REVIEW

The Role of Traditional Chinese Medicine Natural Products in β-Amyloid Deposition and Tau Protein Hyperphosphorylation in Alzheimer's Disease

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Abstract: Alzheimer's disease is a prevalent form of dementia among elderly individuals and is characterized by irreversible neurodegeneration. Despite extensive research, the exact causes of this complex disease remain unclear. Currently available drugs for Alzheimer's disease treatment are limited in their effectiveness, often targeting a single aspect of the disease and causing significant adverse effects. Moreover, these medications are expensive, placing a heavy burden on patients' families and society as a whole. Natural compounds and extracts offer several advantages, including the ability to target multiple pathways and exhibit high efficiency with minimal toxicity. These attributes make them promising candidates for the prevention and treatment of Alzheimer's disease. In this paper, we provide a summary of the common natural products used in Chinese medicine for different pathogeneses of AD. Our aim is to offer new insights and ideas for the further development of natural products in Chinese medicine and the treatment of AD.
Keywords: Alzheimer's disease, β-amyloid deposition, tau-protein hyperphosphorylation, natural products, Chinese herbal medicine, review

Introduction

Alzheimer's disease (AD) is the most prevalent degenerative disease of the central nervous system in elderly individuals. It has a gradual and progressive onset, leading to cognitive decline, mental and behavioral abnormalities, and a reduced ability to perform daily activities.[1] As the population ages, dementia has become a widespread condition among older individuals, with AD dementia accounting for 60% to 80% of cases. It is also the primary cause of disability and mortality in elderly individuals.[2,3]

China currently has the highest number of dementia patients worldwide.[4] Epidemiological surveys indicate that there are approximately 15.07 million individuals over the age of 60 with dementia in China, with approximately 9.83 million of them diagnosed with AD.[5] This places a significant burden on both the families of the patients and society as a whole. The primary pathological characteristics of AD include the formation of senile plaques (SPs) through the accumulation of extracellular amyloid β-protein (Aβ), the presence of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau proteins, and synaptic loss.[6] Current treatment for cognitive symptoms primarily involves the use of cholinesterase inhibitors (donepezil, carboplatin, and galantamine) and glutamate receptor antagonists (memantine and memantine combined with cholinesterase inhibitors).[7] However, it is important to note that cholinesterase inhibitors may lead to increased adverse effects, such as skin irritation, weight loss, nausea, and vomiting.[7] On the other hand, glutamate receptor antagonists, particularly memantine, have shown limited effectiveness in the early stages of AD.[7] Atypical antipsychotics can help alleviate psychiatric and behavioral symptoms associated with AD, but there is a risk of

exacerbating cognitive impairment, among other concerns.[7] Currently, there are no therapeutic drugs available that can effectively halt the occurrence or slow down the progression of AD. As a result, researchers both domestically and internationally continue to actively explore alternative treatment methods for AD.

The literature on dementia treatment predates the first reported case of AD in the world by 283 years.[8] In Chinese medicine, AD is categorized as a type of dementia, with kidney deficiency as the core issue. The basic pathological mechanism involves marrow reduction, brain depletion, and loss of use of the mental mechanism, with phlegm and blood stasis as the main pathological products. Clinical medications often focus on tonifying the kidney and filling the marrow while also addressing symptoms such as depression, phlegm expulsion, blood invigoration, and orifice opening.[9] According to the 2020 edition of the Chinese Alzheimer's disease dementia treatment guidelines, the treatment of AD dementia with traditional Chinese medicine (TCM) is based on the progression of symptoms. The guidelines suggest that AD treatment should focus on 'tonifying the kidneys' in the early stage, "resolving phlegm, activating blood, and dipping fire" in the middle stage, and "detoxifying and fixing the detoxification" in the late stage.[10] In the treatment of patients with mild AD for 12–24 weeks, there were better cognitive ($p = 0.002$) and functional improvements compared to placebo ($p = 0.002$; n = 2291).[7] The cognitive improvement of Qinggong Shoutao pills (14 g/d) was superior to that of *ginkgo biloba* extract EGb761 ($p<0.04$) and placebo ($p<0.001$) in the treatment of prodromal AD patients for 52 weeks (n = 350).[11] Blood activating EGb761 (240 mg/d, 160 mg/d) in the treatment of mild/moderate AD patients for 22–24 weeks showed better cognition ($p<0.00001$; n = 723), behavior ($p = 0.00001$; n = 547), function ($p<0.0001$; n = 547), and overall improvement ($p<0.0006$; n = 542) compared to placebo.[12] In the treatment of dementia patients for 12 weeks, Huanglian Jiedu decoction showed a higher clinical improvement rate ($p = 0.004$) and better functional level compared to placebo *($p<0.00001$*; n = 672).[7] However, overall, there is significant heterogeneity among the studies, which requires further verification. In conclusion, Clinical studies have provided initial evidence that combining conventional Western medicine with TCM has a synergistic effect, improving cognitive function and slowing deterioration. This combination treatment appears to be more beneficial in the early stages of AD than in the middle and late stages.[13] In recent years, there has been growing interest in the potential efficacy of Chinese herbal medicines and their extracts in preventing and treating AD. Research on this topic has received increasing attention, as natural products derived from Chinese herbal medicines offer several advantages, such as multiple targets, fewer toxic side effects, and cost-effectiveness.[14] Consequently, more scholars are dedicating their efforts to studying the natural products and active ingredients of Chinese herbal medicines for AD treatment. This paper aims to review the recent research progress on natural products of Chinese medicine in the context of AD, both domestically and internationally. The findings of this review are expected to provide a theoretical and experimental basis for the clinical treatment of AD.

## Natural Products of Traditional Chinese Medicine and AD

The pathological changes observed in AD are complex and diverse, and the reasons for the appearance of these changes cannot be fully explained. The pathogenesis of AD remains unclear. The mainstream theories regarding the common pathogenesis of AD include extraneuronal amyloid aggregation, intraneuronal Tau protein hyperphosphorylation, the cholinergic theory, the neuroinflammatory theory, and the oxidative stress response theory.[15,16] β-amyloid deposition and Tau protein hyperphosphorylation are well-known pathological markers of AD and play a crucial role in its development.[17] These markers are closely associated with oxidative stress, microglial activation, autophagy, and other factors involved in AD. Therefore, this paper aims to review recent experimental studies on the use of natural products in traditional Chinese herbal medicine to inhibit Aβ deposition and Tau protein hyperphosphorylation, focusing on the pathways mentioned above.

Inhibition of Aβ Deposition by Natural TCM Products

The Aβ theory is the prevailing theory of AD development. One of the key pathological features in the development of AD is the formation of SPs, which results from the extracellular aggregation of Aβ in nerve cells. Aβ is produced from amyloid precursor protein (APP) through a series of protein hydrolysis processes. APP has two main metabolic pathways. Under normal physiological conditions, APP is cleaved by α-secretase and γ-secretase to produce the soluble extracellular fragment sAPPα and other polypeptides with neuroprotective effects. This pathway is referred to as the

nonamyloid hydrolysis pathway. However, under pathological conditions, the production of Aβ is divided into two types. The first involves the sequential cleavage of APP embedded in the cell membrane by β-APP cleavage enzyme 1 (BACE-1) and the γ-secretase complex,[18] resulting in the secretion of Aβ polypeptides outside the cell (polypeptides of different lengths, including Aβ1-40 and Aβ1-42). The second pathway involves the reinternalization of APP followed by cleavage by β-secretase and γ-secretase, leading to the production of intracellular Aβ polypeptides.[19–21] This pathway is known as the amyloid hydrolysis pathway. In the pathological process of AD, there is an imbalance in the production and clearance of Aβ. Normally, the production and degradation of Aβ are in equilibrium. However, in AD, there is excessive production of Aβ that cannot be cleared efficiently, leading to its accumulation in large quantities. This accumulation results in the formation of insoluble amyloid, which is deposited in brain tissue and contributes to the formation of SPs. The process of extracellular amyloid beta deposition leading to AD is depicted in Figure 1.

Li et al[22] conducted a study using intraperitoneal injection of D-galactose to induce senescence, hippocampal injection of Aβ1-40 compound to develop an AD model, and the middle cerebral artery line embolization reperfusion method to create a vascular dementia (VD) rat model. This study evaluated the effects of tanshinone intervention on learning and memory impairment in both AD and VD rats. The results demonstrated that tanshinone significantly reduced the latency of evasion and the number of misfirings into the blind end in both groups, indicating its therapeutic potential in improving learning and memory impairment in AD and VD rats. Zhuang et al[23] conducted a study in which they injected Aβ25-35-induced AD model rats in the bilateral hippocampus and provided them with high, medium and low doses of ginsenoside Rg2 intervention. The study revealed that each dose of ginsenoside Rg2 improved the learning and memory ability of AD model rats. Furthermore, medium and high doses of ginsenoside Rg2 significantly inhibited the formation of SPs caused by Aβ deposition. In a study conducted by Lu et al.[24] APPswe, PSEN1dE9 (APP/PS1) transgenic AD model mice were selected. After 28 days of intervention with berberine, the berberine group showed a reduction in the expression level of Aβ42 and the number of SPs compared to the saline group. This suggests that berberine has the potential to significantly enhance learning and memory abilities while also reducing the expression and aggregation of Aβ42, leading to decreased formation of SPs. Niu et al[25] conducted a study using 4-month-old 5×FAD (APPSwFlLon, PSEN1*M146L*L286V) transgenic mice to simulate the deposition of SPs in patients with AD. The mice were administered β-asarone ether at a concentration of 10 mg/kg for 90 days through continuous gavage. The findings demonstrated that β-asarone ether effectively decreased the formation of SPs in
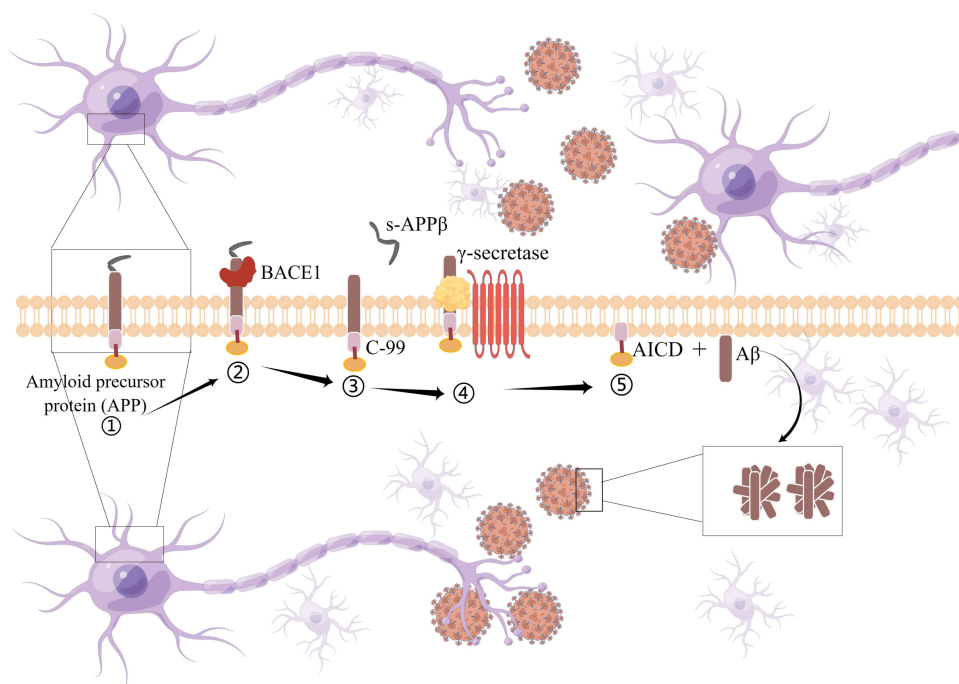
Figure 1 How extracellular β-amyloid deposition occurs. Amyloid precursor protein (APP) is cleaved by β-secretase to produce the transmembrane 99-residue C-terminal fragment (C99). This C99 fragment is then processed by γ-secretase, leading to the release of the amyloid precursor protein intracellular domain (AICD) into the cytoplasm.

