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Review

Signal pathways in the treatment of Alzheimer's disease with traditional Chinese medicine

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ABSTRACT

Aim of the review: This study aimed to reveal the classical signal pathways and important potential targets of traditional Chinese medicine (TCM) for treating Alzheimer's disease (AD), and provide support for further investigation on TCM and its active ingredients.
Materials and methods: Literature survey was conducted using PubMed, Web of Science, Google Scholar, CNKI, and other databases, with "Alzheimer's disease," "traditional Chinese medicine," "medicinal herb," "Chinese herb," and "natural plant" as the primary keywords.
Results: TCM could modulate signal pathways related to AD pathological progression, including NF-κB, Nrf2, JAK/STAT, ubiquitin-proteasome pathway, autophagy-lysosome pathway-related AMPK/mTOR, GSK-3/mTOR, and PI3K/Akt/mTOR, as well as SIRT1 and PPARα pathway. It could regulate crosstalk between pathways through a multitarget, thus maintaining chronic inflammatory interaction balance, inhibiting oxidative stress damage, regulating ubiquitin-proteasome system function, modulating autophagy, and eventually improving cognitive impairment in patients with AD.
Conclusion: TCM could be multilevel, multitargeted, and multifaceted to prevent and treat AD. In-depth research on the prevention and treatment of AD with TCM could provide new ideas for exploring the pathogenesis of AD and developing new anti-AD drugs.

1. Introduction

More than 55 million people worldwide are currently living with dementia, and along with an aging population, more than 78 million people are predicted to be affected by 2030, with Alzheimer's disease (AD) accounting for 60–70 % of dementia cases [1]. AD is the leading cause of disability in people over 65 years of age worldwide [2] and the fifth leading cause of death globally [3]. AD has become a global health

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's disease; ADAM, a disintegrin and metalloproteinase; AKT, protein kinase B; ALP, autophagy–lysosome pathway; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; AMPK, adenosine monophosphate-activated protein kinase; APP, amyloid precursor protein; ARE, antioxidant responsive element; ATG, autophagy-related gene; CAT, catalase; CLEAR, coordinated lysosomal expression and regulation; CMA, chaperone-mediated autophagy; CTF, c-terminal fragment; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin-ligase enzyme; FAD, familial Alzheimer's disease; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier; GSK-3, glycogen synthase kinase-3; HO-1, heme oxygenase-1; HSC, heat shock cognate; HSP, heat shock protein; IL, interleukin; iNOS, nitric oxide synthase; IκB, inhibitor of NF-κB; JAK, Janus kinase; Keap1, Kelchlike ECH-associated protein 1; LC3, microtubule-associated proteins 1A/1B Light Chain 3B; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; NFTs, neurofibrillary tangles; NF-κB, nuclear factor-κB; NLRP, Nod-like receptor protein; NMDAR, N-methyl-D-aspartate receptor; NQO1, NAD(P)H: quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, auto-poly-ADP-ribosylation of poly polymerase; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator activated receptor; Raptor, regulatory-associated protein of mTOR; RHEB, RAS homologue enriched in brain; ROS, reactive oxygen species; SIRT, silent information-regulated transcription factor; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TCM, traditional Chinese medicine; TFEB, tanscription factor EB; Tg, transgenic; TNF, tumor necrosis factor; TSC, tuberous sclerosis complex; TyrRS, tyrosyl transfer-RNA synthetase; ULK, Unc-51 like autophagy activating kinase; UPP, ubiquitin–proteasome pathway; UPS, ubiquitin-proteasome system.

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threat to older adults. It is a heterogeneous disease with complex pathobiology [4]. It is characterized clinically by progressive loss of memory and other cognitive functions [5], and in advanced stages, patients may experience severe amnesic manifestations, hallucinations, disorientation, and ultimately death due to malnutrition, dysphagia, aspiration pneumonia, and infection [6].

