road to understand the mechanism. Mol Neurodegener 2014; 9:51-64.

28. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci U S A 1998; 95:7737-7741.

29. Li F, Tsien JZ. Memory and the NMDA receptors. The N Eng J Med 2009; 361:302-303.

30. Rapp A, Gmeiner B, Huttinger M. Implication of apoE isoforms in cholesterol metabolism by primary rat hippocampal neurons and astrocytes. Biochimie 2006; 88:473-483.

31. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, *et al*. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 2005; 8:1051-1058.

32. Dzamba D, Harantova L, Butenko O, Anderova M. Glial cells - The key elements of Alzheimer s Disease. Curr Alzheimer Res 2016; 13:894-911.

33. Seixas da Silva GS, Melo HM, Lourenco MV, Lyra ESNM, de Carvalho MB, Alves-Leon SV, *et al*. Amyloid-beta oligomers transiently inhibit AMP-activated kinase and cause metabolic defects in hippocampal neurons. J Biol Chem 2017; 292:7395-7406.

34. Buttini M, Masliah E, Yu GQ, Palop JJ, Chang S, Bernardo A, *et al*. Cellular source of apolipoprotein E4 determines neuronal susceptibility to excitotoxic injury in transgenic mice. Am J Pathol 2010; 177:563-569.

35. Kandemirli F, Saracoglu M, Kovalishyn V. Human acetylcholinesterase inhibitors: electronic-topological and neural network approaches to the structure-activity relationships study. Mini Rev Med Chem 2005; 5:479-487.

36. Day T, Greenfield SA. A non-cholinergic, trophic action of acetylcholinesterase on hippocampal neurones *in vitro*: molecular mechanisms. Neuroscience 2002; 111:649-656.

37. Mufson EJ, Ginsberg SD, Ikonomovic MD, DeKosky ST. Human cholinergic basal forebrain: chemoanatomy and neurologic dysfunction. J Chem Neuroanat 2003; 26:233-242.

38. Pacheco G, Palacios-Esquivel R, Moss DE. Cholinesterase inhibitors proposed for treating dementia in Alzheimer's disease: selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase. J Pharmacol Exp Ther 1995; 274:767-770.

39. Reale M, Di Nicola M, Velluto L, D'Angelo C, Costantini E, Lahiri DK, *et al*. Selective acetyl- and butyrylcholinesterase inhibitors reduce amyloid-beta ex vivo activation of peripheral chemo-cytokines from Alzheimer's disease subjects: exploring the cholinergic anti-inflammatory pathway. Curr Alzheimer Res 2014; 11:608-622.

40. Richter N, Beckers N, Onur OA, Dietlein M, Tittgemeyer M, Kracht L, *et al*. Effect of cholinergic treatment depends on cholinergic integrity in early Alzheimer›s disease. Brain 2018; 141:903-915.

41. Ceylan H, Budak H, Kocpinar EF, Baltaci NG, Erdogan O. Examining the link between dose-dependent dietary iron intake and Alzheimer's disease through oxidative stress in the rat cortex. J Trace Elem Med Biol 2019; 56:198-206.

42. Nakabeppu Y. Molecular pathophysiology of insulin depletion, mitochondrial dysfunction, and oxidative stress in Alzheimer's disease brain. Adv Exp Med Biol 2019; 1128:27-44.

43. Roberts LJ, Fessel JP. The biochemistry of the isoprostane, neuroprostane, and isofuran pathways of lipid eroxidation. Brain Pathol 2005; 15:143-148.

44. Reed TT. Lipid peroxidation and neurodegenerative disease. Free Radic Biol Med 2011; 51:1302- 1319.

45. Cosin-Tomas M, Senserrich J, Arumi-Planas M, Alquezar C, Pallas M, Martin-Requero A, *et al*. Role of resveratrol and selenium on oxidative stress and expression of anti-oxidant and anti-aging genes in immortalized lymphocytes from Alzheimer's disease patients. Arch Toxicol 2019; 11: 1-23.

46. Simunkova M, Alwasel SH, Alhazza IM, Jomova K, Kollar V, Rusko M, *et al*. Management of oxidative stress and other pathologies in Alzheimer's disease. Hyperlink "https://link. springer.com/journal/204" Arch Toxicol 2019; 93:2491-2513.

47. Rosini M, Simoni E, Caporaso R, Basagni F, Catanzaro M, Abu IF, *et al*. Merging memantine and ferulic acid to probe connections between NMDA receptors, oxidative stress and amyloid-beta peptide in Alzheimer's disease. Eur J Med Chem 2019; 180:111-120.

48. de la Monte SM, Wands JR. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. J Alzheimers Dis 2006; 9:167-181.

49. Eckman J, Dixit S, Nackenoff A, Schrag M, Harrison FE. Oxidative stress levels in the brain are determined by postmortem interval and ante-mortem vitamin c state but not Alzheimer's disease Status. Nutrients 2018; 10: 1-11.

50. Bueler H, Fischer M, Lang Y, Bluethmann H, Lipp HP, DeArmond SJ, *et al*. Normal development and behaviour of mice lacking the neuronal cell-surface PrP protein. Nature 1992; 356:577-582.

51. van Delft MF, Huang DC. How the Bcl-2 family of proteins interact to regulate apoptosis. Cell Res 2006; 16:203-213.