the hippocampal and cortical tissues of AD mice and improved the characteristic pathological manifestations of AD. Xiao et al[26] developed an in vitro cell model by overexpressing Aβ42 in the M146 cell line through stable transfection with the APP/PS1 gene. They conducted an intervention study using various concentrations of schisandrin b and observed that schisandrin b did not exhibit any toxicity toward M146 cells. Moreover, they found that medium and high doses of schisandrin b effectively reduced the production of Aβ42 in a dose-dependent manner. Zeng et al[27] conducted experiments on the N2a/APP695swe cell line, which is a specialized N2A cell line capable of producing its own Aβ deposition. The results of their study confirmed that schisandrin b reduces BACE1 activity and APP miscleavage by inhibiting BACE1 transcription and translation. This ultimately leads to a reduction in Aβ production and this study provides a new mechanism for schisandrin b in regulating Aβ metabolism. Chen Qin et al[28] established an AD model by injecting cohesive Aβ1-40 combined with gooseberry muscarinic acid into the right basal nucleus region of rats. After 30 days of intervention with senegenin, the results showed that it improved Aβ plaque deposition within the basal nucleus of Meynert and increased the number of neurons around plaques compared to the model group.[28] Transmission electron microscopy revealed significant improvements in the structural integrity of the nuclear bilayer, nuclear state, chromatin distribution, endoplasmic reticulum, and mitochondrial swelling. Based on these findings, it can be hypothesized that senegenin has a protective effect on AD.[28] The above evidence suggests that natural products of TCM may treat AD by inhibiting Aβ deposition.

TCM Natural Products Treat AD by Regulating ERK in Aβ Deposition

In recent years, studies have found that extracellular regulated protein kinases (ERKs) play a role in the development of AD pathology. Scholars conducted a comparison of the expression of ERK in the brain tissue of AD patients at different stages of the disease. The findings revealed that p-ERK levels were increased in white matter astrocytes in early AD patients, and the severity of the lesion showed a strong correlation with p-ERK levels.[29] Moreover, in the brains of late-stage patients, p-ERK was significantly increased in neuronal cell cytosomes and neuronal protrusions around SPs.[29] QI et al[30] discovered that dysregulation of ERK2 alone can result in abnormal phosphorylation of Tau protein, which ultimately leads to the pathological process of AD. This finding provides strong evidence for the involvement of the ERK transduction pathway in the pathogenesis of AD. Li et al[31] induced an AD rat model by injecting Aβ1-40 into the right hippocampus. After intraperitoneal injection of low and high doses of curcumin, they observed that curcumin may influence the production and metabolism of Aβ by reducing the expression of ERK1 and ERK2 proteins, thereby potentially playing a neuroprotective role against neurotoxicity. In another study, curcumin was shown to strongly attract fibrillar Aβ. It also enhances the breakdown of Aβ in its β-folded form and has the ability to directly bind to free Aβ in the brains of AD patients, thereby reducing its accumulation.[32] Ma et al[33] utilized circular dichroism (CD) chromatography to examine the impact of water extract and its naphtha of acorus tatarinowii on the secondary structure of Aβ 25–35. The findings indicated a significant decrease in the α-helix structure of Aβ25-35 and a notable increase in the β-sheet structure over time.[33] After culturing the water extract and its naphtha of acorus tatarinowii with Aβ25-35, the β-fold structure disappeared, and there was a significant increase in α-helix content. When the 100% water extract and 100% naphtha of acorus tatarinowii were incubated together for 7 days, the α-helix content reached 100%.[33] These results suggest that a specific concentration of the water extract and its naphtha of acorus tatarinowii can effectively inhibit the transformation of Aβ25-35 from an α-helix to a β-fold structure.[33]

## TCM Natural Products Treat AD by Regulating PI3K/Akt in Aβ Deposition

The phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) signaling pathway is a well-known pathway found in various regions of the cerebral cortex, hypothalamus, and hippocampus. It can be activated or inhibited through different mechanisms.[34,35] In the brain, the PI3K/Akt signaling pathway plays a crucial role in various physiological functions, including synapse formation, neuronal cell growth, and survival.[36] This pathway can hinder the expression of enzymes necessary for Aβ degradation, resulting in reduced Aβ clearance. Additionally, increased expression of mammalian target of rapamycin (mTOR), a downstream component of the PI3K/Akt signaling pathway, inhibits cellular autophagy and leads to Tau protein phosphorylation. Zhang et al[37] conducted a study using APP/BACE transgenic AD model Drosophila and mouse neurons as subjects. They intervened with salidroside, a phenylpropanoid glycoside isolated from *Rhodiola rosea L.*, and assessed changes in lifespan and motor function in Drosophila using a lifespan assay and climbing test, respectively. The degree of Aβ aggregation in each group was measured using an immunofluorescence

assay. The results indicated that salidroside could reduce Aβ plaque aggregation by modulating the PI3K/Akt/mTOR signaling pathway, thereby providing protective effects against neurotoxicity. Additionally, Wang et al[38] demonstrated that salidroside could reduce Aβ levels and alleviate synaptic dysfunction in APP/PS1 double transgenic AD model mice by activating the PI3K/Akt/mTOR signaling pathway. Glycogen synthase kinase 3β (GSK3β) is a multifunctional serine/ threonine kinase that plays a critical role in regulating energy metabolism, cell growth, and apoptosis.[39] It acts as a key downstream substrate and effector of PI3K/AKT.[40] Another important protein involved in cellular processes is protein phosphodiesterase 2A (PP2A), which is encoded by the PPP2CA gene. PP2A is a heterotrimeric serine/threonine phosphatase that is implicated in cell cycle regulation, growth, metabolism, proliferation, and apoptosis. Notably, dysregulation of PP2A protein expression has been observed in neurodegenerative diseases.[41] In their study, Ma et al[42] investigated the effects of bilateral ventricular injections of Aβ25-35 to induce AD in rats. After 60 days of gavage treatment with astragalus polysaccharide, they observed that astragalus polysaccharide had the ability to repair hippo-campal damage in the model rats. Additionally, it was found to downregulate proteins such as APP, Aβ, p-tau, GSK3β, and BACE1 while upregulating the expression of the protein PP2A. These findings suggest that astragalus polysaccharide has a protective effect against the neurotoxicity caused by Aβ. Schematic representation of the PI3K/AKT/GSK-3β-mediated phosphorylation signaling pathway and its role in autophagy in AD was shown in Figure 2.

Natural TCM Products Treat AD by Regulating Transthyretin (TTR) in Aβ Deposition

Transthyretin (TTR) is a transport protein that is stably folded and exists as a homotetramer. It is present in the blood and cerebrospinal fluid. According to a study, TTR has the ability to bind to Aβ and inhibit its aggregation through the hydrophobic T4 region.[43] In their experiment, Lin et al[44] used a combination of 120 mg/kg D-galactose and 10 mg/kg aluminum chloride to create an AD mouse model. They administered resveratrol orally for a period of 90 days, and the results revealed a significant improvement in cognitive function after intervention with resveratrol.[44] Additionally, there was a notable reduction in the positive expression of Aβ1-40 and Aβ1-42 in the cortical neuronal cells of the mouse brain.[44] In their study, Santos LM et al[45] utilized the AβPPswe/PS1A246E/TTR mouse model to investigate the effects of resveratrol intervention. After a two-month intervention, the researchers observed an increase in plasma TTR protein
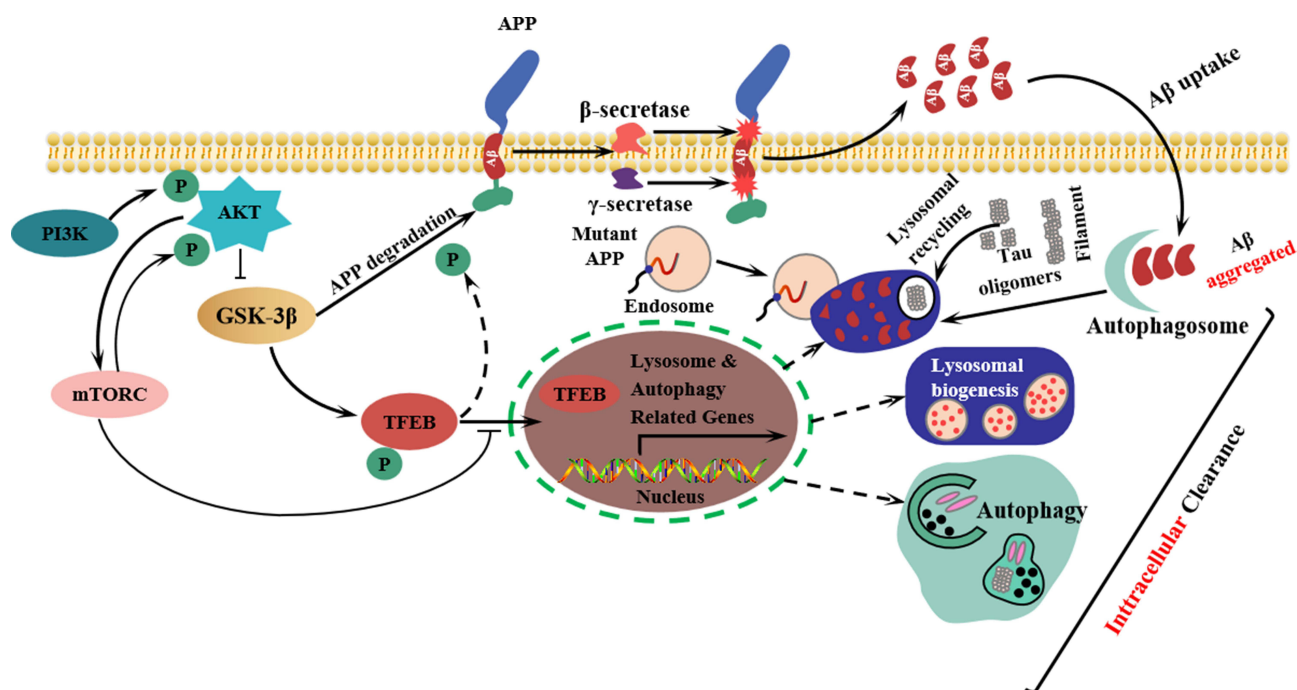
Figure 2 Schematic representation of the PI3K/AKT/GSK-3β-mediated phosphorylation signaling pathway and its role in autophagy in AD. Endosomes are membrane-enclosed organelles found in animal cells. Their primary function is to transport substances that are newly ingested through endocytosis to lysosomes, where they are degraded.

expression levels in the mice treated with resveratrol.[45] They also found that resveratrol enhanced TTR tetramer stability, improved its ability to bind free Aβ peptides in the brain, and reduced Aβ aggregation in the brains of AD mice.[45] These results suggest that targeting TTR stability could be a potential therapeutic approach for AD.