The onset of AD may be caused by a complex interplay of genetic, epigenetic, and environmental factors [5]. The core pathological features of AD are amyloid plaques and neurofibrillary tangles (NFTs) in the brain, with associated synaptic and neuronal damage, resulting in cognitive deficits [7]. Amyloid-β (Aβ) peptide and Tau protein are the main components of plaques and tangles, respectively [8]. Aβ peptides are proteolytic fragments of the transmembrane amyloid precursor protein, and substantial evidence supported a central role for pathological Aβ accumulation in the pathogenesis of AD [9]. Aβ is toxic to neurons in several aspects, leading to the development of apoptosis, synaptic loss, and cytoskeletal disruption [10].

Tau is a microtubule-associated protein in the brain. Hyperphosphorylated Tau fibrillates into paired helical filaments and thus form NFTs in AD compared with healthy brains [11]. Many studies have shown that the number and location of NFTs are closely related to neuronal loss, AD disease severity, and clinical course [12,13]. In addition, growing evidence showed that Aβ and Tau interact. For example, abnormal Tau phosphorylation increases Aβ production by trapping amyloid precursor protein (APP)-containing endosomes; meanwhile, Aβ oligomers drive Tau hyperphosphorylation, creating a vicious cycle that leads to the perpetuation of AD pathology [11].

No drugs are currently available to slow AD progression [3]. Marketed cholinesterase inhibitors and N-methyl D-aspartate antagonists provide only symptomatic relief, and their clinical importance remains controversial [14]. Considering the complex and multifactorial pathology of AD, TCM is safer than synthetic drugs with single-target activity, and it contains multiple active ingredients that could act on multiple targets simultaneously and exert a synergistic intervention in patients with AD [15]. For example, *Polygonum multiflorum* Thunb. (He Shou Wu) extract, *Acrorus tatarinowii* Schott (Shi Chang Pu) extract [16], *Polygala tenuifolia* Willd. (Yuan Zhi) extract [17], *Coptis chinensis* Franch (Huang Lian) extract [18], modified Huanglian-Jie-Du-Tang [19], and NeuroDefend [20] have been shown to improve AD pathological damage and alleviate cognitive deficits. Clinical trials have shown that TCM has positive effects on early AD prevention and the improvement of cognition and brain activity in patients with AD [21]. Further exploration of the regulatory mechanisms of AD-related signal pathways could be beneficial to reveal the therapeutic targets of herbal interventions in AD. However, a systematic review of signal pathways in TCM interventions in AD research has not been conducted. Therefore, this study reviewed the research progress of the signal pathways of TCM and its effective active ingredients against AD in recent years to provide a reference for subsequent studies.

2. Signal pathways in TCM intervening pathological progression of AD

2.1. NF-κB signal pathway

Nuclear factor-κB (NF-κB) is a family of transcription factors that play vital roles in inflammation, immunity, cell proliferation, and apoptosis. In mammals, the NF-κB transcription factor family consists of five proteins: p65 (RelA), c-Rel, RelB, p105/p50, and p100/p52 [22]. All of the above members contain an N-terminal Rel homology domain and could form homodimers or heterodimers. In quiescent cells, these dimers bind to the inhibitor of NF-κB (IκB) protein, and inactive transcription factors are sequestered in the cytoplasm. Upon stimulation by pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)− 1β, and bacterial lipopolysaccharide (LPS), IκB protein is phosphorylated by the IκB kinase complex, leading to ubiquitination and degradation of IκB protein and thus resulting in NF-κB dimer translocating to the nucleus and driving transcription of target genes [23]. The NF-κB signal pathway is considered to be a critical signal pathway involved in the regulation of inflammatory responses [24]. It regulates the transcription of genes such as cytokines, chemokines, pro-inflammatory enzymes, pro-inflammatory transcription factors, and adhesion molecules, which are all essential for regulating neuroinflammation [25].

