

## REVIEW

# Potential Application of Tetrahydroxystilbene Glucoside in Treatment of Alzheimer's Disease

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intervention; its effects may be exerted through APP pathway. TSG also displayed antioxidant activity *in vitro* and *in vivo*. In conclusion, TSG has been demonstrated to improve cognitive performances of AD models through multiple target strategies, and may be a future perspective in development of AD therapy.

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**Key words:** Alzheimer's disease;  $\beta$ -amyloid; Learning and memory; Polygonum Multiflorum; Tetrahydroxystilbene glucoside

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## ABSTRACT

Current strategies for Alzheimer's disease (AD) treatment are mainly symptomatic; development of disease-modifying therapies is urgently needed. Polygonum Multiflorum has been used in Traditional Chinese Medicine for long history in treatment of dementia. Pharmacological studies suggested Polygonum Multiflorum could improve learning and memory abilities in animal models of AD, and inhibit  $\beta$ -amyloid ( $A\beta$ ) production in the brain. 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside(TSG) is one main bioactive stilbene glycoside of Polygonum Multiflorum. The role of TSG in AD treatment has been investigated recently. TSG might antagonize acetylcholine deficiency and cognitive performance impairment in animal models of AD. In  $\beta$ -amyloid precursor protein (APP) transgenic mice, TSG ameliorated learning and memory functions associated with reductions of senile plaques and  $A\beta$ , and inhibitions of  $\gamma$ -secretase and  $\alpha$ -synuclein. In  $A\beta$  injection rat model, TSG increased cognitive behavior performances, and prevented  $A\beta$  deposition and synaptic degeneration. In D-galactose induced aging model, TSG improved abilities of learning and memory, and inhibited expressions of APP and  $A\beta$ . Learning and memory deterioration in aged animals was reformed by TSG

## INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and most common form of dementia; AD accounts for an estimated 60% to 80% of dementia cases<sup>[1]</sup>. Therapies to delay or prevent onset, slow progression, or improve symptoms of AD are urgently needed. Currently there are only five drugs approved by the U.S. Food and Drug Administration (FDA) for treatment of AD: donepezil; rivastigmine; memantine; donepezil; and galantamine. All of these drugs except memantine are cholinesterase inhibitors; memantine is an N-methyl-D-aspartate (NMDA) antagonist. These drugs are symptomatic and do not decelerate or prevent progression of disease. No other classes of drugs have been approved by FDA for treatment of AD despite many phase 3 trials<sup>[2]</sup>. There is increasing needs for developing new approaches.

Traditional Chinese Medicine (TCM) has long history of research and medical practice in treatment of dementia. TCM has its own systematic theories in classification, cause and treatment of dementia. TCM has accumulated extensive clinical experiences in dementia therapies with apparent efficacy and safety. Polygonum

Multiflorum is one of the most important and widely used TCM for dementia<sup>[3]</sup>. One major bioactive component in Polygonum Multiflorum is a stilbene glycoside: 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside (TSG). The effects and mechanisms of TSG on AD treatment have been studied in several different AD models. In  $\beta$ -amyloid precursor protein (APP) transgenic mice model, TSG could improve learning and memory abilities, inhibit formations of senile plaques and  $\beta$ -amyloid (A $\beta$ ), and decrease presenilin gene expressions. In A $\beta$  injection rat model, TSG promoted cognitive behavior performances, and reduced A $\beta$  deposition. TSG may have potential therapy effects in the future treatment of AD patients.