TCM Natural Products Treat AD by Regulating Insulin-Degrading Enzyme (IDE) in Aβ Deposition

In organisms, insulin-degrading enzyme (IDE) plays a crucial role in insulin degradation.[46] Under normal conditions, microglia and astrocytes in the brain secrete IDE into the extracellular fluid, contributing to the degradation of extracellular Aβ.[47] The distribution of IDEs in neurons is more intricate. A study demonstrated that undifferentiated PC12 cells secrete a small amount of IDE extracellularly, while differentiated cells retain most of the IDE in the cell membrane and overexpress IDE intracellularly.[48] This leads to a significant decrease in the levels of Aβ40 and Aβ42, further emphasizing the vital role of IDE in Aβ degradation. Iwata et al[49] discovered that the expression levels of localized Neprilysin (NEP) were decreased in the aging brain, particularly in areas where symptoms related to disease appear early in patients with AD, such as the hippocampus and cortex. In their study, when NEP expression was increased twofold in the brain of an AD model, the deposition of Aβ was reduced eightfold. This suggests that increasing NEP expression can effectively reduce Aβ levels in the brain, highlighting the significant role of NEP in Aβ degradation.[49]

Lei et al[50] conducted a study using the APP/PS1 double transgenic AD mouse model and administered triptolide treatment for 45 days to investigate the effects of triptolide treatment. Immunohistochemical and Congo red staining combined with unbiased somatology methods were used to stain and quantify Aβ deposition and SP formation in the hippocampal region. The results demonstrated that triptolide dose-dependently inhibited Aβ deposition and SP formation, leading to reduced Aβ protein levels in the hippocampus. In a similar study, Cheng et al[51] also utilized APP/PS1 double transgenic AD model mice and administered triptolide for a 60-day intervention. Their findings revealed that triptolide promoted the degradation of Aβ and improved cognitive impairment in AD mice by upregulating IDE and NEP expression. In their study, Wang et al[52] focused on the APP/PS1 mouse model. After an 8-week treatment with triptolide, the researchers analyzed the brain tissues of mice in each group. They used enzyme-linked immunosorbent assay (ELISA) to measure the expression levels of Aβ40, Aβ42, glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), catalase (CAT), and the oxidative products of lipids and proteins, such as malondialdehyde (MDA). Additionally, they detected the levels of SPs and Iba1 in the cortex and hippocampus using immunohistochemistry. Furthermore, the researchers examined the expression of BACE1, APP, and NEP through Western blotting. The findings indicated that triptolide exhibited both anti-inflammatory and antioxidant effects. It achieved this by inhibiting the expression of BACE1, which is the rate-limiting enzyme for Aβ production, and increasing the expression of NEP, which is a key enzyme for Aβ degradation. According to Huang et al[53] N-butanol (NB) of radix notoginseng had positive effects on PC12 cell proliferation and protection against Aβ25-35-induced PC12 cytotoxicity in vitro. In their in vivo experiments, they observed that NB improved spatial learning and memory deficits in rapidly aging SAMP8 mice by inhibiting the expression of APP and BACE1 in their brains. Additionally, NB extract reduced SOD and GSH-PX activities, thereby attenuating oxidative stress levels and reducing Aβ production. The researchers also noted that NB exhibited lower toxicity in vivo,[54] suggesting its potential as an effective alternative to the current treatment of AD. Liu et al[55] conducted a study using AD model mice. They administered D-galactose combined with aluminum trichloride to the mice intraperitoneally for 90 days. Additionally, they administered low and high doses of ligustrazine for 40 days. The results of the study demonstrated that ligustrazine treatment significantly improved the learning and memory ability of the mice. Furthermore, the number of APP-positive cells in the hippocampus was significantly reduced, while the number of NEP-positive cells was significantly increased. This suggests that ligustrazine has the potential to enhance Aβ degradation and protect neurons in brain tissue by upregulating NEP expression. Panax notoginseng saponins (PNS), which have been widely used in the treatment of cardiovascular and cerebrovascular diseases, have also been found to have beneficial effects on nerve cell growth, axon lengthening, and synaptic plasticity. Liu et al[56] conducted a study in which they injected Aβ1-42 into the CA1 region of the hippocampus to establish a rat model of AD. They observed that this injection resulted in a decrease in the number of neurons in the CA1 and dentate gyrus regions of the hippocampus.[56] However, when panax notoginseng saponin Rg1 was administered, it reduced phosphorylation at the phosphorylation site APP-Thr668, lowered the expression of BACE1 and Psen1, and reduced Aβ production.[56] Additionally, the intervention

increased the expression of a disintegrin and metalloprotease domain-containing protein 10 (ADAM10) and IDE, which effectively rescued cognitive dysfunction and neuronal loss and promoted learning and memory abilities.[56]

Natural TCM Products Treat AD by Regulating Neurogenesis in Aβ Deposition

Neurogenesis is crucial in maintaining brain functions such as cognition and emotion regulation in the adult mammalian brain. Numerous studies have indicated that new hippocampal neurons can be generated during adulthood, a process referred to as neurogenesis.[57] In response to brain pathology, neural progenitor cells (NPCs) readily proliferate, migrate to areas of neurodegeneration, and contribute to neurogenesis and the repair of neural injuries.[58,59] In both Alzheimer's disease patients and animal models, dysregulation of NPC proliferation and self-renewal leads to abnormal neurogenesis.[54,60–62] According to Elena et al[57] neurogenesis is still observed in the brains of healthy individuals up to the age of 90. However, in patients with AD, the generation of new neurons is significantly reduced. In ancient China, *Ganoderma lucidum (Leyss. Ex Fr.) Karst.* was revered as an immortal herb due to its purported effects on immortality and rejuvenation. Several studies have demonstrated that the aqueous extract of *Ganoderma lucidum (Leyss. Ex Fr.) Karst.* can stimulate neuronal differentiation and promote neurite growth in PC12 cells. Additionally, it has been found to possess hypnotic and antidepressant effects in vivo.[63–65] Qin et al[66] demonstrated that treatment of APP/PS1 mice with a ganoderma lucidum preparation resulted in a significant increase in the number of naive neuronal cells in the hippocampus and dentate gyrus compared to the AD model group. Additionally, cerebellar neural stem cells appeared early and in high numbers.[66] The nucleus membrane remained intact, along with the cytoplasmic mitochondria, endoplasmic reticulum, Golgi apparatus, microtubular structures, and synapses.[66] Moreover, no abnormalities were observed in microglia.[66] Huang et al[67] conducted a study in which they discovered that oral administration of ganoderma lucidum polysaccharides and aqueous extracts had a positive effect on the proliferation of NPCs and hippocampal neurogenesis in APP/PS1 mice. This administration also helped reduce cognitive deficits. Further investigations revealed that ganoderma lucidum polysaccharides enhanced the activation of fibroblast growth factor receptor 1 (FGFR1), along with the downstream ERK and AKT cascades.[67] These findings indicate that ganoderma lucidum polysaccharides could potentially be used as therapeutic agents for the regenerative treatment of cognitive decline associated with neurodegenerative diseases.

TCM Natural Products Treat AD by Regulating Apoptosis in Aβ Deposition

Apoptosis, also known as programmed cell death, is a highly regulated process involving enzymes, genes, and specific protein families. The Bcl-2 family and caspase family play crucial roles in apoptosis. The Bcl-2 family includes both pro-apoptotic genes such as Bax and Bak and anti-apoptotic genes such as Bcl-2 and Bcl-xL. Bax can form homodimers (Bcl-2/Bcl-2, Bax/Bax) or heterodimers (Bcl-2/Bax) with Bcl-2, inhibiting the anti-apoptotic function of Bcl-2.[68,69] Caspase family enzymes serve as marker enzymes indicating the initiation of apoptosis, with Caspase3 playing a particularly crucial role. When activated, Caspase3 triggers a cascade of reactions that ultimately result in apoptosis.[70,71] Furthermore, the Bcl-2 family is capable of inducing apoptosis by modulating the mitochondrial membrane potential, releasing cytochrome c (Cytc), activating downstream factors of Caspase3, and ultimately leading to apoptosis.[72] Liu et al[73] conducted a study that demonstrated the potential of total saponin from anemarrhena asphodeloides in reducing the rate of Aβ25-35-induced apoptosis in PC12 cells. This effect was achieved by downregulating the expression levels of Bax mRNA and protein. Similarly, Yin Gang et al[74] investigated the impact of cistanche polysaccharide on neuronal cells injected with intracerebral Aβ. Their findings revealed that cistanche polysaccharide effectively inhibited the toxicity of Aβ injection, promoted the expression of Bcl-2 protein, suppressed the activation of Caspase-3 factor, and reduced neuronal apoptosis in rats with Aβ25-35-induced AD. In a study by Roland et al[75] total cistanche glycosides (*GCs*), including echolin and vermiculin, were administered to a rat model of AD induced by bilateral hippocampal injection of Aβ25-35 for 14 days. The researchers observed that the neuronal structure of the hippocampal CA1 region in the rats remained largely normal, and no apoptotic or necrotic cells were detected.[75] Further analysis revealed that in the neuronal cells of the model group, the nuclear border was disrupted, the cell matrix exhibited unevenness, and the coarse endoplasm showed signs of degranulation.[75] The synaptic structure appeared blurred, with the synaptic gap disappearing and the anterior and posterior synaptic membranes becoming unclear. Additionally, the synaptic vesicles exhibited vacuole-like changes.[75] The neural progenitor fibers and microtubules were observed to be disorganized.[75] In glial cells, the nuclear matrix appeared pale, and the mitochondria exhibited vacuole-like changes.[75] *GCs* could reverse the

aforementioned pathological changes, indicating a protective effect of *GCs* on hippocampal neurons.[75] Xiao et al[76] utilized the human APP and mutant PS1 gene double-transfected CHO cell line M146L as a model. They observed that intervention with Guangdong Haifengvine polysaccharide did not result in any cytotoxic effects. Moreover, they found that high and medium doses of the polysaccharide were able to significantly inhibit the production of Aβ42. Xue et al[77] conducted a study to investigate the effects of wogonoside on antioxidant enzyme activity and the accumulation of ROS in H_2O_2 induced SH-SY5Y and PC12 cells. The results showed that wogonoside enhanced the activity of the antioxidant enzyme GSH and reduced the accumulation of ROS by regulating the NRF2/HO-1 signaling pathway, which is associated with oxidative stress.[77] In addition, wogonoside was found to downregulate Bax, upregulate Bcl-2 protein expression, elevate the Bcl-2/Bax ratio, and inhibit apoptosis in Aβ25-35-induced SH-SY5Y and PC12 cell injury models.[77] In addition, wogonoside upregulated the expression of synaptic-related proteins such as synapsin-1, synapto-physin, postsynaptic density 95 (PSD95), and brain-derived neurotrophic factor (BDNF), which improved neuronal cell function and provided a protective effect. Moreover, further in vivo experiments demonstrated that wogonoside significantly reduced the levels of Aβ1-40 and Aβ1-42 in the cerebral cortex and hippocampus of APP/PS1 mice after 60 days of gavage administration.[77] This confirmed that the neuroprotective mechanism observed in vitro was consistently effective in vivo.

Hu et al[78] conducted a study using 25 mmol/L L-glutamic acid (L-Glu) to induce neurotoxicity in HT22 cells. They found that intervention with different concentrations of phillyrin could prevent apoptosis and mitochondrial membrane potential imbalance induced by L-Glu.[78] Further in vivo studies using APP/PS1 double transgenic mice showed that phillyrin inhibited the expression of pro-apoptotic proteins such as Bad, Bax, and Bid while promoting the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-XL.[78] This led to a reduction in neuronal cell apoptosis, decreased Aβ deposits in brain tissues, and improved learning and memory ability in AD mice.