52. Barry AE, Klyubin I, Mc Donald JM, Mably AJ, Farrell MA, Scott M, *et al*. Alzheimer's disease brain-derived amyloid-beta-mediated inhibition of LTP *in vivo* is prevented by immunotargeting cellular prion protein. J Neurosci 2011; 31:7259-7263.

53. Whitehouse IJ, Miners JS, Glennon EB, Kehoe PG, Love S, Kellett KA, *et al*. Prion protein is decreased in Alzheimer's brain and inversely correlates with BACE1 activity, amyloid beta levels and Braak stage. PLoS One 2013; 8:1-8.

54. Kawahara M, Kuroda Y, Arispe N, Rojas E. Alzheimer's beta-amyloid, human islet amylin, and prion protein fragment evoke intracellular free calcium elevations by a common mechanism in a hypothalamic GnRH neuronal cell line. J Biol Chem 2000; 275:14077-14083.

55. O'Banion MK. COX-2 and Alzheimer's disease: potential roles in inflammation and neurodegeneration. Expert Opin Investig Drugs 1999; 8:1521-1536.

56. Hoozemans JJ, van Haastert ES, Veerhuis R, Arendt T, Scheper W, Eikelenboom P, *et al*. Maximal COX-2 and ppRb

expression in neurons occurs during early Braak stages prior to the maximal activation of astrocytes and microglia in Alzheimer's disease. J Neuroinflammation 2005; 2: 1-57.

57. Kimura M, Asada T, Uno M, Machida N, Kasuya K, Taniguchi Y, *et al.* Assessment of cerebrospinal fluid levels of serum amyloid P component in patients with Alzheimer's disease. Neurosci Lett 1999; 273:137-139.

58. Walker KA, Ficek BN, Westbrook R. Understanding the role of systemic inflammation in Alzheimer's disease. ACS Chem Neurosci 2019; 10:3340-3342.

59. Kolstoe SE, Ridha BH, Bellotti V, Wang N, Robinson CV, Crutch SJ, *et al.* Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. Proc Natl Acad Sci U S A 2009; 106:7619-7623.

60. Borisovskaya A, Pascualy M, Borson S. Cognitive and neuropsychiatric impairments in Alzheimer's disease: current treatment strategies. Curr Psychiatry Rep 2014; 16:470-478.

61. Alzheimer's disease in France: too many patients exposed to drug interactions involving cholinesterase inhibitors. Prescrire Int 2014; 23:150-156.

62. Lipton SA. Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders. J Alzheimers Dis 2004; 6:61-74.

63. Allison AC, Cacabelos R, Lombardi VR, Alvarez XA, Vigo C. Celastrol, a potent anti-oxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25:1341-1357.

64. Cai R, Wang LN, Fan JJ, Geng SQ, Liu YM. New 4-N-phenylaminoquinoline derivatives as anti-oxidant, metal chelating and cholinesterase inhibitors for Alzheimer's disease. Bioorg Chem 2019; 93: 1-24.

65. Loera-Valencia R, Cedazo-Minguez A, Kenigsberg PA, Page G, Duarte AI, Giusti P, *et al.* Current and emerging avenues for Alzheimer's disease drug targets. J Int Med 2019; 286:398-437.

66. Kabir MT, Uddin MS, Begum MM, Thangapandiyan S, Rahman MS, Aleya L, *et al.* Cholinesterase inhibitors for Alzheimer disease: Multitargeting strategy based on anti-Alzheimer's drugs repositioning. Curr Pharm Des 2019, 25:3519-3535.

67. Kabir MT, Abu Sufian M, Uddin MS, Begum MM, Akhter S, Islam A, *et al.* NMDA receptor antagonists: Repositioning of memantine as multitargeting agent for Alzheimer's therapy. Curr Pharm Des 2019; 25: 3506-3518.

68. Kim SH, Vlkolinsky R, Cairns N, Fountoulakis M, Lubec G. The reduction of NADH ubiquinone oxidoreductase 24- and 75-kDa subunits in brains of patients with Down syndrome and Alzheimer's disease. Life Sci 2001; 68:2741-2750.

69. Mandal PK, Shukla D, Tripathi M, Ersland L. Cognitive improvement with glutathione supplement in Alzheimer's disease: A way forward. J Alzheimers Dis 2019; 68:531-535.

70. Deardorff WJ, Grossberg GT. Targeting neuroinflammation in Alzheimer's disease: evidence for NSAIDs and novel therapeutics. Expert Rev Neurother 2017; 17:17-32.

71. Weinreb O, Amit T, Bar-Am O, Youdim MB. A novel anti-Alzheimer's disease drug, ladostigil neuroprotective, multimodal brain-selective monoamine oxidase and cholinesterase inhibitor. Int Rev Neurobiol 2011; 100:191-215.

72. Weinreb O, Amit T, Bar-Am O, Youdim MB. Ladostigil: a novel multimodal neuroprotective drug with cholinesterase and brain-selective monoamine oxidase inhibitory activities for Alzheimer's disease treatment. Curr Drug Targets 2012; 13:483-494.

73. Soheili M, Khalaji F, Mirhashemi M, Salami M. The effect of essential oil of *Lavandula angustifolia* on amyloid beta polymerization: An *in vitro* study. IJCCE 2018; 37:201-207

74. Zeng Q, Siu W, Li L, Jin Y, Liang S, Cao M, *et al.* Autophagy in Alzheimer's disease and promising modulatory effects of herbal medicine. Exp Gerontol 2019; 119:100-110.