Growing evidence showed that neuroinflammation has an essential role in the pathogenesis of AD [1]. Astrocytes and microglia are the primary resident cells responsible for the immune/inflammatory response in the brain [26]. Misfolded and aggregated proteins in the brain could bind to microglia and astrocytes, triggering an innate immune response characterized by the release of inflammatory cytokines and ultimately leading to the development of chronic neuroinflammation and promoting the progression of AD disease [27]. Furthermore, NF-κB has binding sites in the promoter regions of genes involved in amyloidogenesis and inflammation, and long-term use of NSAIDs may prevent AD progression and delay its onset [28]. NF-κB is closely associated with the development of AD.

Baicalin (BAI) is a natural flavonoid isolated from *Scutellaria baicalensis* Georgi (Huang Qin), which is of interest for its anti-inflammatory and antioxidant properties in various neurological diseases [29]. After BAI intervention, the number of Iba-1-positive microglia in the brain of APP/PS1 double transgenic mice was reduced; the mRNA levels of inflammatory cytokines nitric oxide synthase (iNOS), interleukin (IL)− 1β, and IL-18 were decreased; and the expression levels of nod-like receptor protein 3 (NLRP3), TLR4, p-NF-κB/p65, and p-IκBα proteins were reduced. These findings suggested that BAI could alleviate microglia-induced neuroinflammation in the brain of AD mice by inhibiting NLRP3 and TLR4/NF-κB signal pathways and promote the improvement of memory and cognitive deficits. Furthermore, in BV-2 microglia, BAI attenuated LPS/Aβ-induced neuroinflammation by inhibiting NLRP3 and TLR4/NF-κB signal pathways [30].

Wang et al. [31] found that NaoXinTong (NXT) capsule alleviated spatial memory impairment and cognitive decline in APP/PS1 double transgenic mice; downregulated IL-1β, IL-6, and TNF-α; inhibited NF-κB and TLR4 expression; and decreased Aβ and p-Tau levels. These findings suggested that NXT may delay AD progression by inhibiting the TLR4/NF-κB/IL-1β signal pathway, antagonizing the neuroinflammatory response, and delaying AD progression. The Chinese herb *Sesamum indicum* L. (Zhi Ma) is rich in sesame oil (SO), which has pharmacological effects such as anti-inflammatory, antioxidant, and antitumor [32]. Mohamed et al. [33] found that SO significantly improved the learning and memory impairment induced by $AlCl_3$ in mice, decreased acetylcholinesterase (AChE) and Aβ levels, downregulated TNF-α and IL-1β, decreased NF-κB and p38MAPK expression levels, and increased BDNF and PPAR-γ expression. These findings suggested that SO attenuated neuroinflammation and oxidative stress damage and promoted cognitive recovery by regulating the NF-κB/p38MAPK/BDNF/PPAR-γ signal pathway.

Moreover, the herbal compounds Sanweidoukou decoction [34] and Qifu-Yin [35] and the natural herbal active ingredients tanshinone IIA [36], Forsythoside B [37], and Corydalis edulis total alkaloid [38] have shown considerable effects in promoting cognitive performance and preventing AD by mechanisms related to the inhibition of the NF-κB signal pathway and the reduction of neuroinflammatory response.

In summary, chronic neuroinflammation is one of the core mechanisms of AD. The NF-κB signal pathway is a classical regulatory pathway of the inflammatory response. It could be targeted by TCM, and it is a pivotal target to slow down the progression of AD disease.

2.2. Nrf2 signal pathway

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a key transcription factor in antioxidant defense, and it intersects with many other

signaling cascade responses [39]. Nrf2 belongs to the Cap'n'Collar subfamily of the basic region-leucine zipper transcription factors and consists of seven conserved NRF2-ECH homology structural domains, each with a different function [40]. Under physiological conditions, Kelchlike ECH-associated protein 1 (Keap1) inhibits Nrf2 activation by isolating Nrf2 in the cytoplasm and targets Nrf2 ubiquitination. By contrast, under oxidative stress conditions, with the production of excess reactive oxygen species (ROS), Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to the antioxidant responsive element (ARE) to trigger transcription of downstream antioxidant enzymes, such as heme oxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), glutamate-cysteine ligase catalytic subunit (GCLC), superoxide dismutase (SOD), and catalase (CAT) [41].