Natural TCM Products Treat AD by Regulating the blood–brain Barrier (BBB) in Aβ Deposition

There are various methods to clear Aβ in the brain, with the most significant one being the blood brain barrier (BBB) pathway.[79] When BBB function is impaired, Aβ clearance is reduced, leading to the accumulation of Aβ in the brain parenchyma. This abnormal accumulation can further disrupt BBB permeability and worsen its dysfunction. Diagram of the association between the breakdown of the BBB and AD was shown in Figure 3. The key proteins involved in this pathway are the receptor of advanced glycation end products (RAGE), ATP-binding cassette transporter (ABC), and low-density lipoprotein receptor-related protein-1 (LRP-1). Among these, RAGE is responsible for transporting Aβ from peripheral blood to the brain, and this transportation is achieved through synergy with ABC and LRP-1.[80] LRP-1, a signaling receptor produced by neuronal cells, plays a crucial role in the transport of Aβ across the BBB and its subsequent clearance. When Aβ binds to the LRP-1 ligand, it forms a complex that facilitates the transport of Aβ out of the brain and into the circulation. This complex also coactivates inflammatory pathways with insulin in the liver, enhancing the clearance of Aβ.[81] Additionally, the LRP-1 endocytic complex translocates to the lysosome for degradation.[82] Autopsy findings from a study on AD patients revealed lower levels of LRP-1 and increased accumulation of Aβ in brain tissue compared to normal aging brain tissue.[83] According to Hongda et al[84] baicalin intervention for 16 weeks resulted in the upregulation of LRP-1 protein expression in the hippocampal region of APP/PS1 double transgenic AD model mice. This intervention also led to a reduction in Aβ1-42 deposition and microvascular injury, as well as an increase in Aβ transport metabolism across the BBB. The study demonstrated that baicalin could enhance LRP-1 expression in neuronal cells and facilitate the outward transport of Aβ through the BBB. As a result, Aβ deposition in the brain was reduced, learning and memory ability improved, and the development of AD was prevented.

TCM Natural Products Treat AD by Regulating microRNAs in Aβ Deposition

MicroRNAs (miRNAs) are small noncoding RNAs that regulate endogenous genes. Their main role is to inhibit the translation or promote the degradation of mRNAs.[85] Pharmacological studies have demonstrated that miRNAs can regulate various physiological processes in the body and can serve as diagnostic markers for many diseases.[86] Recent research has revealed that the occurrence of AD is linked to abnormal expression of multiple miRNAs.[86] Lin Ying et al[87] utilized gene microarray technology to screen for differentially expressed miRNAs following osthole intervention in APP/PS1 mice. Their findings revealed an upregulation in the expression of miRNA-9. Furthermore, when the miRNA-9 inhibitor was introduced into the
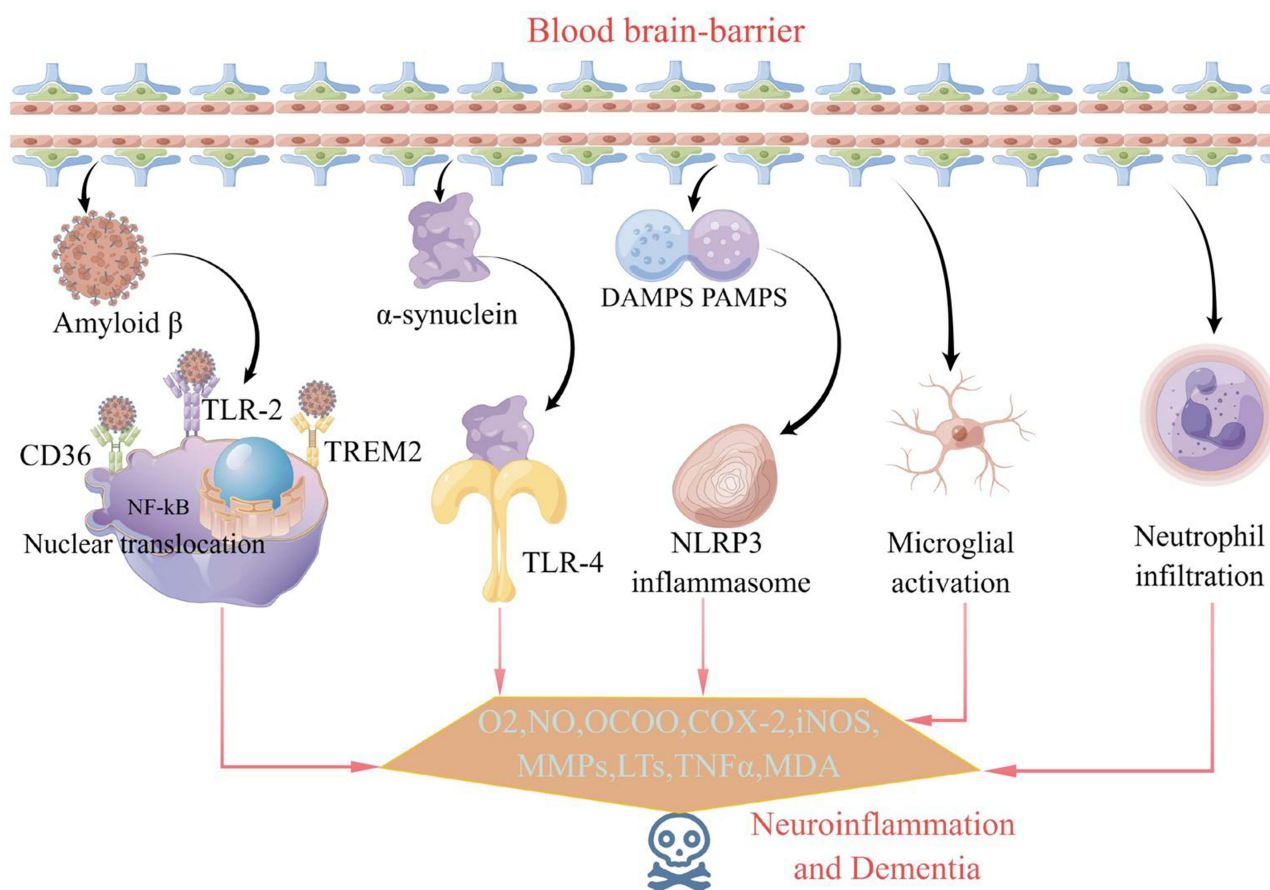
**Figure 3** Diagram of the association between the breakdown of the BBB and AD.

AD cell model with high APP expression (SHSY-5Y), there was an observed elevation in BACE1 protein expression. However, upon administration of osthole, the expression of BACE1 protein was reduced. These results indicate that osthole inhibits BACE-1 activity and decreases Aβ production through the upregulation of miRNA-9.

Therefore, natural products of herbal medicine have been found to have several beneficial effects in promoting Aβ degradation. The mechanisms by which natural products affect Aβ deposition are shown in Table 1. These effects include inhibiting the activity of β-secretase and reducing the expression of the Aβ precursor protein APP. Additionally, they can increase the stability of TTR and upregulate the expression of the Aβ-degrading enzymes IDE and NEP. Furthermore, these natural products promote NPC proliferation, enhance hippocampal neurogenesis, regulate cell autophagy and apoptosis, maintain BBB stability, and regulate noncoding small RNA expression of endogenous genes. All of these mechanisms work together to reduce Aβ content and decrease its neurotoxicity, ultimately leading to an improvement in cognitive dysfunction.

Inhibition of Tau Protein Hyperphosphorylation by Natural Products of Traditional Chinese Medicine

The pathology of AD is characterized by the loss of synapses and neurons, progressive impairment of cognitive function, and accumulation of Aβ and NFTs in the brain. NFTs are specifically caused by hyperphosphorylation of the intracellular microtubule-stabilizing protein known as Tau protein. The severity of clinical dementia symptoms is directly correlated with the amount of NFTs.[88] In recent years, researchers have made efforts to treat AD by focusing on inhibiting Aβ protein aggregation or enhancing its clearance. However, these attempts have not succeeded in reversing AD or slowing down its progression. Notably, the failure of Phase III clinical trials for monoclonal antibodies such as solanezumab and bapineuzumab, which target Aβ clearance, has raised doubts among scholars regarding the effectiveness of Aβ as a

Table 1 The Mechanisms of Natural Products in the Deposition of Aβ Deposition

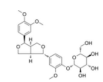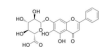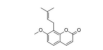| Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Animal Models	Mechanism of Action/Effectiveness	References
Tanshinone	*Salvia miltiorrhiza Bunge*	$C_{18}H_{12}O_3$	276.286		568–73-0	D-galactose intraperitoneal injection of senescence combined with Aβ1-40 injection in the hippocampus	Shortened the latency period of escape and the number of misfiring into the blind end in VD and AD rats	[22]
Ginsenoside Rg2	*Panax ginseng C. A. Meyer*	$C_{42}H_{72}O_{13}$	785.013		52,286–74-5	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Inhibition of SP formation due to Aβ deposition	[23]
Berberine	*Coptis chinensis Franch*	$C_{20}H_{18}NO_4^+$	336.361		2086–83-1	APP/PS1 double transgenic AD mice	Inhibition of Aβ42 expression and aggregation deposition to form SPs	[24]
β-asarone ether	*Acorus tatarinowii Schott*	$C_{12}H_{16}O_3$	208.254		5273–86-9	5×FAD transgenic mice	Reduction of SP production in hippocampal and cortical tissues	[25]
Schisandrin b	*Schisandra chinensis*	$C_{23}H_{28}O_6$	400.465		61,281–37-6	Stable transfection of M146 cell line and N2a/APP695swe cell line	Inhibition of BACE1 transcription and translation, reduction of BACE1 activity and APP miscleavage	[26,27]
Senegenin	*Polygala tenuifolia Willd.*	$C_{30}H_{45}ClO_6$	537.128		2469–34-3	Targeted injection of cohesive Aβ1-40 combined with gooseberry muscarinic acid in the right basal nucleus region inSD rats	Improved Aβ deposition and plaque deposition within the basal nucleus of Meynert and increased the number of neurons around the plaques.	[28]
Curcumin	*Curcuma longa Linn.*	$C_{21}H_{20}O_6$	368.380		458–37-7	Right hippocampal injections of Aβ25-35 induced in SD rats; AD patients	Reduced ERK1 and ERK2 protein expression, thereby affecting Aβ production and metabolism	[31,32]
Water extract and its naphtha of acorus tatarinowii	*Acorus tatarinowii Schott*	–	–	–	–	–	Prevented the conversion of Aβ 25–35 from α-helix to β –fold	[33]
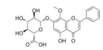
| Salidroside	Rhodiola rosea Linn.	$C_{14}H_{20}O_7$	300.304		10,338–51-9	APP/BACE transgenic AD model Drosophila and mouse	Activated PI3k/Akt/mTOR signaling pathway to enhance autophagy and reduce Aβ plaque aggregation; Alleviated synaptic dysfunction.	[37,38]
Astragalus polysaccharide	Astragalus membranaceus	$C_{10}H_7CIN_2O_2S$	254.6928		89,250–26-0	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Downregulation of protein (APP, Aβ, p-tau, GSK3β and BACE1) expression and upregulation of protein PP2A expression.	[42]
Resveratrol	Reynoutria japonica Houtt.	$C_{14}H_{12}O_3$	228.243		501–36-0	Construction of AD mouse model with D-galactose combined with aluminum chloride; Aβ PPswe/PS1A246E/TTR AD mouse model	Increased TTR protein expression level and TTR tetramer stability, enhanced the ability to bind to free Aβ peptide in the brain, and reduced Aβ aggregation.	[44,45]
Triptolide	Tripterygium wilfordii Hook. f.	$C_{20}H_{24}O_6$	360.401		38,748–32-2	APP/PS1 double transgenic AD mice	Inhibition of Aβ deposition and SP formation in the hippocampal region of APP/PS1 mice.	[50]
Triptolide	Tripterygium wilfordii Hook. f.	$C_{20}H_{24}O_6$	360.401		38,748–32-2	APP/PS1 double transgenic AD mice;	Upregulated IDE and NEP expression and enhances Aβ degradation; Inhibited BACE1 expression and increased NEP expression.	[51,52]
N-butanol of Radix Notoginseng	Panax pseudo-ginseng Wall. var. notoginseng (Burkill)Hoo & Tseng	–	–	–	–	Aβ 25–35 induced in PC12 cells; SAMP8 mice	Promoted cell proliferation; Inhibits APP and BACE1 expression, decreases SOD and GSH-PX activity, and reduces Aβ production.	[53,54]
Ligustrazine	Ligusticum chuanxiong Hort.	$C_8H_{12}N_2$	136.19		1124–11-4	Intraperitoneal injection of D-galactose combined with aluminum in SD rats	Upregulated NEP expression, promoted Aβ degradation.	[55]

(*Continued*)

Table 1 (Continued).

Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Animal Models	Mechanism of Action/Effectiveness	References
Panax notoginseng saponin Rg1	*Panax pseudo-ginseng Wall. var. notoginseng (Burkill)Hoo & Tseng*	–	–	–	–	Hippocampal CA1 area injection of Aβ1-42 in SD rats	Decreased phosphorylation of phosphorylation site APP-Thr668; downregulated expression of BACE1 and Psen1 to reduce Aβ production; upregulated expression of ADAM10 and IDE to promote Aβ degradation.	[56]
Ganoderma lucidum preparation	*Ganoderma lucidum (Leyss. Ex Fr.) Karst.*	–	–	–	–	APP/PS1 double transgenic AD mice	Increased the number of naive neuronal cells in the hippocampus, promoted cerebellar neural stem cell generation	[66]
Ganoderma lucidum Polysaccharides	*Ganoderma lucidum (Leyss. Ex Fr.) Karst.*	–	–	–	–	APP/PS1 double transgenic AD mice	Enhanced activation of FGFR1 and downstream extracellular signal-regulated kinase ERK and AKT cascades promotes NPC proliferation and hippocampal neurogenesis.	[67]
Total saponin of Anemarrhena asphodeloides	*Anemarrhena asphodeloides Bunge*	–	–	–	–	Aβ25~35 induced PC12 cells	Inhibition of Bax mRNA and protein expression levels attenuated Aβ25-35-induced apoptosis.	[73]
Cistanche polysaccharide	*Cistanche deserticola Ma*	–	–	–	–	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Promoted Bcl-2 protein expression, inhibits Caspase-3 factor activation, and attenuates Aβ-induced neuronal apoptosis.	[74]
Total cistanches glycosides	*Cistanche deserticola Ma*	–	–	–	–	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Alleviated the pathological changes and ultrastructural damage of damaged nerve cells.	[75]
Guangdong Haifengvine Polysaccharide	*Piper kadsura (Choisy) Ohwi*	–	–	–	–	Human APP and mutant PS1 gene double transfected with M146L	Inhibition of Aβ42 production	[76]

Wogonoside	*Scutellaria baicalensis Georgi*	$C_{22}H_{20}O_{11}$	460.388		51,059–44-0	H_2O_2 and Aβ25-35-induced SH-SY5Y and PC12 cells; APP/PS1 double transgenic AD mice	Regulated Nrf2/HO-1 signaling pathway and inhibited cell apoptosis. Also upregulated the expression of Synapsin-1, Synaptophysin, PSD95 and BDNF to improve neural cell function.	[77]
Phillyrin	*Forsythia suspensa (Thunb.) Vahl*	$C_{27}H_{34}O_{11}$	534.552		487–41-2	Glutamate induced HT22 cells; APP/PS1 double transgenic mice;	Inhibited the expression of pro-apoptotic proteins such as Bad, Bax and Bid, and promoted the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-XL.	[78]
Baicalin	*Scutellaria baicalensis Georgi*	$C_{21}H_{18}O_{11}$	446.361		21,967–41-9	APP/PS1 double transgenic AD mice	Upregulation of LRP-1 protein expression in neuronal cells promotes Aβ transport outward through the BBB	[84]
Osthole	*Cnidium monnieri(L.) Cuss.*	$C_{15}H_{16}O_3$	244.286		484–12-8	APP/PS1 double transgenic AD mice; SHSY-5Y cells	Inhibition of BACE-1 activity and reduction of Aβ production by upregulating of miRNA-9.	[87]

therapeutic target.[89–91] Currently, there is a growing interest among researchers in investigating the inhibition of Tau protein phosphorylation and aggregation as a possible target for therapeutic interventions. Tau proteins belong to a class of proteins that play a crucial role in stabilizing microtubules within neurons. They are believed to be vital for the assembly and stabilization of the microtubule cytoskeleton, particularly in axons, dendrites and other parts of neurons. In their soluble form, Tau proteins effectively stabilize and bind microtubules, preventing their depolymerization and maintaining normal physiological functions.[92] Overphosphorylated Tau proteins weaken their binding to microtubules, which results in the destruction of the cytoskeleton. Additionally, they shed and aggregate to form paired helical filaments and further aggregate to form NFTs.[93] These abnormal aggregations impede synaptic transport and cause neuronal degeneration, ultimately leading to the development of AD.[94] Therefore, the hyperphosphorylation of tau protein is widely recognized as a crucial early event in the pathogenesis of AD.

Tau is a protein that is prone to phosphorylation and contains 21 abnormal serine/threonine phosphorylation sites (Ser46, Thr123, Ser198, Ser199, Ser202, Thr205, Ser208, Ser210, Thr212, Thr217, Thr231, Ser235, Ser262, Ser396, Ser400, Thr403, Ser404, Ser409, Ser 412, Ser413, and Ser422). The presence of these different phosphorylation sites reflects the progression of the disease. Schematic representation of disease-associated phosphorylation sites in tau was shown in Figure 4. In the early stages of AD, NFTs have not yet formed, and the phosphorylation sites are mainly found at Ser199 and Ser422. As the disease progresses, there is increased phosphorylation of the Ser202 and Thr205 sites. The phosphorylation of the Thr231 site indicates the presence of more mature p-Tau assemblies, leading to the advancement of AD. A recent study discovered a pattern of "dependent regulation" in the phosphorylation of Tau proteins. This means that the phosphorylation of Thr50, Thr69, and Thr181 can regulate the phosphorylation of other sites and consequently affect the overall phosphorylation level of Tau proteins.[95] Intracellular phosphorylation and dephosphorylation of Tau protein are balanced and primarily controlled by intracellular protein kinases and protein phosphatases. Protein kinases catalyze the phosphorylation of Tau protein, while protein phosphatases dephosphorylate abnormally phosphorylated Tau proteins. This process restores the biological activity of Tau protein and reduces the production of NFTs.[96] The protein kinases responsible for phosphorylation reactions in vivo are serine/threonine kinases. These kinases can be classified into proline-directed kinase (PDPK) and nonproline-directed kinase (NPDPK), depending on whether the substrate catalyzing tau protein phosphorylation requires proline. The three most significant tau protein phosphorylation kinases
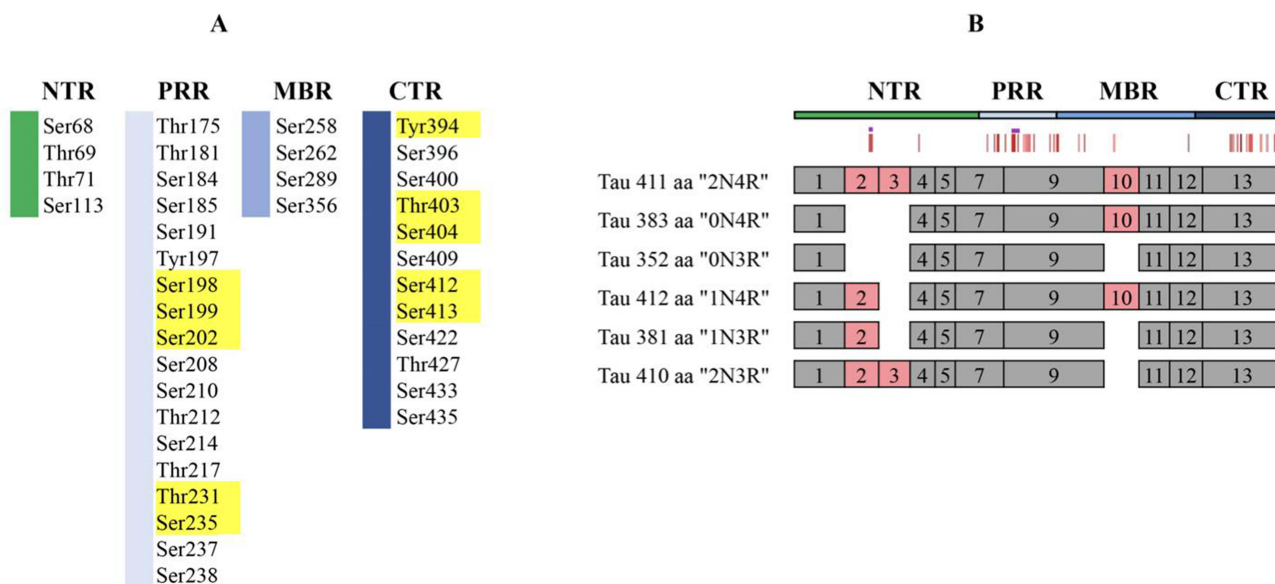
Figure 4 Schematic representation of disease-associated phosphorylation sites in tau. (**A**) The distribution of tau phosphorylation sites in Homo sapiens (441 aa CNS isoform) was determined by mass spectrometry of PHF tau. Different tau regions are indicated in various colors, with major phosphorylation sites shown in yellow. (**B**) Schematic representation of splice isoforms of tau in the CNS is provided, with alternatively spliced exons indicated as red boxes. The vertical red lines on top represent the phosphorylation sites listed in (**A**). Reprinted from Trushina NI, Bakota L, Mulkidjanian AY et al. The Evolution of Tau Phosphorylation and Interactions. *Front Aging Neurosci.* 2019;11:256. Creative Commons.[99]

identified thus far are cyclin-dependent kinase-5 (CDK-5), glycogen synthase kinase-3 (GSK-3), and cyclic-AMP dependent protein kinase A (PKA).[97] PKA plays a crucial role in the early stages of tau protein hyperphosphorylation and in the initial stages of AD pathogenesis. It catalyzes the phosphorylation of three phosphorylation sites of tau protein: Ser214, Ser262, and Ser409. Once PKA phosphorylates tau protein, it can impact the phosphorylation of tau protein by other protein kinases.[97] A study found that prephosphorylation of tau protein with PKA (NPDPK) enhanced the efficiency of GSK-3/CDK-5 (PDPK) phosphorylation of tau protein and even replicated NFT-like structures.[98] In vivo studies demonstrated that coactivation of PKA (NPDPK) and GSK-3/CDK-5 (PDPK) led to more rapid activation of the tau protein phosphorylation sites ser-199/202 and ser-396/404 by GSK-3/CDK-5. This activation is likely facilitated by the activation of the tau protein phosphorylation sites Ser-262 and Ser-214 of PKA (NPDPK), which alters the biological properties of tau protein as a substrate and increases the likelihood of phosphorylation at corresponding sites by GSK-3/CDK-5 (PDPK), etc.[99] The above findings suggest that the phosphorylation of all 21 phosphorylation sites of tau protein may require the combined action of multiple phosphorylation kinases, including NPDPK and PDPK.

Li et al[100] utilized the okadaic acid (OA)-induced rat culture brain slice method to establish an AD model of Tau protein hyperphosphorylation. The findings revealed a significant decrease in the expression of PKA and P-tau following the administration of ginsenoside Rg1 intervention compared to the model group. This suggests that ginsenoside Rg1 effectively mitigates OA-induced Tau protein hyperphosphorylation, leading to a reduction in the production of NFTs. Li et al[101] conducted an experiment in which they injected Aβ25-35 into the left ventricle of SD rats to create an AD model. They then administered panax notoginseng saponin Rg1 as an intervention for 28 days. The results showed that panax notoginseng saponin Rg1 reduced the expression of tau protein phosphorylation at the key site Thr231 in the DG, CAl, and CA3 regions of the hippocampus. Additionally, it decreased the overall level of Tau protein phosphorylation in the hippocampus.