75. Soheili M, Rezaei M, Salami M. Anti-acetylcholine esterase activity of aqueous extract of *lavandula angustifolia* and its toxicity effect on HepG2 cell line. Koomesh 2017; 19:263-268.

76. Buyukokuroglu ME, Gepdiremen A, Hacimuftuoglu A, Oktay M. The effects of aqueous extract of *Lavandula angustifolia* flowers in glutamate-induced neurotoxicity of cerebellar granular cell culture of rat pups. J Ethnopharmacol 2003; 84:91-94.

77. Soheili M, Salami M. *Lavandula angustifolia* biological characteristics: An *in vitro* study. J Cell Physiol 2019:1-7.

78. Hajhashemi V, Ghannadi A, Sharif B. Anti-inflammatory and analgesic properties of the leaf extracts and essential oil of *Lavandula angustifolia* Mill. J Ethnopharmacol 2003; 89:67-71.

79. Hancianu M, Cioanca O, Mihasan M, Hritcu L. Neuroprotective effects of inhaled lavender oil on scopolamine-induced dementia via anti-oxidative activities in rats. Phytomedicine 2013; 20:446-452.

80. Adsersen A, Gauguin B, Gudiksen L, Jager AK. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. J Ethnopharmacol 2006; 104:418-422.

81. Soheili, Salami M, Haghir A, Zali H, Rezaei Tavirani M. Aqueous extract of *Lavandula angustifolia* alter protein expression in Alzheimer rats. JRPS 2014; 3:1-9.

82. Soheili M, Tavirani MR, Salami M. Clearance of amyloid beta plaques from brain of Alzheimeric rats by *Lavandula angustifolia*. Neurosc Med 2012; 3: 4-6.

83. Watson K, Hatcher D, Good A. A randomised controlled trial of Lavender (*Lavandula Angustifolia*) and Lemon Balm (*Melissa Officinalis*) essential oils for the treatment of agitated behaviour in older people with and without dementia. Complement Ther Med 2019; 42:366-373.

84. Oskouie AA, Yekta RF, Tavirani MR, Kashani MS, Goshadrou F. *Lavandula angustifolia* effects on rat models of Alzheimer's disease through the investigation of serum metabolic features using NMR metabolomics. Avicenna J Med Biotechnol 2018; 10:83-92.

85. Rai VK, Sinha P, Yadav KS, Shukla A, Saxena A, Bawankule DU, *et al.* Anti-psoriatic effect of *Lavandula angustifolia* essential oil and its major components linalool and linalyl acetate. J Ethnopharmacol 2020; 261:113-127.

86. Le Bars PL. Magnitude of effect and special approach to *Ginkgo biloba* extract EGb 761 in cognitive disorders. Pharmacopsychiatry 2003; 36: 44-49.

87. Napryeyenko O, Borzenko I. *Ginkgo biloba* special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. Arzneimittelforschung 2007; 57:4-11.

88. Thancharoen O, Limwattananon C. *Ginkgo biloba* extract (EGb761), cholinesterase inhibitors, and memantine for the treatment of mild-to-moderate alzheimer's disease: a network meta-analysis. Drugs & Aging 2019; 36:435-452.

89. Waleekhachonloet O, Rattanachotphanit T, Limwattananon P, Limpawattana P, Muller WE, Eckert A, *et al.* Therapeutic efficacy of the Ginkgo special extract EGb761((R)) within the framework of the mitochondrial cascade hypothesis of Alzheimer's disease. Drugs Aging 2019; 20:173-189.

90. Yancheva S, Ihl R, Nikolova G, Panayotov P, Schlaefke S, Hoerr R. *Ginkgo biloba* extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomised, double-blind, exploratory trial. Aging Ment Health 2009; 13:183-190.

91. Kehr J, Yoshitake S, Ijiri S, Koch E, Noldner M, Yoshitake T. *Ginkgo biloba* leaf extract (EGb 761(R)) and its specific acylated flavonol constituents increase dopamine and acetylcholine levels in the rat medial prefrontal cortex: possible implications for the cognitive enhancing properties of EGb 761(R). Int Psychogeriatr 2012; 24: 25-34.

92. Shi C, Zhao L, Zhu B, Li Q, Yew DT, Yao Z, *et al.* Protective effects of *Ginkgo biloba* extract (EGb761) and its constituents quercetin and ginkgolide B against beta-amyloid peptide-induced toxicity in SH-SY5Y cells. Chem Biol Interact 2009; 181:115-123.

93. Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, Quirion R. The *Ginkgo biloba* extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. Eur J Neurosci 2000; 12:1882-1890.

94. Smith JV, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract EGb 761. J Alzheimers Dis 2003; 5:287-300.

95. Yao ZX, Han Z, Drieu K, Papadopoulos V. *Ginkgo biloba* extract (Egb 761) inhibits beta-amyloid production by lowering free cholesterol levels. J Nutr Biochem 2004; 15:749-756.

96. Colciaghi F, Borroni B, Zimmermann M, Bellone C, Longhi A, Padovani A, *et al.* Amyloid precursor protein metabolism is regulated toward alpha-secretase pathway by *Ginkgo biloba* extracts. Neurobiol Dis 2004; 16:454-460.

97. Jahanshahi M, Nikmahzar E, Yadollahi N, Ramazani K. Protective effects of *Ginkgo biloba* extract (EGB 761) on astrocytes of rat hippocampus after exposure with scopolamine. Anat cell biol 2012; 45:92-96.