## ALZHEIMER'S DISEASE TREATMENT

On 1936, Alois Alzheimer first reported "A peculiar severe disease process of the cerebral cortex", and described a 50-year-old woman who had suffered with presenile dementia. He also noted distinctive plaques and neurofibrillary tangles in the brain histology<sup>[4,5]</sup>. There are several major hypotheses exist to explain the causes of AD. The acetylcholine hypothesis was initially presented over 30 years ago, and suggests the idea that some of AD symptoms are due to acetylcholine deficiency in the brain. This premise served as bases for majority of treatment strategies and drug development approaches<sup>[6]</sup>. The amyloid cascade hypothesis remains the best defined and most studied conceptual framework. Missense mutations in APP, presenilin-1 (PS-1) and presenilin-2 (PS-2) genes in familial AD increased  $\beta$ -amyloid 42 (A $\beta$ 42) production and accumulation. A $\beta$ 42 oligomerization and deposition as diffuse plaques led to progressive synaptic and neuritic injury, impaired long term depression and potentiation, and induced NMDA receptor-mediated excitotoxicity<sup>[7]</sup>. Another hypothesis is tau hypothesis: Tau is a microtubule-associated phosphoprotein that supports axonal transport and promotes cell stability. Increase of tau in AD is in the form of abnormally phosphorylated protein<sup>[8]</sup>. Abnormal hyperphosphorylation of tau inhibits microtubule function, and impairs neuronal axonal transport. Hyperphosphorylated tau forms inert polymers, becomes neurofibrillary tangles, and gains a toxic function<sup>[9]</sup>.

AD diagnosis was usually made by a physician based on medical history, cognitive and neurological tests, and magnetic resonance imaging. The new criteria and guidelines of diagnosis proposed by the National Institute of Aging and Alzheimer's Association in 2011 identify three stages of AD: preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD. Treatment to slow or stop progression of AD and of disease-modifying will be particularly effective when administered during preclinical and MCI stages<sup>[10-13]</sup>. The first approved drug is cognex, a cholinesterase inhibitor. Other cholinesterase inhibitors with improved safety followed, with approval of donepezil, galantamine, and rivastigmine. Memantine was approved in 2004 as an NMDA antagonist. There have been many failures in drug development of AD. These agents showed no drug-placebo differences on prespecified primary outcomes even completing phase 3 trials, such as B6, B12, folate, estrogen, bapineuzumab, and omega-3 fatty acids, et.c<sup>[2]</sup>.

Current pharmacotherapy mainly focus on impairment of cholinergic and glutamatergic systems, and are only symptomatic. They do not decelerate or prevent progression of disease. Searches for disease-modifying therapies have largely focused on compounds targeting amyloid cascade pathway. Other disease modifying therapeutics in areas of tau hypothesis, immunotherapy, antioxidant, and anti-inflammatory were also investigated. To our knowledge, treatments targeting these pathways have been unsuccessful in

demonstrating efficacies in clinical trials. Currently development of novel therapy is essential for advancement of AD treatment.

## POLYGONUM MULTIFLORUM IN TREATMENT OF ALZHEIMER'S DISEASE

Polygonum Multiflorum, also called He Shou Wu (Shou Wu, Chi Shou Wu) in China and Fo-ti in North America<sup>[14]</sup>, is one popular perennial traditional medicinal vine-like herb which used as main component of powders, decoctions or infusion. It has been used as a TCM for many centuries in treatment of dementia, inflammation, leptotrichia, hyperlipidaemia, hyp immunity, and aging<sup>[15]</sup>. Polygonum Multiflorum was seldomly used as a single herb medicine in clinical applications; instead it showed better therapeutic effects in combination with other TCM. Polygonum Multiflorum is one of frequently used TCM formulas for AD treatment on statistical bases of medication frequency and efficacy; other TCM include Rehmannia, Acorus Gramineus, Polygalaceae, Salvia Divinorum, and Ligusticum Chuanxiong Hort.

Pharmacological studies supported that Polygonum Multiflorum possessed various effects such as anti-aging, antioxidant, neuroprotection, immunomodulation, anti-hyperlipidaemia, hepatoprotection, anti-cancer, anti-bacterial, anti-inflammatory, anti-diabetes, and other effects<sup>[15,16]</sup>. Several clinical trials have been investigated in dementia treatment by Polygonum Multiflorum. Clinical effects of compound Polygonum Multiflorum extracts on AD patients were observed. 120 patients were treated with compound Polygonum Multiflorum extracts; 60 were treated with single Polygonum Multiflorum extract; 29 were treated with a western medicine. Scores for Mini-Mental State and ability of Daily Living Scales were improved in all groups. Compound Polygonum Multiflorum was superior to single Polygonum Multiflorum and western medicine<sup>[17]</sup>. Polygonum Multiflorum was studied as monotherapy for vascular dementia in a randomized, piracetam-controlled, single-center clinical trial; total clinical effective rate was found to be 71.25%. Polygonum Multiflorum had obvious therapeutic effects on vascular dementia with no relative adverse reactions.

