

## Research progress on natural products from traditional Chinese medicine in treatment of Alzheimer's disease

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**ABSTRACT:** Alzheimer's disease (AD) is a severe condition in aging societies. Although research on this disease is advancing rapidly, thus far few very effective drugs are available for AD patients. The currently widely used medicines such as donepezil and galantamine transiently improve the symptoms of patients with mild to moderate AD. They are hardly capable of preventing, halting or reversing the progression of this disease. In the long history of development of traditional Chinese medicine, many herbs have been discovered and employed to treat dementia diseases in clinics in China. In recent decades, a number of agents were isolated from these herbs and their efficacies against AD were tested. Some flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, and polysaccharides were demonstrated to have potential efficacies against AD *via* targeting multiple pathological changes of this disease. In this article, we reviewed research progress on the efficacies and underlying mechanisms of these agents.

**Keywords:** Flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, polysaccharides

### 1. Introduction

Alzheimer's disease (AD) is characterized by progressive deterioration in intellect including memory and cognitive functions. It is the most common type of dementia among older people, accounting for 50-75% of all dementia cases (1). The number of AD patients was estimated at 36 million in 2010 and will triple in the world by 2050 (2). In China, this figure is estimated at 9 million currently and the prevalence rate of AD in the population over the

age of 60 years is 2.43% (3,4). Proportionate increases over the next forty years in the number of people with AD will be much steeper in China since it is witnessing the aging of a society in which the population over the age of 60 years will account for approximately 31% (about 400 million calculated on the current population base) of the whole population by the year of 2050 (5). These epidemiological data have painted a less than optimistic outlook in prevention and treatment of this disease in the world, especially in those countries with a rapidly aging society such as China.

The currently approved drugs for treatment of AD, *e.g.* donepezil, rivastigmine, galantamine, and memantine, aim to either inhibit acetylcholine esterase to increase the levels of the neurotransmitter acetylcholine, or antagonize *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptors to prevent aberrant neuronal stimulation (6,7). These medicines, however, exhibit modest and transient effects in improving disease manifestation and could hardly prevent, halt, or reverse the disease (2). The typical course of AD lasts for a decade or so, from the mildest stage when the symptoms like memory problems appear to the most severe stage when the patients must depend on others for basic activities of daily living and finally die in a completely helpless state. The long duration of AD and shortage of effective or curative treatments bring an enormous emotional and financial burden on patients, their families and society.

Exploration of natural active ingredients from medicinal herbs for treatment of AD has attracted substantial attention worldwide. Thus far drugs, including galantamine and huperzine A which originated from traditional Chinese herbs have been developed and used in clinics to treat mild to moderate AD (8,9). In addition to that, various natural agents isolated from traditional Chinese medicines were reported to have anti-AD efficacies through diverse mechanisms and require further investigation. In this article, we give a retrospective view of the research progress on natural products isolated from traditional Chinese medicine in treatment of AD and their underlying mechanisms.

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## 2. Etiology of AD

AD is related with, but shows intrinsic differences from normal aging (2). The underlying mechanisms of onset of this disease have not been thoroughly clarified thus far. Postmortem AD patients demonstrated atrophy of cerebral tissue, especially loss of neurons in hippocampus and the base of the forebrain (2). The most evident characteristics of pathological changes in the brain of AD patients are extracellular deposits of  $\beta$  amyloid protein ( $A\beta$ ) and an intracellular presence of neurofibrillary tangles (NFTs). Analyses of genes in familial AD patients, which probably accounts for less than 1% of AD cases, have brought important research progress regarding the mechanisms of onset of this disease (10). Studies indicated that the deposits of  $A\beta$  is correlated with gene variations of amyloid precursor protein (APP) and/or an abnormal transformation process (2). APP is encoded by the *APP* gene located at chromosome 21 and is transformed to  $A\beta$  by cleavage with  $\beta$ -secretase. Knockdown of the gene encoding  $\beta$ -secretase, *i.e.*,  $\beta$ -site APP cleaving enzyme 1 (*BACE1*), leads to reduction of  $A\beta$  production (11). The aggregation and accumulation of  $A\beta$  may result from increased production of  $A\beta$ , decreased degradation by  $A\beta$ -degrading enzymes, or reduced clearance across the blood-brain barrier. The neurotoxic activities of  $A\beta$  are exerted through mechanisms of cell apoptosis and/or inflammation in brain tissue. These research findings suggested promising targets for drug design. However, since the onset of familial AD is not prevalent, other hypotheses of pathogenesis, including hyperphosphorylation of Tau protein, cerebral ischemia, glutamate excitotoxicity, oxidative stress, mitochondria damage, and disequilibrium of calcium homeostasis have also attracted attention and have become acceptable targets (12-16).