98. Nikmahzar E, Jahanshahi M, Babakordi F. *Ginkgo biloba* extract decreases scopolamine-induced congophilic amyloid plaques accumulation in male rat's brain. Jundishapur J Nat Pharm Prod 2018; In Press.

99. Shi C, Liu J, Wu F, Yew DT. *Ginkgo biloba* extract in Alzheimer's disease: from action mechanisms to medical practice. Int J Mol Sci 2010; 11:107-123.

100. Du ZY, Li XY. Effects of ginkgolides on interleukin-1, tumor necrosis factor-alpha and nitric oxide production by rat microglia stimulated with lipopolysaccharides *in vitro*. Arzneimittelforschung 1998; 48:1126-1130.

101. Shi C, Fang L, Yew DT, Yao Z, Xu J. *Ginkgo biloba* extract EGb761 protects against mitochondrial dysfunction in platelets and hippocampi in ovariectomized rats. Platelets 2010; 21:53-59.

102. Shi C, Xiao S, Liu J, Guo K, Wu F, Yew DT, *et al. Ginkgo biloba* extract EGb761 protects against aging-associated mitochondrial dysfunction in platelets and hippocampi of SAMP8 mice. Platelets 2010; 21:373-379.

103. Smith JV, Luo Y. Studies on molecular mechanisms of *Ginkgo biloba* extract. Appl Microbiol Biotechnol 2004; 64:465-472.

104. Rimbach G, Gohil K, Matsugo S, Moini H, Saliou C, Virgili F, *et al.* Induction of glutathione synthesis in human keratinocytes by *Ginkgo biloba* extract (EGb761). Biofactors 2001; 15:39-52.

105. Sasaki K, Hatta S, Wada K, Ueda N, Yoshimura T, Endo T, *et al.* Effects of extract of *Ginkgo biloba* leaves and its constituents on carcinogen-metabolizing enzyme activities and glutathione levels in mouse liver. Life Sci 2002; 70:1657-1667.

106. Maclennan KM, Darlington CL, Smith PF. The CNS effects of *Ginkgo biloba* extracts and ginkgolide B. Prog Neurobiol 2002; 67:235-257.

107. Miraj S, Rafieian K, Kiani S. *Melissa officinalis* L. A review study with an anti-oxidant prospective. J Evid Based Complementary Altern Med 2017; 22:385-394.

108. Smith PF, Maclennan K, Darlington CL. The neuroprotective properties of the *Ginkgo biloba* leaf: a review of the possible relationship to platelet-activating factor (PAF). J Ethnopharmacol 1996; 50:131-139.

109. Ude C, Paulke A, Nöldner M, Schubert-Zsilavecz M, Wurglics M. Plasma and brain levels of terpene trilactones in rats after an oral single dose of standardized *Ginkgo biloba* extract EGb 761®. Planta Med 2011; 77:259-264.

110. Ehsani A, Alizadeh O, Hashemi M, Afshari A, Aminzare M. Phytochemical, anti-oxidant and antibacterial properties of *Melissa officinalis* and Dracocephalum moldavica essential oils. Vet Res Forum 2017; 8:223-229.

111. Pereira RP, Fachinetto R, de Souza Prestes A, Puntel RL, Santos da Silva GN, Heinzmann BM, *et al.* Anti-oxidant effects of different extracts from *Melissa officinalis*, Matricaria recutita and Cymbopogon citratus. Neurochem Res 2009; 34:973-983.

112. Taiwo AE, Leite FB, Lucena GM, Barros M, Silveira D, Silva MV, *et al.* Anxiolytic and antidepressant-like effects of *Melissa officinalis* (lemon balm) extract in rats: Influence of administration and gender. Indian J Pharmacol 2012; 44:189-192.

113. Bounihi A, Hajjaj G, Alnamer R, Cherrah Y, Zellou A. *In vivo* potential anti-Inflammatory activity of *Melissa officinalis* L. essential oil. Adv Pharmacol Sci 2013; 2013:1-7.

114. Mencherini T, Picerno P, Scesa C, Aquino R. Triterpene, anti-oxidant, and antimicrobial compounds from *Melissa officinalis*. J Nat Prod 2007; 70:1889-1894.

115. Lopez V, Martin S, Gomez-Serranillos MP, Carretero ME, Jager AK, Calvo MI. Neuroprotective and neurological properties of *Melissa officinalis*. Neurochem Res 2009; 34:1955-1961.

116. Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. Afr J Tradit Complement Altern Med 2013; 10:210-229.

117. Javid AZ, Haybar H, Dehghan P, Haghighizadeh MH, Mohaghegh SM, Ravanbakhsh M, *et al.* The effects of *Melissa officinalis* (lemon balm) in chronic stable angina on serum biomarkers of oxidative stress, inflammation and lipid profile. Asia Pac J Clin Nutr 2018; 27:785-791.

118. Bolkent S, Yanardag R, Karabulut-Bulan O, Yesilyaprak B. Protective role of *Melissa officinalis* L. extract on liver of hyperlipidemic rats: a morphological and biochemical study. J Ethnopharmacol 2005; 99:391-398.

119. Luno V, Gil L, Olaciregui M, Jerez RA, de Blas I, Hozbor F. Anti-oxidant effect of lemon balm (*Melissa officinalis*) and mate tea (Ilex paraguensys) on quality, lipid peroxidation and DNA oxidation of cryopreserved boar epididymal spermatozoa. Andrologia 2015; 47:1004-1011.