Many pharmacological studies investigated effects of Polygonum Multiflorum on learning and memory abilities, as well as A $\beta$  deposition<sup>[3]</sup>. Protective effects of Polygonum Multiflorum were investigated on  $\beta$ -amyloid 25-35 (A $\beta$ 25-25) induced mice model. Behavioral changes of passive avoidance and water-maze tests were examined after mice were fed with Polygonum Multiflorum water extracts and received intracerebroventricular injection of A $\beta$ 25-35. Polygonum Multiflorum significantly improved cognitive impairment caused by A $\beta$ 25-35. Acetylcholinesterase activity was lower in Polygonum Multiflorum treatment groups. Authors suggested these effects were mediated by antioxidant properties of Polygonum Multiflorum<sup>[18]</sup>. Beneficial effects of different Polygonum Multiflorum extracts on memory and hippocampus morphology were studied on senescence-accelerated mice. Dietary supplementation with Polygonum Multiflorum extracts reduced brain pathological changes and promoted learning and memory capabilities<sup>[19]</sup>. In *Drosophila* AD model, neuroprotective activities of Polygonum Multiflorum were characterized; A $\beta$ 42-expressing flies fed with Polygonum Multiflorum showed strong suppression of AD neurological phenotypes, such as decreased survival and motility, and increased cell death and reactive oxygen species level<sup>[20]</sup>. PMC-12, a prescription used in Korean, is a mixture of four herbs including Polygonum Multiflorum. Studies showed memory impairments in mice induced by A $\beta$ 25-35 injection could be reversed by PMC-12 in

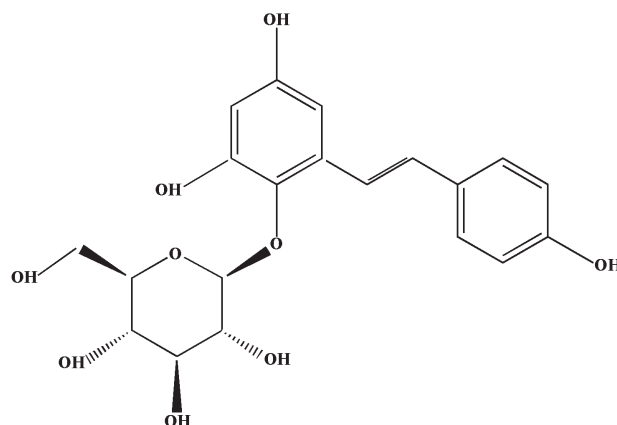
dose-dependent manners; PMC-12 also decreased A $\mu$  up-regulation and activation of microglia and astrocytes in the A $\mu$ 25–35-injected brain<sup>[21]</sup>. Fifteen herbs were screened for A $\beta$  inhibition and APP processing modulation in mouse neuroblastoma cells expressing Swedish APP; only *Polygonum Multiflorum* and *Convolvulus Pluricaulis* showed profound inhibition of A $\beta$  production. *Polygonum Multiflorum* inhibited A $\beta$  production only through APP modulation, which was exhibited together with up-regulation of soluble peptide APP $\alpha$  (sAPP $\alpha$ ) and down-regulation of soluble peptide APP $\beta$  (sAPP $\beta$ )<sup>[22]</sup>. In a rat AD model established by A $\beta$ 40 injection, *Polygonum Multiflorum* could attenuate learning and memory injuries associated with AD. *Polygonum Multiflorum* further improved fluidity of mitochondria membrane and activity of mitochondria cytochrome oxidase<sup>[23]</sup>. Another study used a rat AD model induced by A $\beta$ 40 injection. *Polygonum Multiflorum* reduced learning impairment in a Y-maze behavior test<sup>[24,25]</sup>; *Polygonum Multiflorum* also reversed down-regulation of brain-derived neurotrophic factor expression<sup>[26]</sup>. Senescence accelerated mice were fed with *Polygonum Multiflorum* extracts. Active shuttle avoidance test showed *Polygonum Multiflorum* improved cognitive performances, and reduced pathological changes in the brain<sup>[27]</sup>.