## 3. Natural active ingredients against AD

In the past several decades, much research has been done to evaluate the anti-AD effects of natural agents isolated from traditional Chinese medicines from perspectives such as scavenging free radicals, inhibiting lipid peroxidation, suppressing neuronal apoptosis, enhancing the function of cholinergic neurons, and/or improving behavioral abnormalities in experimental animal models. Some flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, and polysaccharides were demonstrated to have potential efficacies against AD.

### 3.1. Flavonoids

Flavonoids are a series of compounds that are spread widely in higher plants and ferns and have attracted much attention due to their various biological actions (17). The characteristic chemical structures of these

compounds is two benzene rings with hydroxyl groups linked by a three-carbon chain. The most commonly known biological action of flavonoids is their antioxidant activity, which could be understood from the reduction properties of phenol hydroxyls in the chemical structures. That said, compounds of this type exhibit various pharmacological effects and clinical efficacies that may not be solely related to their anti-oxidative activities, such as effects on the vascular system, inflammatory response, and estrogen-like effects (17). These actions of flavonoids constitute the underlying basis for their anti-AD effects. Thus far, flavonoids including ginkgo flavonoids, soy isoflavones, puerarin, total flavonoids of Baical Skullcap stem and leaf, apigenin, rhodosin, hyperoside, and liquiritin were reported to have potent effects against AD (Table 1).

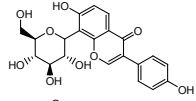
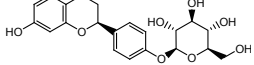
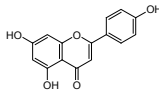
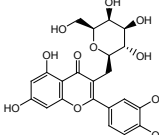
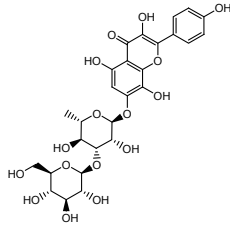
#### 3.1.1. Ginkgo flavonoids

Ginkgo flavonoids are the main constituents in the extract of Ginkgo biloba (EGB). Ginkgo flavonoids consist mainly of flavonols such as quercetin, kaempferol, and isorhamnetin and biflavonoids like ginkgetin, isoginkgetin, and amentoflavone (18,19). These ginkgo flavonoids have free radical scavenging effects and could inhibit lipid peroxidation. Studies demonstrated that mitochondrial DNA from the brain of old rats exhibited oxidative damage that is significantly higher than that from young rats (20). In addition, mitochondrial glutathione was more oxidized and peroxide formation in mitochondria was higher in old than in young rats (20). Treatment with EGB could partially prevent the indices of oxidative damage in brain from old animals (20). Other studies demonstrated that ginkgo flavonoids exhibited neuroprotective effects *via* antioxidant activity in brain damaged mice caused by ischemia-reperfusion (21). One randomized, double-blind, placebo-controlled, and multicenter clinical trial indicated that EGB was safe and capable of stabilizing and improving the cognitive performance and the social functioning of AD patients for 6 months to 1 year (22). Currently, EGB is used in clinics as a medical drug for treatment of AD in China, France, and Germany.

#### 3.1.2. Soy isoflavones

Soy isoflavones including daidzin daidzin, daidzein, genistin, genistein, glycitin, and glycitein (23,24) attracted much interest in recent years due to its estrogen-like effects and role in influencing sex hormone metabolism. Estrogen exerts anti-AD effects through several mechanisms such as reducing  $A\beta$  production (25), antagonizing the toxicities of  $A\beta$  (26), promoting synaptic growth and expressions of nerve growth factor (NGF) and its receptor (27), *etc.* Although estrogen exhibits the various above potential actions, its application in clinics for treatment of AD is dismal since