120. Huang L, Abuhamdah S, Howes MJ, Dixon CL, Elliot MS, Ballard C, *et al.* Pharmacological profile of essential oils derived from *Lavandula angustifolia* and *Melissa officinalis* with anti-agitation properties: focus on ligand-gated channels. J Pharm Pharmacol 2008; 60:1515-1522.

121. Kennedy DO, Scholey AB, Tildesley NT, Perry EK, Wesnes KA. Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* (lemon balm). Pharmacol Biochem Behav 2002; 72:953-964.

122. Soodi M, Naghdi N, Hajimehdipoor H, Choopani S, Sahraei E. Memory-improving activity of *Melissa officinalis* extract in naive and scopolamine-treated rats. Res Pharm Sci 2014; 9:107-114.

123. Leśniewicz A, Jaworska K, Żyrnicki W. Macro- and micro-nutrients and their bioavailability in polish herbal medicaments. Food Chemistry 2006; 99:670-679.

124. Abuhamdah S, Huang L, Elliott MS, Howes MJ, Ballard C, Holmes C, *et al.* Pharmacological profile of an essential oil derived from *Melissa officinalis* with anti-agitation properties: focus on ligand-gated channels. J Pharm Pharmacol 2008;

60:377-384.

125. Pereira RP, Boligon AA, Appel AS, Fachinetto R, Ceron CS, Tanus-Santos JE, *et al*. Chemical composition, anti-oxidant and anticholinesterase activity of *Melissa officinalis*. Ind Crops Prod 2014; 53:34-45.

126. Hassanzadeh G, Pasbakhsh P, Akbari M, Shokri S, Ghahremani M, Amin G, *et al*. Neuroprotective properties of *Melissa officinalis* L. Extract against ecstasy-induced neurotoxicity. Cell J 2011; 13:25-30.

127. Qian J, Chen X, Chen X, Sun C, Jiang Y, Qian Y, *et al*. Kaempferol reduces K63-linked polyubiquitination to inhibit nuclear factor-kappaB and inflammatory responses in acute lung injury in mice. Toxicol Lett 2019; 306:53-60.

128. Kanakis CD, Tarantilis PA, Tajmir-Riahi HA, Polissiou MG. Crocetin, dimethylcrocetin, and safranal bind human serum albumin: stability and anti-oxidative properties. J Agric Food Chem 2007; 55:970-977.

129. Papandreou MA, Kanakis CD, Polissiou MG, Efthimiopoulos S, Cordopatis P, Margarity M, *et al*. Inhibitory activity on amyloid-beta aggregation and anti-oxidant properties of *Crocus sativus* stigmas extract and its crocin constituents. J Agric Food Chem 2006; 54:8762-8768.

130. Moure A, Franco D, Sineiro J, Dominguez H, Nunez MJ, Lema JM. Evaluation of extracts from Gevuina avellana hulls as anti-oxidants. J Agric Food Chem 2000; 48:3890-3897.

131. Alavizadeh SH, Hosseinzadeh H. Bioactivity assessment and toxicity of crocin: a comprehensive review. Food Chem Toxicol 2014; 64:65-80.

132. Farahmand SK, Samini F, Samini M, Samarghandian S. Safranal ameliorates anti-oxidant enzymes and suppresses lipid peroxidation and nitric oxide formation in aged male rat liver. Biogerontology 2013; 14:63-71.

133. Ochiai T, Ohno S, Soeda S, Tanaka H, Shoyama Y, Shimeno H. Crocin prevents the death of rat pheochromyctoma (PC-12) cells by its anti-oxidant effects stronger than those of alpha-tocopherol. Neurosci Lett 2004; 362:61-64.

134. Bisti S, Maccarone R, Falsini B. Saffron and retina: neuroprotection and pharmacokinetics. Vis Neurosci 2014; 31:355-361.

135. Ochiai T, Soeda S, Ohno S, Tanaka H, Shoyama Y, Shimeno H. Crocin prevents the death of PC-12 cells through sphingomyelinase-ceramide signaling by increasing glutathione synthesis. Neurochem Int 2004; 44:321-330.

136. Mousavi SH, Tayarani NZ, Parsaee H. Protective effect of saffron extract and crocin on reactive oxygen species-mediated high glucose-induced toxicity in PC12 cells. Cell Mol Neurobiol 2010; 30:185-191.

137. Asadi F, Jamshidi AH, Khodagholi F, Yans A, Azimi L, Faizi M, *et al*. Reversal effects of crocin on amyloid beta-induced memory deficit: Modification of autophagy or apoptosis markers. Pharmacol Biochem Behav 2015; 139:47-58.

138. Finley JW, Gao S. A Perspective on *Crocus sativus* L. (Saffron) Constituent Crocin: A potent water-soluble antioxidant and potential therapy for Alzheimer's disease. J Agric Food Chem 2017; 65:1005-1020.

139. Sugiura M, Shoyama Y, Saito H, Abe K. The effects of ethanol and crocin on the induction of long-term potentiation in the CA1 region of rat hippocampal slices. Jpn J Pharmacol 1995; 67:395-397.

140. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi AH, Khalighi-Cigaroudi F. Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. BMC Complement Altern Med 2004; 4:12.