TCM Natural Products Treat AD by Regulating Kinases in Tau Protein Hyperphosphorylation

GSK-3 is an important proline-directed protein kinase responsible for phosphorylating multiple sites on the tau protein, including Thr181, Ser199, Ser202, Thr205, Thr212, Thr217, Thr231, Thr235, Ser396, Ser404, and Ser422. The activity of GSK3β is primarily regulated by phosphorylation at two sites: tyrosine (Tyr216) and serine (Ser9). GSK3β is activated when the Tyr216 site is phosphorylated, while its activity is inhibited when the Ser9 site is phosphorylated. In their study, Sun et al[102] investigated the effects of curcumin on APP/V717 double transgenic mice. They observed that after 8 weeks of curcumin intervention, the positive expression of Aβ and P-tau protein in the brain tissues of mice was reduced. Additionally, curcumin also decreased the mRNA content of Aβ and P-tau protein. Wang et al[103] conducted further research on an animal model of AD that was induced by Tau hyperphosphorylation through OA. This study examined the effects of curcumin-macrophage exosome (Exo-cur) intervention. The results demonstrated that Exo-cur interacts with endothelial intercellular adhesion molecule 1 (ICAM-1) through lymphocyte function-associated antigen 1 (LFA-1). This interaction facilitated Exo-cur's ability to penetrate the BBB and reduce Tau hyperphosphorylation. The reduction in Tau hyperphosphorylation was achieved by inhibiting the AKT/GSK-3β signaling pathway, leading to neuroprotective effects. The study also revealed that overactivation of GSK-3β can cause hyperphosphorylation of Tau by regulating the Ser-396 site. This, in turn, promotes microtubule depolymerization and the formation of NFTs. These processes disrupt cellular metabolism and affect the transport of substances between axons and dendrites.[104,105] Under normal conditions, the intracellular Akt/GSK3β pathway is inhibited to maintain the normal physiological function of the Tau protein. Chronic cerebral hypoperfusion is a frequently observed pathophysiological process in both AD and vascular dementia. Studies have indicated that 40% of AD patients exhibit cerebrovascular pathology, indicating a substantial connection between AD and vascular dementia. Yan et al[106] conducted a study using a bilateral common carotid artery ligation (2VO) model with *a*ngelica sinensis intervention for 28 days. The study revealed that the levels of hippocampal phosphorylated Tau (Thr231), phosphorylated Tau (Ser396), and phosphorylated Tau/Tau expression were significantly higher in the 2VO group than in the sham-operated group. However, these levels were significantly lower in the low- and high-dose angelica sinensis groups. Further studies have shown that angelica sinensis has the ability to suppress Tau protein hyperphosphorylation and Aβ production in the hippocampus of rats with chronic cerebral hypoperfusion. This leads to a delay in the progression of AD-like changes. The mechanism behind this effect involves the inhibition of the Akt/GSK3β pathway and the promotion of BACE-1 and BDNF expression. BDNF is a crucial peptide hormone in the

mammalian central nervous system that plays a significant role in promoting the survival, growth, and maintenance of neural network plasticity. It does so by binding to Trk tyrosine kinase transmembrane receptors. During early development, high levels of BDNF expression are necessary for hippocampal neurons to maintain synaptic integrity and dendritic spine stability.[107]

Several studies have shown that abnormalities in the Wnt/β-catenin signaling pathway play a significant role in the development of AD. The expression levels of β-catenin, GSK 3β, and transcription factor 7-like 1 (TCF7L1)/T-cell factor 3 (TCF3) in the Wnt/β-catenin signaling pathway differed significantly between the internal olfactory cortical area and the hippocampal area in AD patients compared to non-AD patients.[108] In a mouse model of AD, the early activation of the Wnt/β-catenin signaling pathway through the use of lithium has been found to promote the proliferation and differentiation of neural precursor cells and inhibit Aβ deposition in the hippocampal region of adult mice. During the progressive phase, lithium inhibits Aβ deposition in the hippocampal region of adult mice. However, it does not promote neural precursor cell proliferation.[109] The product encoded by the Wnt gene is secreted extracellularly and specifically binds to the frizzled protein receptor on neighboring or own cell surfaces. This binding forms a coreceptor with the LRP family, leading to the inhibition of intracellular GSK-3β. Additionally, the scaffolding protein Axin and adenomatous polyposis coli (APC) form a complex that increases the concentration of intracellular β-catenin. This elevated concentration allows β-catenin to enter the nucleus,[110] where it binds to TCF/lymphoid enhancer factor (LEF). This binding activates downstream transcription factors and leads to the transcription of target genes such as oncogene c (c-myc), cell cycle protein D (Cyclin D), and paired box gene 6 (Pax 6), among others.[111] When the Wnt signaling pathway is downregulated, the levels of GSK-3β, Axin, and APC complexes increase, leading to the degradation of β-catenin through N-terminal ubiquitination. This highlights the central role of β-catenin in the classical Wnt signaling pathway.[112] Huo et al[113] conducted a study to demonstrate the effects of ligustrazine on the hippocampal tissue of AD rats. The results showed that ligustrazine can downregulate GSK-3β expression, inhibit β-catenin degradation, and consequently inhibit Tau protein hyperphosphorylation. Additionally, ligustrazine was found to activate the Wnt signaling pathway and inhibit Aβ-induced neurotoxicity, thereby exerting neuroprotective effects. Yao et al[114] utilized D-galactose in combination with Aβ1~40 to establish an AD model. They observed that the positive staining of tau protein in the CA3 region of the hippocampus was reduced, while the positive staining of p-tau(Ser422) and p-tau(Ser396) proteins was significantly increased in the model group. In comparison to the model group, the *Cornus officinalis* polysaccharide group exhibited a significant decrease in the positive staining of p-tau(Ser422) and p-tau(Ser396) proteins, along with a notable increase in the positive staining of tau protein. In a study conducted by Su et al[115] it was discovered that administering *Cornus officinalis* polysaccharide to AD model rats for 30 days had a positive impact. The administration resulted in a decrease in the expression of p-tau(Ser422) phosphosites and a reduction in Tau protein hyperphosphorylation. This effect was achieved by inhibiting the expression of GSK-3β in the hippocampal CA1 region of AD rats. Li He et al[116] administered schisandra chinensis acidic polysaccharide as a drug through continuous gavage for 14 days. On the 8th day, they induced an AD model in SD rats by injecting Aβ25-35 into the lateral ventricle. The results indicated that in the hippocampal tissue of rats in the model group, there was an increase in the relative expression levels of Tau protein phosphorylation sites (Tau Ser199, Tau Ser396, and Tau Ser404) as well as GSK-3β and phosphorylated protein GSK-3β Tyr216. Additionally, the expression level of GSK-3β Ser9 was found to be decreased. Conversely, the SCP-A group exhibited the opposite trend, and these differences were statistically significant. The findings suggest that schisandra chinensis acidic polysaccharide has an anti-AD effect, which may be attributed to its ability to regulate GSK-3β activity and subsequently decrease the phosphorylation level of Tau protein.[116] In a study by Ni et al[117] 6-month-old APP/PS1 mice were selected and treated with osthole for 42 days. The findings revealed a significant reduction in the expression of p-tau (ser202) protein in the osthole group compared to the model group. Additionally, there were notable increases in the expression levels of PI3K, p-Akt/Akt, and p-Gsk3β/Gsk3β. These results suggest that osthole may regulate the activity of the PI3K/AKT/GSK-3β signaling pathway to reduce tau protein hyperphosphorylation.

Normal CDK-5 is primarily obtained by binding to its neuron-specific activator p35, which is crucial for normal cellular function. Previous studies have demonstrated that neurotoxic substances such as Aβ, glutamate, and oxidative stress can cause calcium inward flow and trigger the cleavage of p35 into p25.[118] The half-life of p25 is 5–10 times longer than that of p35. p25 is predominantly found in and around the nucleus, while p35 is concentrated in the cell

periphery and plasma membrane. Notably, the binding of p25 to CDK-5 leads to the constitutive activation of CDK-5 and the formation of a p25/CDK-5 complex. This complex hyperphosphorylates tau protein, reducing its ability to bind to microtubules, disrupting the cytoskeleton, and promoting neuronal apoptosis.[119,120] The abnormal expression levels of p25 in the brains of AD patients and its overexpression in transgenic mice result in tau protein hyperphosphorylation, neurofibrillary tangles, and the development of cognitive deficits.[121] In a study using the Aβ25-35-induced AD injury model in primary cultured cortical neurons, it was demonstrated that tanshinone IIA inhibits Aβ25-35-induced tau protein hyperphosphorylation by suppressing cytoplasmic p25 expression and CDK-5 activation.[121] In their study, Li et al[122] observed an increase in the expression of the GSK-3β phosphorylation site Tyr216 and a decrease in the expression of the Ser9 site in an Aβ1-42-induced injury model in AD rats. Additionally, the expression of unphosphorylated Tau1 protein was downregulated. Treatment with tanshinone IIA was found to restore the spatial learning and memory deficits induced by Aβ1-42, along with the aforementioned changes. This suggests that tanshinone IIA has the potential to inhibit tau hyperphosphorylation by modulating GSK-3β activation.

TCM Natural Products Treat AD by Regulating Phosphatases in Tau Protein Hyperphosphorylation

PKA plays a crucial role in catalyzing tau protein phosphorylation, either directly or indirectly. It can alter the conformation of tau protein, making it more susceptible to phosphorylation by protein kinases such as GSK-3β and CDK5. PKA achieves this by phosphorylating multiple sites on the tau protein.[123] PP2A, the most active phosphatase in neuronal cells, plays a crucial role in promoting the dephosphorylation of abnormally phosphorylated tau proteins. This process leads to the release of free tau proteins and restoration of their biological activity, resulting in the loosening of the NFT tangle structure.[124,125] Inhibitors of PP2A have been found to cause synaptic and dendritic loss of hippocampal neurons in AD rats, accompanied by hyperphosphorylation of tau proteins.[126] The interaction of PP2A and tau proteins in Alzheimer's disease is shown in Figure 5. Furthermore, studies have shown that PP2A activity in the brains of AD patients is lower than that in the brains of normal elderly individuals. These findings suggest that defective PKA and PP2A in neuronal cells of AD patients' brains
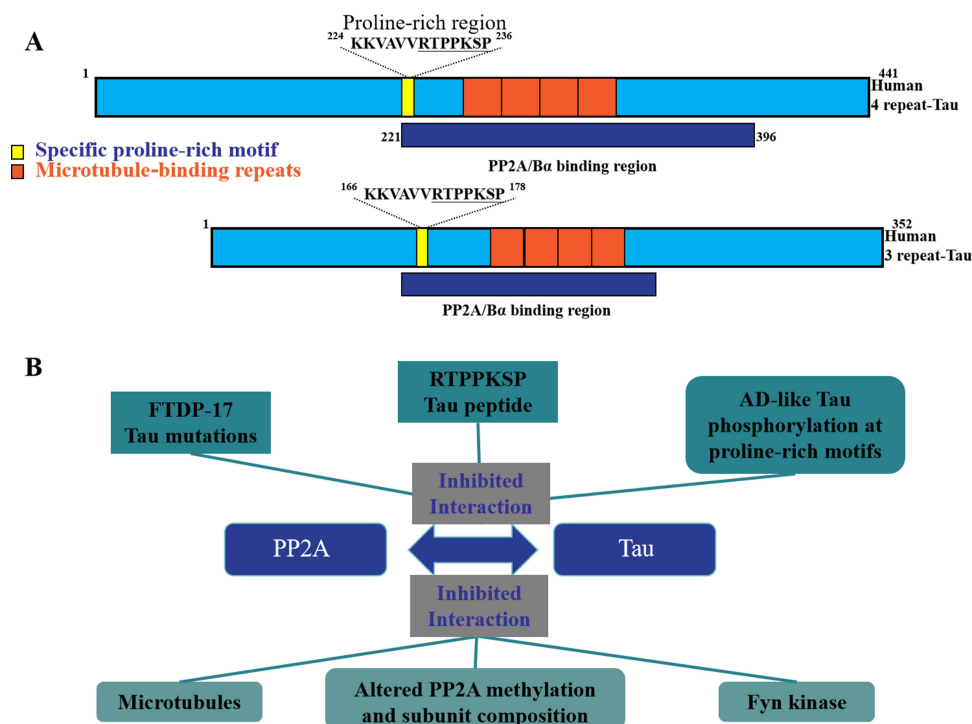
Figure 5 Deregulation of PP2A-tau protein–protein interactions in AD. ((**A**) The PP2A/Bα holoenzyme has the ability to directly interact with human tau isoforms that have three or four repeats. This interaction occurs through a domain that includes the microtubule-binding repeats, leading to the dephosphorylation of tau. A crucial role in regulating the protein–protein interactions between PP2A and tau is played by a specific proline-rich motif that contains the Thr231 phosphorylation site. (**B**) The PP2A-Tau protein–protein interaction can be inhibited in vitro by these six methods). Adapted from Sontag JM, Sontag E. Protein phosphatase 2A dysfunction in Alzheimer's disease. *Front Mol Neurosci.* 2014;7. Creative Commons.[127]

may be the primary cause of tau protein hyperphosphorylation. Xu et al[96] discovered that in the brain neurons of the Aβ1-40-induced AD model group, there was a notable increase in the total tau protein content, phosphorylation level of tau protein at the Ser396 site, and expression level of PKA protein compared to the control group. Conversely, the expression level of PP2A protein was significantly lower. However, after 30 days of senegenin administration, these effects were significantly reversed.