**Table 1. Flavonoids isolated from traditional Chinese medicine in treatment of AD**

Agents	Structures or contents	Typical origin	Reference
Ginkgo flavonoids	Mixture: mainly including quercetin, kaempferol, isorhamnetin, and biflavonoids like ginkgetin, isoginkgetin, and amentoflavone	<i>Ginkgo biloba</i> L.	18,19
Soy isoflavones	Mixture: mainly including daidzin, daidzein, genistin, genistein, and glycitin, glycitein	<i>Glycine max</i>	23,24
Total flavonoids of Baical Skullcap stem and leaf	Mixture: mainly including scutellarin, baicalin, and chrysin	<i>Scutellaria baicalensis</i> Georgi	45,46
Puerarin		<i>Radix puerariae</i>	40
Liquiritin		<i>Glycyrrhiza uralensis</i> Fisch.	49
Apigenin		<i>Apium graveolens</i>	52
Hyperin		<i>Hypericum perforatum</i> L.	57
Rhodiosin		<i>Rhodiola rosea</i>	59

it also causes side effects to non-neuronal cells, such as increasing the incidence of breast and endometrial cancer (28-30). Studies demonstrated that phytoestrogens such as genistein, one of the main ingredients of soy isoflavones, exerted pharmacological effects in a tissue specific manner (31). They selectively act on non-reproductive tissues to a certain degree and thus reduce the risk of side effects.

Animal studies indicated that soy isoflavones were capable of improving learning and memory abilities through influencing the brain cholinergic system and reducing age-related neuron loss especially in female rats (32-34). A clinical study demonstrated that postmenopausal women who undertook estrogen-replacement therapy had a significantly lower risk for the onset of AD than women who did not (35). Another randomized, double-blind, cross-over, and placebo-controlled trial revealed that soy isoflavones were safe and had positive effects on cognitive function, especially verbal memory, in postmenopausal women (36). The underlying mechanisms of favorable effects of soy isoflavones on cognitive function were thought to relate to their potential to mimic the actions and functions of estrogens in the brain (37), and promote the synthesis of acetylcholine and neurotrophic factors such

as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in the hippocampus and frontal cortex (38,39). These studies provided evidence for the potential usefulness of soy isoflavones in treatment of AD patients.

### 3.1.3. Puerarin

Puerarin is an isoflavanone glycoside extracted from species in the family Leguminosae such as *Radix puerariae* and is currently used to treat ischemic cerebrovascular disease and other vascular dysfunctions in China (40). Studies found that puerarin had potent effects in improving learning and memory disorders induced by scopolamine or D-galactose in a mouse model (41). Yan *et al.* reported that puerarin protected neurons against apoptosis in the cortex and hippocampus of AD rats caused by A $\beta$ <sub>25-35</sub> through downregulating A $\beta$ <sub>1-40</sub> and Bax expression in brain tissues, therefore alleviating the spatial learning and memory impairment of diseased animals (42). The anti-AD effects of puerarin were also suggested to be related to its abilities to decrease lipid peroxidase levels and increase superoxide dismutase levels in brain tissues, enhancing cerebral blood flow, and improving brain microcirculation (43,44).

### 3.1.4. Total flavonoids of Baical Skullcap stem and leaf

Baical Skullcap is a frequently used traditional Chinese medicine. Studies on its active ingredients revealed that the total flavonoids extracted from the stem and leaf, mainly including scutellarin, baicalin, and chrysin, exhibited a series of pharmacological effects such as anti-inflammation, prevention from myocardial damage induced by ischemia-reperfusion, and improved cerebral ischemia (45,46). Regarding its effects against AD, Zuo *et al.* found that total flavonoids of Baical Skullcap stem and leaf were capable of protecting hippocampal neurons against damage induced by injection of A $\beta_{25-35}$  into hippocampus in rat (47). The underlying mechanisms were related to its actions of decreasing the accumulation of lipid peroxide and proliferation of glial cells induced by A $\beta_{25-35}$  (47). Another study conducted by Ye *et al.* demonstrated that the total flavonoids alleviated memory and learning injury and protected hippocampal neurons from morphological changes in AD rats induced by A $\beta_{25-35}$  injection (48). These studies suggested the potential efficacies of total flavonoids of Baical Skullcap stem and leaf against AD.

### 3.1.5. Liquiritin

Liquiritin is an extract from the root of *Glycyrrhiza uralensis* Fisch. (49). Yang *et al.* investigated the protective effects of liquiritin on primary cultured rat hippocampal neurons (50). They found that pre-treatment with liquiritin for 6 h decreased the elevated levels of intracellular Ca<sup>2+</sup> concentration and neuron apoptosis caused by A $\beta_{25-35}$ . Liquiritin is also capable of enhancing the effects of nerve growth factor in extending neuroaxons (50). It is worth noting that liquiritin could also specifically inhibit the activity of acetylcholinesterase and promote the differentiation of neuronal stem cells into cholinergic neurons (50,51). The neuroprotective and neurotrophic effects make liquiritin a promising agent against AD.