Oxidative stress is known to play a vital role in developing AD [42]. Excessive accumulation of ROS associated with oxidative stress may promote Aβ deposition and Tau hyperphosphorylation and lead to subsequent synaptic and neuronal loss, affecting synaptic activity and neurotransmission in neurons and leading to cognitive dysfunction [43]. Evidence showed that oxidative stress was manifested early in the course of AD [44], and decreased expression of Nrf2 [45] and its target genes NQO1 [46], HO-1 [47], GCLC, and glutamate-cysteine ligase modifier (GCLM) [48] were observed in the brains of patients with AD. Moreover, ongoing evidence highlighted the protective role of the Nrf2 signal pathway in AD. Activation of Nrf2 upregulated the expression of antioxidant enzymes and various proteins that reduce oxidative stress damage and neuroinflammation, thereby delaying the progression of AD [49].

Various Chinese herbs have been shown to activate the Nrf2 signal pathway. For example, Rhynchophylline (Rhy) is the main active component of the medicinal herb *Uncaria rhynchophylla* (Miq.) Jacks. (Gou Teng), which has been shown in many studies to ameliorate cognitive deficits in animal AD models [50]. Jiang et al. [51] used Rhy to intervene in an $A\beta_{1-42}$-induced mouse model of AD and found that the treated mice showed improved cognitive function; reduced brain ROS and MDA levels; increased GSH levels; and significantly increased expression of Nrf2 and its downstream proteins HO-1, NOQ1, and GCLM. Rhy could exert antioxidative stress effects and attenuate $A\beta_{1-42}$-induced neurotoxicity through activating the Nrf2/ARE signal pathway, with positive therapeutic effects in AD mice.

Qin et al. [52] found that Astragalus polysaccharide increased the expression of Nrf2 in the nucleus and the expression of SOD and GSH-Px, and reduced the accumulation of MDA, thereby reducing oxidative stress damage and significantly improving the spatial learning memory ability of APP/PS1 mice. Bian et al. [53] reported that oxyphylla A, an extract of *Alpinia oxyphylla* Miq. (Yi Zhi), contributed to the improvement of cognitive function in senescence-accelerated mouse prone 8 mice by reducing the expression of APP, $A\beta_{1-40}$, and $A\beta_{1-42}$ in the brain. The antioxidant mechanism was associated with increased expression of Nrf2 and its downstream genes HO-1 and NQO1 in the brain and the inhibition of the expression of Nrf2 regulatory protein Keap1.

Various herbal active ingredients could slow down the progression of AD. For example, *Centella asiatica* (L.) Urb. (Ji Xue Cao) improved cognitive performance and reduced Aβ deposition in the brain of 5 × Familial Alzheimer's disease (5XFAD) mice; it acted by increasing the expression of Nrf2 and its downstream genes HO-1, NQO1, and GCLC [54,55]. Hydroxy-α-sanshool, the active ingredient of *Zanthoxylum schinifolium* Sieb. et Zucc. (Hua Jiao), exerted antioxidant stress and neuroprotective effects through activation of the Nrf2/HO-1 signal pathway, thus improving the cognitive function of D-gal/$AlCl_3$-induced AD-like mice [56].

In conclusion, oxidative stress is one of the core pathological mechanisms in AD, and the Nrf2 signal pathway plays a significant role in maintaining cellular redox homeostasis [57]. Many herbal medicines and their active ingredients could target the activation of Nrf2, thereby reducing oxidative stress damage and providing neuronal protection against the progression of AD. They are potential therapeutic agents for alleviating AD pathology.