## TSG IS THE MAJOR BIOACTIVE COMPONENT OF POLYGONUM MULTIFLORUM

The main constituents isolated from *Polygonum Multiflorum* included stilbene, anthraquinone, phenolic acid, flavonoid and their glycosides. Many studies revealed that stilbene possessed antioxidant, anti-aging, anti-tumor, anti-inflammatory and liver protective activities. Anthraquinone was proved to exhibit beneficial effects such as anti-bacterial, anti-fungal, anti-viral, antioxidant, and anti-cancer. Phenolic acid and flavonoid exhibited antioxidant activity<sup>[15,16,28,29]</sup>. TSG may be the most bioactive and most fully researched ingredient in *Polygonum Multiflorum*. TSG was first isolated and identified from *Polygonum Multiflorum* in 1976. Natural TSG mainly exists as the form of stilbene aglycone side chain binding a monosaccharide group. TSG is white amorphous powder, soluble in water, ethanol, and methanol. The molecular formula of TSG is C<sub>20</sub>H<sub>22</sub>O<sub>9</sub>; its molecular weight is 406 (Figure 1)<sup>[30-35]</sup>.

According to Chinese Pharmacopoeia 2010 edition, contents of TSG in the raw and processed decoction pieces should be more than 1% and 0.70%, respectively. Many techniques have been used to determine contents of TSG in *Polygonum Multiflorum* and herb formulations, such as thin-layer chromatography, high performance liquid chromatography (HPLC), ultraviolet-visible (UV) spectrophotometry, fluorescence spectrophotometry, and high-performance capillary electrophoresis. HPLC was a frequently used quantitative tool with high precision. HPLC measurement coupled with mass spectrometry, photo-diode array, and chemiluminescence detection have been developed for quantification of TSG<sup>[31,36-39]</sup>. HPLC-UV method was also developed for TSG measurement in rat tissue and plasma after oral administration of *Polygonum Multiflorum*<sup>[33,34]</sup>.

The aim of drug therapy is to cure, prevent, or control disease status. To achieve this goal, adequate drug doses must be delivered to target tissues so that therapeutic yet nontoxic levels are obtained. Pharmacokinetics examines movement of a drug overall through the body. Speed of drug action onset, intensity of drug effect, and duration of drug action are controlled by these factors: (1) Drug absorption from administration site permits entry into plasma; (2) Drug may then reversibly leave bloodstream and distribute into



**Figure 1** Chemical structure of 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside.

interstitial and intracellular fluids; (3) Drug may be metabolized by liver, kidney, or other tissues; (4) Drug and its metabolites are eliminated from body into urine, bile, or feces. Normally anti-AD drugs also have pharmacological effects on health people. Therefore, pharmacology properties of TSG are also observation indexes in treated people. To our knowledge, pharmacokinetic studies about TSG have not been reported in the human. However, there are *Polygonum Multiflorum* toxicology studies conducted in the human. Hepatic adverse effects have been reported since 1900s in China and other counties, and acute toxic hepatitis was the most common reported. Rash, fever, abdominal pain, dyspnea, vision problems and palpitations were common adverse effects of *Polygonum Multiflorum*<sup>[15,40-46]</sup>. Pharmacokinetics and pharmacology studies of TSG will provide valuable information to ensure the safety and efficacies of TSG administration.

One pharmacokinetic study was reported in rats after oral administration of *Polygonum Multiflorum* by using a reversed-phase HPLC coupled with liquid-liquid phase extraction. TSG was rapidly absorbed into body fluids and widely distributed throughout the body, with great efficiency of utility, followed by quick elimination. The maximum concentration can be reached to tissues at 40 minute post dose. The highest levels of TSG were detected in liver and lung whereas little in brain and testis, indicating TSG could hardly penetrate the blood-brain and blood-testicle barriers<sup>[34]</sup>. These authors also observed pharmacokinetic profiles of TSG in mice after oral administration of *Polygonum Multiflorum* extracts. Time to reach maximum concentration in plasma is 60 minute. Compartmental and non-compartmental pharmacokinetic parameters suggested that TSG had a rapidly absorption, wide distribution, great utility, and fast elimination<sup>[33]</sup>.