### 3.1.6. Apigenin

Apigenin is a flavone usually obtained from *Apium graveolens* (52). It is a potent chelating agent that could decrease the metal ions participating in radical reactions and therefore reduce the creation of free radicals (53). In addition, apigenin could serve as an antioxidant to scavenge free radicals such as oxygen, nitric oxide (NO), and superoxide anion. On the other hand, apigenin possesses estrogen-like effects which are similar to the actions of estradiol (54). Due to these biological actions, apigenin was reported to protect human neuroblastoma cells SH-SY5Y against apoptosis induced by oxidative stress *in vitro* (55). *In vivo*, apigenin was found to improve the memory and learning disorders of aging mice induced by D-galactose (56).

### 3.1.7. Other flavonoids

Hyperoside is a flavonol isolated from species of *Hypericum* (57). In the mouse ischemia-reperfusion injury model, hyperoside was shown capable of inhibiting lactate dehydrogenase activity decline in brain tissues and obviously improve memory and learning disorders of model mice (58). Rhodosin is also a flavonol obtained from the root of *Rhodiola rosea* (59). Rhodosin functions as an antioxidant which scavenges free radicals, reduces the content of lipid peroxide, and inhibits degeneration of mitochondria in cerebrum cells and hippocampal pyramidal cells (44). Administration of rhodosin was reported to be capable of improving the memory and learning abilities of aging or AD mice (60).

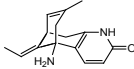
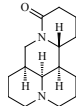
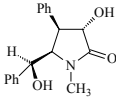
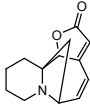
## 3.2. Alkaloids

Alkaloids are a group of naturally occurring cyclic compounds with a number of bioactivities that contain negative oxidation state nitrogen atoms. Compounds in this category exert anti-AD effects mainly through increasing the activity of the cholinergic system, suppressing inflammation, and/or exciting the central nervous system. Galantamine, an alkaloid isolated from plants in species of *Lycoris*, has been widely accepted as an effective drug for treatment of AD worldwide. Other alkaloids including huperzine A, sophocarpidine, clausenamide, arecoline, and securinine are either locally used as an anti-AD agent in clinics or still at the stage of studies (Table 2).

### 3.2.1. Huperzine A

Huperzine A is a reversible and selective cholinesterase inhibitor isolated from Chinese herb *Huperzia serrate* (61). It is also an NMDA receptor antagonist which may reduce glutamate induced damage in brain (62). It is highly lipid soluble and thus easy to pass through the blood-brain barrier and distribute to the brain after oral administration. Animal studies found that it is capable of enhancing the memory functions of rats (63). Clinical trials in China have shown that it is similarly effective compared to galantamine and donepezil, and may even be safer in terms of side effects (62). It has been approved and widely used to treat dysmnnesia of elder people, amnesia or AD patients in China since 1994. In recent years, huperzine A has attracted increasing attention in the US and European countries for its potential anti-AD efficacies. A multi-center, double-blind, placebo-controlled phase II trial, which enrolled 177 participants with mild to moderate AD, was completed in the US in November 2007 (64). Results of this trial demonstrated that cognition and activities of daily living were mildly improved in patients who received 400  $\mu$ g of huperzine A twice daily for 16 weeks. However, no significant changes were noted in overall disease change

**Table 2. Alkaloids isolated from traditional Chinese medicine in treatment of AD**

Agents	Structures	Typical origin	Reference
Huperzine A		<i>Huperzia serrate</i>	61
Sophocarpidine		<i>Sophora flavescens</i>	65
L-Clausenamide		<i>Clausena lansium (lour) Skeels</i>	67
MA9701	Arecoline derivative	---	69
Securinine		<i>Securinega suffruticosa</i>	70

or in psychiatric ratings according to the AD Assessment Scale-Cognitive (ADAS-Cog) scale. Currently, huperzine A is used as a dietary supplement for memory support in the US. That said, a Cochrane Database review reported in 2009, including four randomized, controlled trials in China involving 474 patients who received 300-500 µg of huperzine A daily for 8-24 weeks, that huperzine A is a well-tolerated drug that could significantly improve cognitive performance and activities on a daily living scale in patients with AD (62). Given this discrepancy, further clarifications on the efficacy of huperzine A against AD are still needed.