141. Batarseh YS, Bharate SS, Kumar V, Kumar A, Vishwakarma RA. *Crocus sativus* extract tightens the blood-brain barrier, reduces amyloid beta load and related toxicity in 5XFAD mice.

ACS Chem Neurosci 2017; 8:1756-1766.

142. Sahoo AK, Dandapat J, Dash UC, Kanhar S. Features and outcomes of drugs for combination therapy as multi-targets strategy to combat Alzheimer's disease. J Ethnopharmacol 2018; 215:42-73.

143. Ghahghaei A, Bathaie SZ, Kheirkhah H, Bahraminejad E. The protective effect of crocin on the amyloid fibril formation of Abeta42 peptide *in vitro*. Cell Mol Biol Lett 2013; 18:328-339.

144. Wang J, Sun C, Zheng Y, Pan H, Zhou Y, Fan Y. The effective mechanism of the polysaccharides from Panax *ginseng* on chronic fatigue syndrome. Arch Pharm Res 2014; 37:530-538.

145. Remya C, Dileep KV, Tintu I, Variyar EJ, Sadasivan C. Flavanone glycosides as acetylcholinesterase inhibitors: computational and experimental evidence. Indian J Pharm Sci 2014; 76:567-570.

146. Kim YJ, Joo SC, Shi J, Hu C, Quan S, Hu J, *et al*. Metabolic dynamics and physiological adaptation of Panax *ginseng* during development. Plant Cell Rep 2018; 37:393-410.

147. Xiong X, Huang G, Huang H. The anti-oxidant activities of phosphorylated polysaccharide from native *ginseng*. Int J Biol Macromol 2019; 126:842-845.

148. Choi JG, Kim N, Huh E, Lee H, Oh MH, Park JD, *et al*. White *ginseng* protects mouse hippocampal cells against amyloid-beta oligomer toxicity. Phytother Res 2017; 31:497-506.

149. Zhao HF, Li Q, Li Y. Long-term ginsenoside administration prevents memory loss in aged female C57BL/6J mice by modulating the redox status and up-regulating the plasticity-related proteins in hippocampus. Neuroscience 2011; 183:189-202.

150. Dong L, Wang Y, Lv J, Zhang H, Jiang N, Lu C, *et al*. Memory enhancement of fresh *ginseng* on deficits induced by chronic restraint stress in mice. 2019; 22:235-242.

151. Lyubimov, II, Borzenkov VM, Chepurnova NE, Chepurnov SA. Effect of a polysaccharide fraction of *ginseng* root on learning and memory in rats (using an active escape response as an example). Neurosci Behav Physiol 1997; 27:555-558.

152. Nishijo H, Uwano T, Zhong YM, Ono T. Proof of the mysterious efficacy of *ginseng*: basic and clinical trials: effects of red *ginseng* on learning and memory deficits in an animal model of amnesia. J Pharmacol Sci 2004; 95:145-152.

153. Ye R, Li N, Han J, Kong X, Cao R, Rao Z, *et al*. Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. Neurosci Res 2009; 64:306-310.

154. Cong WH, Liu JX, Xu L. [Effects of extracts of *Ginseng* and *Ginkgo biloba* on hippocampal acetylcholine and monoamines in PDAP-pV717I transgenic mice]. Zhongguo Zhong Xi Yi Jie He Za Zhi 2007; 27:810-813.

155. Jiang ZL, Chen YR, Zhou C, Shi JS, Duan SM. [Glutamate-related mechanism of ginsenosides against anoxic-ischemic brain damage]. Zhongguo Ying Yong Sheng Li Xue Za Zhi 2001; 17:105-108.

156. Kim YC, Kim SR, Markelonis GJ, Oh TH. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J Neurosci Res 1998; 53:426-432.

157. Ahn S, Singh P, Castro-Aceituno V, Yesmin Simu S, Kim YJ, Mathiyalagan R, *et al*. Gold nanoparticles synthesized using Panax *ginseng* leaves suppress inflammatory - mediators production via blockade of NF-kappaB activation in macrophages. Artif Cells Nanomed Biotechnol 2017; 45:270-276.

158. Kim SJ, Jeong HJ, Yi BJ, Kang TH, An NH, Lee EH, *et al*. Transgenic Panax *ginseng* inhibits the production of TNF-alpha, IL-6, and IL-8 as well as COX-2 expression in human mast cells. Am J Chin Med 2007; 35:329-339.

159. Song SB, Tung NH, Quang TH, Ngan NT, Kim KE, Kim YH.

Inhibition of TNF-alpha-mediated NF-kappaB transcriptional activity in HepG2 Cells by dammarane-type saponins from Panax *ginseng* leaves. J Ginseng Res 2012; 36:146-152.

160. Lee SM. Anti-inflammatory effects of ginsenosides Rg5, Rz1 , and Rk1 : inhibition of TNF-alpha-induced NF-kappaB, COX-2, and iNOS transcriptional expression. Phytother Res 2014; 28:1893-1896.

161. Kang S, Kim J-E, Song N, Jung S, Lee M, Park J, *et al*. The Ginsenoside 20-O-β-D-Glucopyranosyl-20(S)-Protopanaxadiol Induces Autophagy and Apoptosis in Human Melanoma via AMPK/JNK Phosphorylation. PloS one 2014; 9:e104305.