## MULTIPLE TARGET EFFECTS OF TSG ON ALZHEIMER'S DISEASE TREATMENT

Recent progresses suggested that TSG might have much pharmacological properties including antioxidant, anti-aging, anti-inflammation, anti-atherosclerosis, anti-hyperlipidaemia, anti-platelet activity, ameliorate diabetic nephropathy, neuroprotection, hair growth, and cardioprotective effects<sup>[47-58]</sup>. There are increasing reports about the roles of TSG on learning and memory changes of animal AD models, as well as possible action mechanisms.

### TSG on acetylcholine deficiency

In a mouse dementia model induced by scopolamine, mice were

treated with TSG, and then subjected to Morris water maze and passive avoidance tests. TSG could reduce swimming time and distance of Morris water maze test, prolong latency and reduce error frequency of passive avoidance test. These results suggested that TSG might antagonize acetylcholine deficiency induced cognitive injuries. Effects of TSG on cholinergic system and cognitive improvement were examined in a rat AD model induced by otenic acid injection into the basal forebrain. TSG increased choline acetyl transferase activity and improved M-cholinergic receptor binding in the hippocampus and cortex. TSG also increased acetylcholinesterase (AChE) activity in the cortex<sup>[59]</sup>. Authors also observed changes of cholinergic system in a rat AD model induced by ibotenic acid injection into the basal forebrain; acetylcholine deficiency in AD rats was enhanced by TSG intervention<sup>[60]</sup>.

### TSG on amyloid cascade

Learning and memory abilities were examined by Morris water maze and object recognition tests in different ages of AD-like PDAPPV717I transgenic mice; cognitive impairment aggravated along with aging in transgenic mice. TSG was found not only to prevent memory damage at early stage of transgenic mice, but also reverse performance impairment in late stage of transgenic mice<sup>[61]</sup>. They further studied effects of TSG on APP, A $\beta$ ,  $\beta$ -secretase (BACE1) and PS-1 expressions in the hippocampus of transgenic mice. TSG significantly improved learning and memory abilities of transgenic mice, inhibited A $\beta$  production and PS-1 expression; its neuroprotective mechanisms may be associated with reduction of APP and inhibition of  $\gamma$ -secretase. Messenger RNA and protein alterations of  $\alpha$ -synuclein were investigated in the hippocampus of APPV717I transgenic mice. TSG not only prevented  $\alpha$ -synuclein over expression at early stage, but also reversed increased upregulation of  $\alpha$ -synuclein and inhibited aggregation at late stage of transgenic mice<sup>[62]</sup>. APP695V717I transgenic mouse model was used to evaluate effects of TSG on behaviors of Morris water maze and Y-Maze tests, as well as autophagy pathway. TSG might promote learning and memory abilities by inhibiting autophagy-associated proteins Beclin-1 and LC3-II in the hippocampus<sup>[63]</sup>.

In a rat AD model induced by A $\beta$ 42 injection intracerebroventricularly, TSG improved learning and memory abilities and synaptic structure degeneration. TSG might play the roles through upregulation of Src, p-CREB and NR2B<sup>[64]</sup>. Other studies injected A $\beta$ 42 into rat hippocampus; cognitive capabilities were significantly ameliorated in the TSG intervened group tested by electric Y-Maze; A $\beta$  deposition was also reduced in the hippocampus after TSG treatment.

There was a study using D-galactose induced dementia mice model. TSG treatment decreased escape latency during hidden platform test of Morris water maze. TSG also extended staying time and frequency of crossing original platform quadrant in spatial probe test. Compared with dementia model group, TSG significantly decreased APP and A $\beta$  expressions in the hippocampus, so as to protect neurons from A $\beta$  neurotoxicity<sup>[65]</sup>. In a rat AD model induced by D-galactose injection, spatial memory of Morris water maze and passive avoidance response were examined. Learning and memory performances of AD rats were significantly improved after TSG intervention. TSG also facilitated A $\beta$  degradation and transport, increased expressions of neprilysin and low density lipoprotein receptor-1 in the CA1 region<sup>[66]</sup>.