### 3.2.2. Sophocarpidine

Sophocarpidine is isolated from the root of *Sophora flavescens* (65). Studies found that sophocarpidine decreased the expression levels of interleukin-1β in cerebral cortex and hippocampus and alleviated injury of mitochondria of hippocampal neuronal cells in an AD rat model which was established by injection of ibotenic acid into hippocampus (66). Therefore, the anti-AD effects of sophocarpidine may be ascribed to its actions in mitigating inflammation through suppressing the release of inflammatory cytokines in the brain, thereby improving the status of injured neuronal cells and reducing neuron apoptosis.

### 3.2.3. Clausenamide

Clausenamide is isolated from the leaves of *Clausena lansium* (lour) Skeels in the family of Rutaceae [67]. Animal studies demonstrated that L-clausenamide is capable of improving the spatial discrimination disorders of rats induced by Aβ via enhancing the activities of cholineacetyltransferase of the cortex (68). Further,

L-clausenamide promoted the release of glutamic acid from synaptosomes of cerebellum, enhanced the amplitude of long term potentiation (LTP) in the hippocampus CA1 zone, and increased cerebral cortex thickness, thereby improving learning and memory ability of rats (68). It was demonstrated that the nootropic effect of L-clausenamide is more potent than that of piracetam (44).

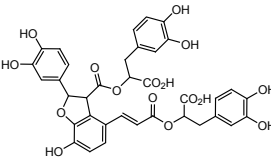
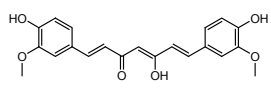
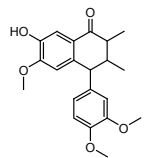
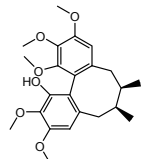
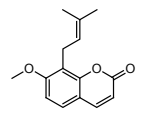
### 3.2.4. Other alkaloids

Compound MA9701 is synthesized based on the structure of arecoline which is an alkaloid isolated from the seeds of *Areca catechu*. It obviously improved the learning and memory disorder of mice which was induced by administration of ethanol or scopolamine (69). These effects of MA9701 were regarded to be related to its activities in agonizing the M acetylcholine receptor in the cortex and hippocampus. Securinine is an alkaloid isolated from the leaves of *Securinega suffruticosa* (70). It was demonstrated that securinine is capable of exciting the central nervous system and antagonizing the γ-aminobutyric acid (GABA) receptor. Administration of securinine significantly ameliorated the memory hypo-reproducibility of mice caused by 40% alcohol (71).

### 3.3. Phenylpropanoids

The phenylpropanoids are a diverse family of organic compounds that are synthesized by plants from the amino acid phenylalanine. The characteristics of the chemical structures of these compounds is that they consist of one or more structural units of C<sub>6</sub>-C<sub>3</sub>. Compounds in this category that have anti-AD potentials include salvianolic acid B (SAB), curcumin, schisandrone, schisanhenol, and osthole (Table 3).

**Table 3. Phenylpropanoids isolated from traditional Chinese medicine in treatment of AD**

Agents	Structures	Typical origin	Reference
Salvianolic acid B		<i>Salvia miltiorrhiza</i>	72
Curcumin		<i>Curcuma longa L.</i>	76
Schisandrone		<i>Schisandra chinensis</i>	84
Schisanhenol		<i>Schisandra chinensis</i>	84
Osthole		<i>Cnidium monnieri</i>	86