2.3. Nrf2 and NF-κB signal pathway interplay in AD

Recent studies have found that interacting oxidative disorders and neuroinflammation underlie the pathological mechanisms of AD [58]. Oxidative stress results from the excessive release of ROS in the brain [59]. ROS can induce glial cell activation, stimulate the expression of inflammatory cytokines, and trigger chronic neuroinflammation. In turn, continuously activated microglia and astrocytes can produce large amounts of ROS, thus promoting oxidative stress [60]. Oxidative stress and deleterious inflammation form a vicious cycle that synergistically promotes AD development [61]. This cycle involves stimulating transcription factors, such as NF-κB and Nrf2, that are sensitive to oxidative stress and inflammation.

NF-κB is the main transcription factor that controls the expression of pro-inflammatory genes in microglia [62]. Nrf2 is a redox-sensitive transcription factor located in the cytoplasm that helps cells adapt to oxidative stress and chronic inflammation by upregulating the expression of protective genes [63]. The Nrf2 and NF-κB signal pathways are vital pathways that synergistically regulate the balance between cellular redox status and inflammatory responses [49]. The current study showed that downregulation of Nrf2 could increase in NF-κB activity and promote the expression of inflammatory markers. Nrf2 interacts with NF-κB to coordinate antioxidant stress and inflammatory responses, and it may be a promising target against AD pathological progression.

Recent studies have continued to point out that in addition to being a central regulator of the antioxidant stress response, the Nrf2 signal pathway plays an essential role in suppressing inflammation. The Nrf2 signal pathway is often accompanied by inhibition of the NF-κB signal pathway and diminished inflammatory response [64–66]. Reduction in intracellular ROS to inhibit oxidative stress-mediated NF-κB activation, upregulation of HO-1 expression to prevent IκB-α proteasomal degradation, and inhibition of NF-κB nuclear translocation were also found [67]. Common Nrf2 agonists, including sulforaphane [68], astaxanthin [69], curcumin [70], and epigallocatechin-3-gallate [71], have been found to exert anti-inflammatory properties by inhibiting the NF-κB signal pathway.

In addition to inflammatory damage, NF-κB is involved in regulating oxidative stress response. NF-κB could regulate the transcription and activity of Nrf2, with positive or negative effects on the expression of its target genes [72]. NF-κB could regulate the expression of various antioxidant proteases, including manganese superoxide dismutase [73], glutathione transferase [74], and HO-1 [75]. The NF-κB/p65 subunit could inhibit the Nrf2/ARE signal pathway by depriving CREB binding protein from Nrf2 [76], and Nrf2 target genes, such as NQO1, GCLC, and GCLM, have NF-κB binding sites [67].

Growing evidence showed that TCM and its active ingredients have positive effects on the complex interaction mechanisms between Nrf2 and NF-κB signal pathways, and this may be an essential strategy to combat AD. As the main active ingredient of *Citrus reticulata* Blanco (Chen Pi) [77], Hesperidin (HP) is a common neuroprotective agent that has received much attention for its significant antioxidant and anti-inflammatory properties in neurodegenerative diseases [78]. HP treatment significantly ameliorated cognitive function in APP/PS1 double transgenic mice; increased the activity of antioxidant enzymes SOD, CAT, and GSH-Px in the brain; increased Nrf2 and HO-1 expression; decreased inflammatory cytokines TNF-α, C-reactive protein, and monocyte chemoattractant protein-1 levels; and inhibited p-IκBα protein expression and NF-κB/p65 nuclear translocation. These findings suggested that HP could inhibit oxidative stress injury and neuroinflammation in the brain of AD mice by upregulating Nrf2 expression and inhibiting NF-κB signal pathway, ultimately promoting their cognitive function [79].