162. He SB, Zhang BX, Wang HH, Wang Y, Qiao YJ. [Study on mechanism of *Salvia miltiorrhiza* treating cardiovascular disease through auxiliary mechanism elucidation system for Chinese medicine]. Zhongguo Zhong Yao Za Zhi 2015; 40:3713-3717.

163. Yang L, Miao ZQ, Yang G, Shao AJ, Huang LQ, Shen Y, *et al*. [Research wilt disease of *Salvia miltiorrhiza* and its pathogen]. Zhongguo Zhong Yao Za Zhi 2013; 38:4040-4043.

164. Zhang XZ, Qian SS, Zhang YJ, Wang RQ. *Salvia miltiorrhiza*: A source for anti-Alzheimer's disease drugs. Pharm Biol 2016; 54:18-24.

165. Wong KK, Ho MT, Lin HQ, Lau KF, Rudd JA, Chung RC, *et al*. Cryptotanshinone, an acetylcholinesterase inhibitor from *Salvia miltiorrhiza*, ameliorates scopolamine-induced amnesia in Morris water maze task. Planta Med 2010; 76:228-234.

166. Zhang F, Zheng W, Pi R, Mei Z, Bao Y, Gao J, *et al*. Cryptotanshinone protects primary rat cortical neurons from glutamate-induced neurotoxicity via the activation of the phosphatidylinositol 3-kinase/Akt signaling pathway. Exp Brain Res 2009; 193:109-118.

167. Jiang WY, Jeon BH, Kim YC, Lee SH, Sohn DH, Seo GS. PF2401-SF, standardized fraction of *Salvia miltiorrhiza* shows anti-inflammatory activity in macrophages and acute arthritis *in vivo*. Int Immunopharmacol 2013; 16:160-164.

168. Huang YS, Zhang JT. [Anti-oxidative effect of three water-soluble components isolated from *Salvia miltiorrhiza in vitro*]. Yao Xue Xue Bao 1992; 27:96-100.

169. Huimin Yu LY, Hongzu Zhou, Sichang Qu, Xianghai Zeng, Delong Zhou, Yulian Zhou, Xinglin Li, Zhicheng Liu. Neuroprotection against Aβ25-35-induced apoptosis by *Salvia miltiorrhiza* extract in SH-SY5Y cells. Neurochem Int 2014; 75:89-95.

170. Mei Z, Zhang F, Tao L, Zheng W, Cao Y, Wang Z, *et al*. Cryptotanshinone, a compound from *Salvia miltiorrhiza* modulates amyloid precursor protein metabolism and attenuates beta-amyloid deposition through upregulating alpha-secretase *in vivo* and *in vitro*. Neurosci Lett 2009; 452:90-95.

171. Lee YW, Kim DH, Jeon SJ, Park SJ, Kim JM, Jung JM, *et al*. Neuroprotective effects of salvianolic acid B on an Abeta25-35 peptide-induced mouse model of Alzheimer›s disease. Eur J Pharmacol 2013; 704:70-77.

172. Cao YY, Wang L, Ge H, Lu XL, Pei Z, Gu Q, *et al*. Salvianolic acid A, a polyphenolic derivative from *Salvia miltiorrhiza* bunge, as a multifunctional agent for the treatment of Alzheimer's disease. Mol Divers 2013; 17:515-524.

173. Zhong GX, Li P, Zeng LJ, Guan J, Li DQ, Li SP. Chemical characteristics of *Salvia miltiorrhiza* (Danshen) collected from different locations in China. J Agric Food Chem 2009; 57:6879-6887.

174. Durairajan SS, Yuan Q, Xie L, Chan WS, Kum WF, Koo I, *et al*. Salvianolic acid B inhibits Abeta fibril formation and disaggregates preformed fibrils and protects against Abeta-induced cytotoxicty. Neurochem Int 2008; 52:741-750.

175. Hu L, Yu J, Li F, Chen B, Li L, Liu G. Effects of Salvia miltorrhiza in neural differentiation of rat mesenchymal stem cells with optimized protocol. J Ethnopharmacol 2011; 136:334-340.

176. Liu CS, Chen NH, Zhang JT. Protection of PC12 cells from hydrogen peroxide-induced cytotoxicity by salvianolic acid B, a new compound isolated from Radix Salviae miltiorrhizae. Phytomedicine 2007; 14:492-497.

177. Zhang N, Kang T, Xia Y, Wen Q, Zhang X, Li H, *et al*. Effects of salvianolic acid B on survival, self-renewal and neuronal differentiation of bone marrow derived neural stem cells. Eur J Pharmacol 2012; 697:32-39.

178. Liu T, Jin H, Sun QR, Xu JH, Hu HT. The neuroprotective effects of tanshinone IIA on beta-amyloid-induced toxicity in rat cortical neurons. Neuropharmacology 2010; 59:595-604.

179. Wang Q, Yu X, Patal K, Hu R, Chuang S, Zhang G, *et al*. Tanshinones inhibit amyloid aggregation by amyloid-beta peptide, disaggregate amyloid fibrils, and protect cultured cells. ACS Chem Neurosci 2013; 4:1004-1015.

180. Joe Y, Zheng M, Kim HJ, Kim S, Uddin MJ, Park C, *et al*. Salvianolic acid B exerts vasoprotective effects through the modulation of heme oxygenase-1 and arginase activities. J Pharmacol Exp Ther 2012; 341:850-858.

181. Ren Y, Houghton PJ, Hider RC, Howes MJ. Novel diterpenoid acetylcholinesterase inhibitors from Salvia miltiorhiza. Planta Med 2004; 70:201-204.