### 3.3.1. SAB

SAB, isolated from the root of *Salvia miltiorrhiza*, is a representative compound in this category (72). Its anti-AD effects and mechanisms have been extensively explored by Zhang and his colleagues (73). They demonstrated a series of results supporting that SAB is a promising agent in treatment of neurodegenerative diseases. First, SAB is a potent natural antioxidant, which could scavenge superoxide anion and hydroxyl radicals and inhibit lipid peroxidation. Studies demonstrated that it significantly decreased the levels of malondialdehyde (MDA), a product of lipid peroxidation, in the brain tissue of rats which were treated with FeSO<sub>4</sub>-cysteine or vitamin C-NADPH (74). Second, SAB protects the mitochondria of neurons from being damaged and suppresses neuronal apoptosis caused by a cerebral ischemia-reperfusion operation. The investigators indicated that cell apoptosis occurred in the ischemic area after occluding the cerebral artery for 1 h ischemia followed by 24 h reperfusion (73,75). Further studies revealed that this cerebral ischemia-reperfusion damaged mitochondrial membrane structure and decreased membrane potential, thus inducing the release of cytochrome *c* and causing elevated expression of caspase-3 (73,75). Pretreatment of rats with 10 mg/kg SAB effectively prevented those alternations of mitochondria and blocked the apoptosis of brain cells (73). Third, SAB suppresses the accumulation of A $\beta$ <sub>1-40</sub>, prevents the mitochondria of neuronal cell line PC12 being injured by A $\beta$ <sub>1-40</sub>, thereby

reducing neuronal apoptosis. It was observed under the microscope that A $\beta$ <sub>1-40</sub> at a concentration of 100 mg/L started to assemble and form fibrils when incubated at 25°C for 30 h (73). SAB at a concentration of 10 nmol/L almost entirely suppressed fibril formation of A $\beta$ <sub>1-40</sub> (73). Further studies found that SAB at a concentration range of 0.01-1  $\times$  10<sup>-6</sup> M inhibited the apoptosis of PC12 cells caused by A $\beta$ <sub>1-40</sub> (73). In addition, the assembled A $\beta$ <sub>25-35</sub> was found to be toxic to PC12 cells after 48 h treatment, which could be significantly alleviated by 1  $\mu$ mol/L SAB (73). Fourth, SAB is capable of suppressing the increase of intracellular calcium and reactive oxygen species (ROS) caused by A $\beta$ <sub>1-40</sub>. Studies demonstrated that the intracellular concentration of calcium increased from 188 to 326 mmol/L in neuronal cells PC12PS2N1411 after 24 h treatment with A $\beta$ <sub>1-40</sub> (73). The levels of intracellular calcium were reduced to 249 and 233 mmol/L when incubated with 0.1  $\times$  10<sup>-6</sup> and 1  $\times$  10<sup>-6</sup> mmol/L SAB, respectively. The A $\beta$ <sub>1-40</sub> caused elevated levels of ROS in mitochondria were also significantly decreased by the same concentrations of SAB (73). These studies suggested the potential value of SAB in treatment of AD. However, clinical trials are still required to investigate its safety and anti-AD efficacy.

### 3.3.2. Curcumin

Curcumin, isolated from the root of *Curcuma longa* L., is another representative compound in this category

(76). Studies in recent years demonstrated that it has a series of bioactivities such as anti-AD, antitumor, anti-inflammation, anti-oxidative, and anti-HIV effects. The underlying mechanisms of anti-AD effects of curcumin were revealed to include the following aspects. First, curcumin suppresses the formation of amyloid plaques. It was found that curcumin is capable of not only interfering with A $\beta$  aggregation which leads to formation of A $\beta$  fibrils, but also destabilizing preformed A $\beta$  fibrils (77). In addition, it was reported that curcumin suppressed the up-regulation of APP and  $\beta$ -secretase mRNA levels caused by copper or manganese ions in a time- and dose-dependent manner (78). Second, curcumin inhibits A $\beta$  induced inflammation. Giri *et al.* demonstrated that curcumin at a concentration range of 12.5-25  $\mu$ M reduced the expression of cytokines TNF $\alpha$  and IL-1 $\beta$  and chemokines MIP-1 $\beta$ , MCP-1, and IL-8 in monocytes by suppressing the interaction of early growth response-1 (Egr-1) with A $\beta$ <sub>1-40</sub> or fibrillar A $\beta$ <sub>1-42</sub> (79). Third, curcumin possesses potent antioxidative effects. Kim *et al.* showed that curcumin protected neuronal cells PC12 and human umbilical vein endothelial cells from being injured by A $\beta$ <sub>42</sub> due to its strong antioxidant properties (80). Another study showed that pretreatment of PC12 cells with 10  $\mu$ g/mL curcumin decreased the level of antioxidant enzyme and DNA damage caused by A $\beta$ <sub>25-35</sub> (81). Fourth, curcumin inhibits acetylcholinesterase activity. In an *in vitro* study, curcumin inhibited the activity of acetylcholinesterase with an IC<sub>50</sub> value of 67.69  $\mu$ M (82). Given the above activities of curcumin, thus far at least 6 clinical trials have been implemented to evaluate the efficacies of curcumin alone or in combination with other medications in treatment of AD or cognition impaired diseases (83). Among these studies, two were completed, one was terminated for various reasons, and three are under way. The disclosed results demonstrate no significant differences in cognitive function between placebo and curcumin groups. Results of clinical trials currently being conducted are expected and required to further testify to the efficacies of curcumin in treatment of AD.