Another study evaluated effects of TSG on cognitive damage and over expression of hippocampal APP induced by chronic exposure to aluminum in rats. After exposure to aluminum

chloride, rats displayed decreased step-through latency in passive avoidance task, and increased expression of APP in the hippocampus. TSG significantly ameliorate impairment of behavior tasks, and suppressed APP over expression in a time-dependent manner<sup>[67]</sup>.

### Anti-aging effect of TSG

Effects of TSG on learning and memory deterioration in aged rats were evaluated, as well as the relation with APP pathway. TSG significantly improved cognitive performances of Morris water maze in aged rats, and increased messenger RNA and protein expressions of disintegrin and metalloproteinase 10. Authors considered TSG possibly exerted therapeutic effects through APP pathway<sup>[68]</sup>. Morris water maze and passageway water maze tests were performed on aged rats. TSG improved learning and memory performances, protected neuronal synaptic structures<sup>[69]</sup>, and enhanced synaptophysin expression in the hippocampus of aged rats<sup>[59]</sup>. Researchers identified effects of TSG on memory capabilities and movement functions in aged mice, and further mechanisms. Administration of TSG promoted memory and movement functions through protecting synapses, inhibiting  $\alpha$ -synuclein overexpression and aggregation in multiple brain regions<sup>[70]</sup>. Learning and memory behaviors were tested in senescence accelerated mouse SAMP8 by Morris water maze; escape latency, staying time, and frequency of crossing platform were all ameliorated by TSG feeding. The effects and mechanisms of TSG on memory capabilities, life span, and neural insulin signaling in SAMP8 mouse were assessed. Results suggested TSG improved memory and life span, via up regulating neural klotho and down regulating neural insulin or insulin-like growth factor 1 in the brain<sup>[71]</sup>.

### Antioxidant effect of TSG

Oxidative stress is one of risk factors of AD development; free radical scavenging may be one strategy to treat AD<sup>[72,73]</sup>. Radical scavenging activity of TSG *in vitro* was studied through Fenton reaction; TSG was shown to have strong free radical scavenging ability. Radical scavenging active components from Polygonum Multiflorum thumb were examined by 2,2-diphenyl-1-picrylhydrazyl (DPPH) test; three compounds showed strong antioxidant activity including TSG<sup>[74]</sup>. Antioxidant activity of TSG was assessed by DPPH radical scavenging activity *in vitro*; TSG demonstrated a moderate free radical scavenging ability; while corresponding deglycosylated stilbene displayed higher antioxidant ability<sup>[75]</sup>. Effects of TSG were analyzed in *C. elegans*. TSG exhibited much higher antioxidative activity both in a cell-free assay and in nematode than resveratrol, increased stress resistance, alleviated accumulation of lipofuscin, and prolonged life span of nematode. TSG may also possessed indirect antioxidative effect via modulation of SOD-3 and GST-4<sup>[58]</sup>.

Other studies found that TSG facilitated tetanus stimulation-induced hippocampal long-term potentiation through activation of NMDA receptor in the hippocampal CA1 region of normal mice; phosphorylation of CaMKII and activation of ERK1/2 cascades possibly mediated TSG-induced enhancement<sup>[76]</sup>. There are also investigations suggested that TSG attenuated lipopolysaccharide (LPS)-mediated induction of pro-inflammatory factors in microglia through reducing binding activity of NF- $\kappa$ B<sup>[57]</sup>, and attenuated LPS-induced NADPH oxidase activation and subsequent reactive oxygen species production<sup>[49]</sup>; while microglia are believed to mediate development of AD and that neurons injury is usually secondary to microglia activation<sup>[77-80]</sup>.



## CONSLUSION

Natural products, particularly those utilized in TCM, have an advantage in their safety and efficacy profiles because they have already been utilized in human practice for long history. As a main bioactive ingredient of *Polygonum Multiflorum*, TSG has been demonstrated to improve learning and memory capabilities of different AD models through multiple target strategies: TSG could inhibit formation of senile plaques and A $\beta$ , decrease PS-1 and  $\gamma$ -secretase expressions; TSG might antagonize acetylcholine deficiency in the brain; TSG might also exert anti-aging effects through APP pathway; in addition, TSG could enhanced antioxidant activity. Therefore, TSG was regarded as a promising therapy perspective in the future development of AD treatment strategy.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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