182. Kim DH, Jeon SJ, Jung JW, Lee S, Yoon BH, Shin BY, *et al*. Tanshinone congeners improve memory impairments induced by scopolamine on passive avoidance tasks in mice. Eur J Pharmacol 2007; 574:140-147.

183. Chen Y, Wu X, Yu S, Fauzee NJ, Wu J, Li L, *et al*. Neuroprotective capabilities of Tanshinone IIA against cerebral ischemia/reperfusion injury via anti-apoptotic pathway in rats. Biol Pharm Bull 2012; 35:164-170.

184. Qian YH, Xiao Q, Xu J. The protective effects of tanshinone IIA on beta-amyloid protein (1-42)-induced cytotoxicity via activation of the Bcl-xL pathway in neuron. Brain Res Bull 2012; 88:354-358.

185. Man Y, Yang L, Zhang D, Bi Y. Cryptotanshinone inhibits lung tumor growth by increasing CD4+ T cell cytotoxicity through activation of the JAK2/STAT4 pathway. Oncol Lett 2016; 12:4094-4098.

186. Song WZ, Cui JF, Zhang GD. [Studies on the medicinal plants of Magnoliaceae tu-hou-po of Manglietia]. Yao Xue Xue Bao 1989; 24:295-299.

187. Zhang P, Liu X, Zhu Y, Chen S, Zhou D, Wang Y. Honokiol inhibits the inflammatory reaction during cerebral ischemia reperfusion by suppressing NF-kappaB activation and cytokine production of glial cells. Neurosci Lett 2013; 534:123-127.

188. Dikalov S, Losik T, Arbiser JL. Honokiol is a potent scavenger of superoxide and peroxyl radicals. Biochem Pharmacol 2008; 76:589-596.

189. Hoi CP, Ho YP, Baum L, Chow AH. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. Phytother Res 2010; 24:1538-1542.

190. Lee YJ, Choi DY, Yun YP, Han SB, Kim HM, Lee K, *et al*. Ethanol extract of *Magnolia officinalis* prevents lipopolysaccharide-induced memory deficiency via its antineuroinflammatory and antiamyloidogenic effects. Phytother Res 2013; 27:438-447.

191. Lee YJ, Lee YM, Lee CK, Jung JK, Han SB, Hong JT. Therapeutic applications of compounds in the Magnolia family. Pharmacol Ther 2011; 130:157-176.

192. Lee YK, Yuk DY, Kim TI, Kim YH, Kim KT, Kim KH, *et al*. Protective effect of the ethanol extract of *Magnolia officinalis* and 4-O-methylhonokiol on scopolamine-induced memory impairment and the inhibition of acetylcholinesterase activity. J Nat Med 2009; 63:274-282.

193. Oh JH, Kang LL, Ban JO, Kim YH, Kim KH, Han SB, *et al*.

Anti-inflammatory effect of 4-O-methylhonokiol, compound isolated from *Magnolia officinalis* through inhibition of NF-kappaB [corrected]. Chem Biol Interact 2009; 180:506-514.

194. Kim BH, Cho JY. Anti-inflammatory effect of honokiol is mediated by PI3K/Akt pathway suppression. Acta Pharmacol Sin 2008; 29:113-122.

195. Lin YR, Chen HH, Ko CH, Chan MH. Neuroprotective activity of honokiol and magnolol in cerebellar granule cell damage. Eur J Pharmacol 2006; 537:64-69.

196. Lee JW, Lee YK, Lee BJ, Nam SY, Lee SI, Kim YH, *et al*. Inhibitory effect of ethanol extract of *Magnolia officinalis* and 4-O-methylhonokiol on memory impairment and neuronal toxicity induced by beta-amyloid. Pharmacol Biochem Behav 2010; 95:31-40.

197. Lee YJ, Choi DY, Han SB, Kim YH, Kim KH, Hwang BY, *et al*. Inhibitory effect of ethanol extract of *Magnolia officinalis* on memory impairment and amyloidogenesis in a transgenic mouse model of Alzheimer's disease via regulating beta-secretase activity. Phytother Res 2012; 26:1884-1892.

198. Chen YL, Lin KF, Shiao MS, Chen YT, Hong CY, Lin SJ. Magnolol, a potent anti-oxidant from *Magnolia officinalis*, attenuates intimal thickening and MCP-1 expression after balloon injury of the aorta in cholesterol-fed rabbits. Biomed Res Int 2001; 96:353-363.

199. Wu L, Chen C, Cheng C, Dai H, Ai Y, Lin C, *et al*. Evaluation of tyrosinase inhibitory, anti-oxidant, antimicrobial, and antiaging activities of *Magnolia officinalis* extracts after Aspergillus niger fermentation. BioMed Res Int 2018; 2018:1-11.

200. Hou YC, Chao PD, Chen SY. Honokiol and magnolol increased hippocampal acetylcholine release in freely-moving rats. Am J Chin Med 2000; 28:379-384.

201. Matsui N, Takahashi K, Takeichi M, Kuroshita T, Noguchi K, Yamazaki K, *et al*. Magnolol and honokiol prevent learning and memory impairment and cholinergic deficit in SAMP8 mice. Brain Res 2009; 1305:108-117.

202. Ho J, Hong C-. Cardiovascular protection of magnolol: Cell-type specificity and dose-related effects. J biomed sci 2012; 19:70.