### 3.3.3. Schisandrone and schisanhenol

Schisandrone is a linan isolated from the fruit of *Schisandra chinensis* (84). Studies found that schisandrone

is capable of scavenging superoxide anion free radical and other ROS including H<sub>2</sub>O<sub>2</sub> and  $\cdot$ OH generated by the xanthine-xanthine oxidase system and reducing the production of MDA in the process of lipid peroxidation (44). In addition, schisandrone significantly suppressed the oxidative stress and inflammatory response induced by A $\beta$ . Furthermore, schisandrone suppressed the elevation of intracellular calcium induced by A $\beta$ , thereby maintaining the intracellular calcium homeostasis equilibrium and protecting neurons from apoptosis (85). Schisanhenol is another active ingredient isolated from the fruit of *S. chinensis*. It was found to have effects in protecting rat brain synapses and mitochondria from ROS insult (44). Further animal studies are required to investigate the anti-AD effects of schisandrone and schisanhenol.

### 3.3.4. Osthole

Osthole is a coumarin isolated from plants in the Umbelliferae family such as *Cnidium monnieri* (86). Studies demonstrated that it significantly improved mouse spatial discrimination and memory disorders (87). This effect of osthole is thought to be related to its properties of suppressing lipid peroxidation and acetylcholinesterase activity in brain tissue of rats. It was also reported that osthole improved memory impairments in AlCl<sub>3</sub>-induced senescence-accelerated mice, which was ascribed to its actions of enhancing activities of glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD) and thus mitigating ROS-induced neuron injury (88). Previous studies on osthole mainly focused on its effects in antihypertension, antiarrhythmia, immunoenhancement, and anti-infection. Its potential application in treating dysmnnesia related diseases such as AD requires additional investigation in the future.

### 3.4. Triterpenoid saponins

Triterpenoid saponin is composed of triterpene sapogenin and saccharide. Triterpenes include a large group of compounds mostly arranged in a four or five ring configuration of 30 carbons with several oxygens attached. Compounds in this category including Panax notoginseng saponins (PNS), ginsenoside, and gypenosides were found to exhibit potential anti-AD activities (Table 4).

**Table 4. Triterpenoid saponins isolated from traditional Chinese medicine in treatment of AD**

Agents	Contents	Typical origin	Reference
Panax notoginseng saponins	Mainly including sapoin monomers Rb1, Rd, and Rg1	<i>Panax notoginseng</i>	89
Ginsenosides	Mainly including saponin monomers Rb1, Rb2, Rc, Rd, Rg1, Re, Rf, and Rg2	<i>Panax ginseng</i> C. A. Mey.	92
Gypenosides	Including more than 100 dammarane-type triterpenoid saponins	<i>Gynostemma pentaphyllum</i>	95

### 3.4.1. PNS

These saponins belonging to the dammarane type are the main effective components of *Panax notoginseng* (89). PNS exhibits broad biological activities including anti-inflammation, anti-fibrosis, scavenging free radicals, anti-aging, etc. Guo *et al.* reported that PNS increased learning and memory ability in rat dementia caused by injection of ibotenic acid into the nucleus basalis of Meynert (NBM) (90). It was found that PNS alleviated the neuron injury by  $A\beta_{25-35}$ , thereby reducing neuron apoptosis (44). In addition, PNS protected nerve cells NG108-15 from apoptosis caused by  $A\beta$  via stabilizing the membrane of nerve cells (44). Furthermore, PNS also promoted the growth of nerve cells, extended the length of axons, and enhanced synaptic plasticity (44). Besides those effects, PNS prevented the reduction of choline acetyltransferase and thus enhanced the functions of cholinergic neurons in AD model rats which were established by intra-peritoneal injection of D-galactose combined with excitatory neurotoxin ibotenic acid injection into bilateral NBM (91). These activities of PNS may constitute the pharmacological basis responsible for its actions against AD.