Chen et al[128] demonstrated that Banqiao Codonopsis Pilosula (BCP) effectively improves cognitive dysfunction in rats with AD induced by OA. The possible mechanism of action involves inhibiting the expression of PME protein in the hippocampus and increasing the methylation level of PP2Ac. This leads to a reduction in the demethylation and phosphorylation levels of PP2A, resulting in the upregulation of PP2A activity.[128] Consequently, the hyperphosphorylation of Tau protein is reduced by decreasing the phosphorylation levels of Tau protein phosphorylation sites pT181, pT231, pS396, and pS404.[128] Additionally, BCP enhances the expression levels of Synapsin-1, NMDA-2B, and Synaptophysin in hippocampal tissue by upregulating PP2A activity, promoting neuronal repair.[125] It is worth noting that the effectiveness of BCP may vary with the duration and dosage of use. Xie et al[129] discovered that *Trillium Tschonoskii Maxim* has the ability to enhance the methylation level of PP2Ac and decrease the demethylation level. Consequently, the inhibition of PP2A activity in the hippocampus of AD rats caused by OA can be effectively mitigated. This leads to a reduction in the level of Tau hyperphosphorylation induced by OA and an increase in the number of Nissl bodies in the hippocampus in a dose-dependent manner. Additionally, the duration of administration has a certain degree of correlation with these effects. rTg4510 mice are transgenic mice that express the P301L mutant tau protein. They have been developed as an animal model for tauopathy, including AD. In a study by Ma et al[130] it was demonstrated that cornel iridoid glycoside increased the activity of PP2A, elevated the levels of PP2Ac at leucine 309, decreased the phosphorylation of PP2Ac at tyrosine 307, and increased the protein expression of leucine carboxyl methyltransferase 1 (LCMT-1), protein tyrosine phosphatase 1B (PTP1B), and protein phosphatase 2A phosphatase activator (PTPA). These effects improved learning and memory abilities, prevented neuronal and synapse loss and reduced tau hyperphosphorylation and aggregation in the brains of rTg4510 mice.[130]

TCM Natural Products Treat AD by Enhancing Autophagy in Tau Protein Hyperphosphorylation

Autophagy is a highly conserved catabolic process that is mediated by lysosomes. Its main function is to remove abnormally folded proteins and senescent or damaged organelles, which is crucial for maintaining intracellular homeostasis.[131–134] Autophagic dysfunction has been implicated in various disorders, including neurodegenerative diseases.[135–139] The pathogenesis of AD is associated with multiple stages of autophagic damage, such as autophagosome maturation, autophagosome formation, and autophagosome-lysosome fusion. Certain AD-related genes, such as PS1, PS2, and phosphatidylinositol binding clathrin assembly protein (PICALM), have been found to impact autophagy and/or lysosomal function.[133] In AD mouse models, the lack of essential autophagy-related genes such as ATG7 affects the production and secretion of Aβ.[140,141] Autophagy has been shown to clear Aβ deposits, soluble tau proteins, and NFT polymers from neurons in animals with AD.[142] These findings suggest that autophagy plays a significant role in the pathogenesis of AD. LC3, originally known as microtubule-associated proteins 1A and 1B (MAP1LC3), is commonly used to monitor autophagy. During autophagy initiation, LC3-I is converted to LC3-II, and the amount of LC3-II corresponds to the number of autophagic vesicles, which diminishes as autophagy progresses.[143] Another crucial factor in autophagy induction is the Beclin 1 protein, which plays a central role in autophagy initiation.[144] Previous studies have demonstrated that the expression of Beclin 1 is decreased in patients with AD as well as in transgenic mice.[136,145] Moreover, the deletion of Beclin 1 has been found to enhance the accumulation of intracellular and extracellular Aβ, thereby accelerating the progression of AD.[137] Zhou et al[146] observed a noteworthy rise in the expression of autophagy-related protein p62 and a significant decline in the expression of Beclin-1 and LC3B in the hippocampus and cortex of Tau transgenic mice (TauP310L). This suggests that autophagy activity was significantly suppressed in Tau transgenic mice. In contrast, baicalin decreased the expression of p62 protein and increased the levels of Beclin-1 and LC3B, suggesting that baicalin enhances autophagy in transgenic mice. Additionally, baicalin was observed to reduce cellular aging in the hippocampus and cortex of Tau transgenic mice, enhance autophagy capability, decrease the formation of tau protein and phosphorylated tau protein, and ultimately improve cognitive dysfunction in Tau transgenic mice. Transcription factor EB (TFEB) is a crucial regulator of the autophagic lysosomal pathway.[147–149] In various animal

models of AD, TFEB overexpression has been shown to enhance autophagy, leading to the degradation of Tau protein and the improvement of cognitive function.[150–152] Yang et al[153] demonstrated that celastrol, a new TFEB activator, facilitates the translocation of TFEB from the cytoplasm to the nucleus. This activation enhances autophagy and lysosomal biological activity, specifically reducing insoluble phosphorylated Tau protein aggregates and promoting the degradation of phosphorylated Tau aggregates.

Natural products of TCM have been found to reduce Tau protein hyperphosphorylation, increase the dephosphorylation of abnormally phosphorylated Tau protein, restore the biological activity of Tau protein, and reduce the production of NFTs. This is achieved by inhibiting intracellular protein kinases such as PKA and GSK-3β or by promoting the expression of protein phosphatases such as PP2A and PP2B. The mechanisms of natural products in the deposition of Tau protein hyperphosphorylation are shown in Table 2. Additionally, these natural products can promote autophagy mediated by lysosomes, which helps remove abnormally folded proteins or senescent and damaged organelles. They can also facilitate the degradation of phosphorylated Tau aggregates, thereby reducing the formation of NFTs in brain tissue and potentially treating AD.

Microglia May Be Critical Intermediaries of Aβ–Tau Synergy

Evidence from multiple models and experimental settings presents compelling evidence for the synergistic interaction between Aβ and tau. In in vitro studies, the introduction of Aβ to human cells expressing tau (wild-type) led to the formation of tau aggregates known as paired helical filaments (PHFs), which are the principal components of tangles.[154] Moreover, the administration of Aβ (either synthetic or derived from the brain) into P301L-mutant tau mice via cortical and/or hippocampal injections not only expedited tangle development near the injection site but also in interconnected synaptic regions.[155,156]

The results from animal studies often indicate that tau hyperphosphorylation is a downstream change induced by Aβ. However, this is not the case clinically. It has been observed that in patients with cognitive impairment and negative hyperphosphorylated Tau (p-Tau) in cerebrospinal fluid, there is no correlation between cerebrospinal fluid Aβ content and cerebral cortical atrophy. On the other hand, the degree of cerebral atrophy is correlated with the expression of Aβ in cerebrospinal fluid in patients with positive p-Tau. This suggests that the presence of p-Tau is an essential factor for the effect of Aβ on cortical atrophy.[157,158]

Investigations revealed that the mere presence of Aβ lacked the ability to induce neuronal degeneration in the hippocampus lacking endogenous Tau protein. A separate examination demonstrated that solely reducing Aβ levels did not alleviate the impairments in learning and memory observed in AD mice. It was only through the reduction of both Aβ and Tau proteins that cognitive function in AD mice improved. The researchers discovered that levels of tau phosphorylation only correlated with cognitive performance when Aβ deposits were identified in the cerebrospinal fluid.[159] Several additional studies have demonstrated that alterations in glucose metabolism and brain atrophy in AD brains are attributable to the synergistic combination of Aβ and tau.[160] These findings strongly imply the existence of a highly intricate interplay between Aβ and tau, suggesting that the disease process is not solely driven by a causal effect. Combining anti-Aβ deposition with anti-tau-induced neurofibrillary tangles may potentially be the most effective therapeutic approach for AD.[157,158]

The TREM2 gene, which is expressed by microglia, has emerged as a prominent risk factor in the development of AD. The activation of microglia plays a crucial role as a neuropathological characteristic of AD.[161] It is responsible for releasing inflammatory factors such as interleukin-1β and tumor necrosis factor-α (TNF-α), as well as reactive oxygen and nitrogen species.[162] Similarly, microglial activation is also induced by the overexpression of tau, and this activation can be observed even before the formation of neurofibrillary tangles.[163] These findings suggest that microglia may act as potential mediators in the interaction between Aβ and tau. However, further investigations are required to determine the impact of differing genetic backgrounds of mouse models on microglial activation profiles and tau propagation patterns.

The spreading and bioactivity of tau in the presence of Aβ can be influenced by various factors. For instance, senescent oligodendrocytes near plaques can release cytokines that may activate microglia. This activation of microglia can lead to the uptake, processing, and subsequent release of tau in a more bioactive form. Neurons, possibly through an interaction with LRP1, can take up the released tau and then release it into the neuropil in a manner dependent on their

Table 2 The Mechanisms of Natural Products in the Deposition of Tau Protein Hyperphosphorylation

Natural Products/ Extracts	Natural Product/ Extract Source	Molecular Formula	Molecular Weight	Chemical Structure	CAS No.	Animal Models	Mechanism of Action/Effectiveness	References
Ginsenoside Rg1	*Panax ginseng C. A. Meyer*	$C_{42}H_{72}O_{14}$	801.01		22,427–39-0	OA induced Tau hyperphosphorylation in rats cultured brain slices method	Reduced the expression of P-tau and PKA, and attenuated the OA-induced Tau protein hyperphosphorylation.	[100]
Panax notoginseng saponin Rg1	*Panax pseudo-ginseng Wall. var. notoginseng (Burkill)Hoo & Tseng*	–	–	–	–	The left ventricle injection of Aβ25-35 in SD rats.	The expression of tau protein phosphorylation at Thr231 in the DG, CA1, and CA3 regions of the hippocampus was reduced,	[101]
Curcumin	*Curcuma longa Linn.*	$C_{21}H_{20}O_6$	368.38		458–37-7	APP/V717 double transgenic mice	Reduced the positive expression of Aβ and P-tau protein in the brain tissues.	[102]
Curcumin-macrophage exosome	–	–	–	–	–	OA-induced Tau hyperphosphorylation	Reduced Tau hyperphosphorylation by inhibiting the AKT/GSK-3β signaling pathway.	[103]
Angelica sinensis	*Angelica sinensis (Oliv.) Diels*	–	–	–	–	Bilateral common carotid artery ligation model (2VO)	Reduced the expression of phosphorylated Tau (T231, S396); inhibited the Akt/GSK3β pathway and promoting the expression of BACE-1 and BDNF.	[106]
Ligustrazine	*Ligusticum chuanxiong Hort.*	$C_8H_{12}N_2$	136.19		1124–11-4	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Downregulated GSK-3β positive expression and inhibited β-catenin degradation; Activate Wnt signaling pathway.	[113]
Cornus officinalis polysaccharide	*Cornus officinalis Sieb. et Zucc.*	–	–	–	–	D-galactose combined with Aβ1~40 to prepare AD model	Inhibited of GSK-3β expression in the hippocampal CA1 region of AD rats; reduced the positive expression of p-tau(Ser422) phosphorylation sites.	[114,115]
Schisandra chinensis acidic polysaccharide (SCP-A)	*Schisandra chinensis*	–	–	–	–	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Reduced Tau protein phosphorylation at Tau Ser199, Tau Ser396 and Tau Ser404 loci and GSK-3β (Tyr216) expression levels; and increased GSK-3β (Ser9) expression levels.	[116]