### 3.4.2. Ginsenosides

Ginsenosides, isolated from *Panax ginseng* C. A. Mey., are saponins with broad biological properties (92). Wang *et al.* reported that ginsenoside Rg1 improved the learning and memory disorders in AD model mice induced by  $A\beta$  (93). Mechanisms underlying the anti-AD effects of ginsenoside include boosting the levels of acetylcholine in the synaptic cleft, increasing the numbers of cholinergic receptors, and promoting the synthesis of nucleic acids and proteins. *In vitro* studies demonstrated that ginsenoside Rg1 alleviated ROS injury on nerve cells and suppressed apoptosis of rat nerve cells (94). Animal studies demonstrated that ginsenoside Rg1 promoted the development of cranial nerves and increased the number of synapses and the density of muscarinic receptors in mice (94). Currently, Radix Ginseng, as a traditional Chinese medicine, is widely used to treat dementia diseases including AD in China. The above studies provide scientific evidence for using Radix Ginseng as an anti-AD medicine.

### 3.4.3. Gypenosides

Gypenosides are a series of saponins isolated from *Gynostemma pentaphyllum* (95). They exhibit strong antioxidative properties manifesting as scavenging free radicals and increasing the levels of SOD in brain tissues. In addition, gypenosides are capable of stabilizing the membrane of neurons. *In vivo* studies showed that gypenosides reversed the degeneration of learning and memory abilities induced by  $A\beta$ , which may be ascribed

to their effects in suppressing the abnormal expression of cyclins and rectifying the disequilibrium of calcium homeostasis in hippocampal neurons (96). This evidence supports the use of Herba Gynostemmatidis Pentaphylli in treatment of AD patients in clinics.

### 3.5. Polysaccharides

Currently, studies on the anti-AD effects of polysaccharides mainly focus on their activities in immunoregulation, antioxidation, and life extension. For example, spirulina polysaccharides are capable of improving the symptoms of aging mice caused by D-galactose (97). Polysaccharides from *Cistanche deserticola* increased the hypoxia tolerance and antioxidation action of aging mice (98). Polysaccharides from *Ganoderma lucidum* reduced the level of MDA through enhancing SOD activities in hippocampus of rats and suppressing the activation of astrocytes caused by  $A\beta_{25-35}$  via immunoregulatory mechanisms (99). *Rehmannia glutinosa* oligosaccharides (RGOs) dose-dependently enhanced learning and memory ability in the rat insulted by cerebral ischemia-reperfusion via reducing the level of glutamic acid in hippocampus and increasing the levels of phosphorylated extracellular signal-regulated kinase (ERK) and acetylcholine (100). In addition, RGOs protected hippocampal neurons from being injured by glutamic acid, which is related to their effects in suppressing the excessive intake of glucose by neurocytes (100).

## 4. Conclusion and prospects

In the long history of development of traditional Chinese medicine, many herbs have been discovered and employed to treat dementia diseases in China. In recent decades, with the advancement of chromatographic and spectroscopic techniques, a number of agents have been isolated from these herbs and their efficacies against AD have been tested both *in vitro* and *in vivo*. The endeavors, on one hand, illustrated the principle of evidence-based medicine to clinically use these medicines to treat AD, and, on the other hand, discovered many monomer compositions as promising drugs or lead compounds for drug design in treatment of AD.

The currently used medications for treatment of AD are mainly symptom-management drugs. Although they do improve symptoms such as memory disorders and play a key role in treatment of AD at present, these drugs are not capable of reversing the progress of AD. In light of the pathogenic complexities of AD, it is probably unlikely that single-target drugs will achieve satisfactory curative effects. Some agents in categories of flavonoids and phenylpropanoids exhibit multiple biological properties that aim to eradicate the root causes of AD onset and may represent the future direction of new drug development.



Some issues also exist in the research and development of natural agents as anti-AD medicines. The results of experiments are sometimes difficult to repeat or compare because it varies for the same herb in methods of isolation or purification and the contents of effective constituents in different studies. In addition, effectiveness is hard to define due to the lack of positive control drugs in some cases. Research on natural products in prevention and treatment of AD started late and currently mostly has stayed at the stage of *in vitro* and animal studies. In the long run, efforts should be paid to screen and select optimal crude drugs, establish regulatory standards, and normalize the evaluation principles of drug efficacy to open new ways for AD drug research and development.

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