Osthole	*Cnidium monnieri (L.)Cuss.*	$C_{15}H_{16}O_3$	244.286		484–12-8	APP/PS1 double transgenic mice;	Reduced p-tau(ser202) protein expression and enhanced PI3K, p-Akt/Akt and p-Gsk3β/Gsk3β protein expression levels.	[117]
Tanshinone IIA	*Salvia miltiorrhiza Bunge*	$C_{19}H_{18}O_3$	294.344		100,210–65-9	Aβ25-35-induced primary cultured cortical neurons; Aβ1-42-induced AD rats	Inhibition of cytoplasmic p25 expression and CDK-5 activation; decreased GSK-3β phosphorylation at the Tyr216 site and increased GSK-3β phosphorylation at the Ser9 site	[121,122]
Senegenin	*Polygala tenuifolia Willd.*	$C_{30}H_{45}ClO_6$	537.128		2469–34-3	Bilateral hippocampal injections of Aβ25-35 induced in SD rats	Decreased the total tau protein content, tau protein Ser396 phosphorylation level and PKA protein expression level; increased the expression level of PP2A protein.	[96]
Baicalin	*Scutellaria baicalensis Georgi*	$C_{21}H_{18}O_{11}$	446.361		21,967–41-9	Tau transgenic mice (TauP310L)	Reduced the expression level of p62 protein and increased the levels of Beclin-1 and LC3B, thereby enhancing the autophagy ability of transgenic mice.	[146]
Celastrol	*Tripterygium wilfordii Hook. f.*	$C_{29}H_{38}O_4$	450.61		34,157–83-0	Aβ25-35 induced PC12 cells; rapidly aging SAMP8 mice	Promoted TFEB translocation from the cytoplasm to the nucleus, enhances autophagy and lysosomal biological activity; degradated of phosphorylated Tau aggregates.	[153]
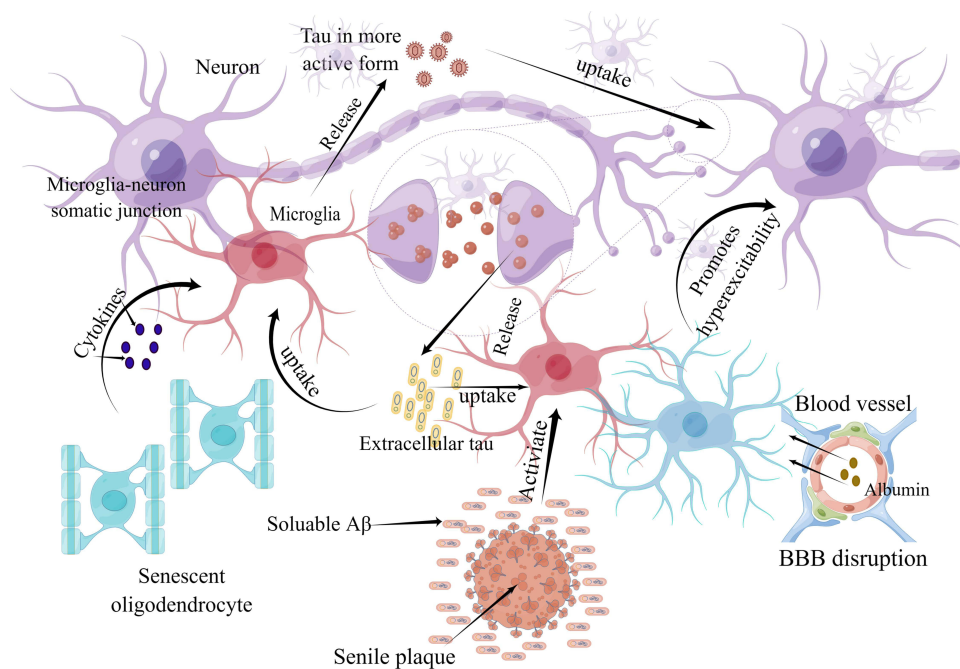
Figure 6 Microglia may be critical intermediaries of Aβ–tau synergy.

activity levels. Multiple mechanisms enhance neuronal activity, including the inhibition of glutamate reuptake caused by Aβ, impaired synaptic inhibition, and the breakdown of the blood–brain barrier, which leads to the leakage of neurotoxic substances (eg, albumin) and the activation of astrocytic TGF-β signaling. Microglia can also contribute to tau seeding and propagation through the release of cytokines, chemokines, and nitric oxide, which enhance tau phosphorylation. It is also possible that there is a direct transfer of tau through the somatic junctions between microglia and neurons. It should be noted that Aβ can also directly seed tau. Therefore, it is crucial to understand the complex interactions between Aβ, tau, microglia, and neurons in the context of tau seeding and propagation. The detailed hypothesized mechanism is shown in Figure 6.

Reconceptualizing AD in terms of Aβ-tau synergies could offer a promising treatment avenue for the future. However, our current understanding of Aβ-tau synergy is still in its early stages, and several unanswered questions remain. These include the underlying cause of inconsistencies and other crucial processes, such as the role of glial cell activation. Furthermore, identifying the key mechanism behind the Aβ-tau synergy and conducting additional experiments to validate it are necessary for future research.

Conclusion

According to the World Health Organization (WHO), there are approximately 50 million individuals worldwide suffering from dementia, with an additional 10 million new cases reported annually.[164] A meta-analysis conducted between 1990 and 2016 revealed that the prevalence of AD among the elderly population was approximately 4.9%.[165] The clinical symptoms of AD are diverse, mainly resulting in cognitive function impairment.[164] This condition imposes significant mental pressure and financial burden on patients and their families.[164] Currently, there are no drugs available for curing AD. Clinical practice often involves the use of cholinesterase inhibitors and megaline to improve AD symptoms. However, the effectiveness, safety, and cost-effectiveness of these treatments vary. Unfortunately, there is no definitive cure for AD yet, and the available drug treatment options are limited.[164] Moreover, there is a lack of uniformity in drug selection, making it difficult to determine the best clinical treatment.[164]

Currently, the majority of research and development efforts in AD by scholars worldwide are focused on the widely recognized "β-amyloid deposition" and "tau protein hyperphosphorylation". Aducanumab (BIIB037) is a fully human IgG1 monoclonal antibody that targets Aβ and facilitates the binding to Aβ aggregates, prompting microglia to phagocytose and

clear Aβ.[4] Lecanemab (BAN2401), another humanized IgG1 antibody, targets soluble Aβ fibrils and has shown good safety and tolerability in Phase 2b clinical trials.[166] An 18-month analysis of patients with AD-derived mild cognitive impairment demonstrated a significant reduction of Aβ in the brain and improved cognitive decline in the high-dose group.[4] Other phase III studies targeting Aβ, such as gantenerumab, are also currently underway. In terms of new drugs targeting tau protein, there are various categories including small molecule inhibitors, tau monoclonal antibodies, vaccines, etc. LMTM (TRx0237) is a small molecule tau protein aggregation inhibitor that prevents tau protein aggregation,[167] but the results of two clinical studies on all-cause dementia and AD were negative.[168] Other tau drugs entering the Phase II clinical stage include monoclonal antibodies semorinemab and zagotenemab (LY3303560). The tau protein vaccine, AADvac1, effectively reduced P-tau production in patients with mild AD in Phase II clinical studies.[169] Overall, these developments indicate promising progress in the development of drugs targeting the "β-amyloid deposition" and the "tau protein hyperphosphorylation".

However, a variety of abnormalities in signaling molecules and pathway changes contribute to the pathogenesis of AD. TCM monomer and compound preparations have been shown to effectively regulate multiple signaling pathways associated with AD. They possess characteristics of multitarget and wide-ranging action, which results in distinctive advantages and notable therapeutic effects in the treatment of AD. Chinese medicine scholars, in particular, have made significant efforts in the clearance of β-amyloid deposition and tau protein hyperphosphorylation. They exhibit characteristics of multitarget and wide-ranging action, leading to unique advantages and significant therapeutic effects in the treatment of AD. Nevertheless, the mechanism of drug action in AD has not been fully explored in relevant studies. Most traditional Chinese medicine research has focused on a single signaling pathway experiment, with limited reports on other highly correlated pathways. Furthermore, the identification of signal molecules is unclear, and the indicators used for detection in experiments are often repetitive. To overcome these limitations, future studies can employ biological approaches such as proteomics, transcriptomics, and metabolomics to analyze specific changes and identify key molecules that play a central role in differentiating AD. This will help in the discovery of new therapeutic targets.

The purpose of this review is to provide a comprehensive overview of recent studies on the role of common TCM natural products in β-amyloid deposition and Tau protein hyperphosphorylation in AD. The authors acknowledge that this review does not present quantitative findings but rather offers a consensus of thought among all authors. Although it is not a systematic review, the study includes a thorough examination of the literature and presents the latest research on this topic.

Abbreviations

Aβ, amyloid β-protein; ABC, ATP-binding cassette transporter; AD, alzheimer's disease; ADAM10, a disintegrin and metalloprotease domain-containing protein 10; APC, adenomatous polyposis coli; APP, amyloid precursor protein; APP/PS1:APPswe/PSEN1dE9; BACE-1, β-APP cleavage enzyme 1; BBB:blood brain barrier; BDNF, brain-derived neurotrophic factor; CAT, catalase; CD, circular dichroism; Cytc:cytochrome c; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular regulated protein kinases; Exo-cur, curcumin-macrophage exosome; *GCs:cistanche glycosides*; FGFR1, fibroblast growth factor receptor 1; GSH-Px, glutathione peroxidase; ICAM-1, intercellular adhesion molecule 1; IDE, insulin-degrading enzyme; L-Glu, L-glutamic acid; LFA-1, lymphocyte function-associated antigen 1; LRP-1:low-density lipoprotein receptor-related protein-1; MDA, malondialdehyde; miRNAs, MicroRNAs; mTOR, mammalian target of rapamycin; NB, N-butanol; NEP, neprilysin; NFT, neurofibrillary tangles; NPC, neural progenitor cells; NPDPK, nonproline-directed kinase; OA, okadaic acid; PDPK, proline directed kinase; PI3K/Akt, phosphoinositide-3 kinase/protein kinase B; PNS, Panax notoginseng saponins; PSD95, Postsynaptic density 95; RAGE, Receptor of Advanced Glycation Endproducts; SOD, superoxide dismutase; SP, senile plaques; TCF3, T-cell factor 3; TCF7L1, Transcription factor 7-like; TCM, traditional Chinese Medicine; TFEB:Transcription factor EB; TTR, transthyretin; VD, vascular dementia; 2VO, bilateral common carotid artery ligation.

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