Lei et al. [80] investigated the therapeutic effects of pinoresinol

diglucoside (PDG), the main active ingredient of *Eucommia ulmoides* Oliv. (Du Zhong), on cognitive impairment in an $A\beta_{1-42}$-induced AD mouse model. PDG was found to significantly improve cognitive performance, reduce the levels of ROS and MDA, increase the release of SOD and CAT in the brain, and increase the protein expression of Nrf2 and HO-1 in the hippocampus of AD mice. PDG also decreased the release levels of IL-1β and TNF-α and downregulated the protein expression of NF-κB/p65. Furthermore, the Bcl-2/Bax ratio was upregulated in the brains of PDG-treated mice, the protein expression of cytochrome C and cleaved caspase-3 was reduced, and $A\beta_{1-42}$-induced neuronal apoptosis was inhibited. These findings indicated that PDG could effectively regulate oxidative stress state, inflammation, and neuronal apoptosis by activating the Nrf2/NF-κB transcriptional pathway, thus reducing neuronal damage and improving cognitive dysfunction, which has a certain therapeutic effect on AD mice.

In-vitro data showed that isoliquiritigenin, the active ingredient of the Chinese herb *Glycyrrhiza uralensis* Fisch. (Gan Cao), reduced the production of inflammatory cytokines iNOS, COX-2, IL-1β, IL-6, and TNF-α by upregulating the expression of Nrf2, HO-1, and NQO1 and inhibiting NF-κB activation [81]. This study suggested that activating Nrf2 antagonizes NF-κB activity and thus exerts anti-inflammatory effects. Besides, the active ingredients of TCM, such as platycodin D [82], higenamine [83], α-cyperone [84], sulforaphane [85], and lycopene [86], exhibited certain neuroprotective activities. The mechanisms were related to anti-inflammatory and antioxidant properties through the regulation of the Nrf2/NF-κB signal pathway.

To sum up, the onset and development of AD is a complex process caused, in large part, by crosstalk between oxidative stress and neuroinflammation. NF-κB and Nrf2 signal pathway-mediated chronic inflammation and oxidative stress contribute to AD development. The synergy between Nrf2 and NF-κB signal pathways is an important entry point for delaying the pathological progression of AD. TCM has multi-target and bi-directional regulation, and the multi-faceted coordination of NF-κB and Nrf2 may reduce oxidative stress, pathological neuroinflammation, and neuronal apoptosis in the brains of patients with AD, thus slowing down the progression of AD disease, which is a potential target for the prevention and treatment of AD.

2.4. JAK/STAT signal pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signal pathway is central to extracellular cytokine-activated receptor-mediated signal transduction. In mammals, the JAK family has four members: JAK1, JAK2, JAK3, and TYK2, and the STAT family includes seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [87]. The JAK/STAT signal pathway is involved in regulating several CNS functions, including neurogenesis, gliogenesis, synaptic plasticity, and microglia activation. Aberrant activation or phosphorylation of its pathway components is closely associated with many neurodegenerative diseases, such as AD [88]. IFN-γ and IL-6 are the most potent activators of the JAK/STAT signal pathway [89]. Interestingly, both of these cytokines have also been found to be overexpressed in patients with AD [90,91]. Activation of JAK leads to the phosphorylation and dimerization of STATs, which are then transferred from the cytoplasm to the nucleus, where they bind to specific DNA elements to regulate the transcription of cytokine-related genes [92]. A growing number of studies have shown that the JAK/-STAT signal pathway plays an essential role in AD development [93].

Suan-Zao-Ren decoction (SZRD) is widely used to treat neurological disorders, including dementia, depression, and insomnia, with potential benefits for AD treatment. Long et al. [94] observed changes in the expression of the JAK2/STAT3 signal pathway in an AD mouse model and the effect of SZRD on this pathway. They showed that SZRD intervention significantly reduced cognitive impairment; decreased Aβ plaque deposition and neuronal loss; improved synaptic plasticity in the hippocampus; decreased p-JAK2-Tyr1007 and p-STAT3-Tyr705 protein expression; and inhibited inflammatory cytokines IL-6, IL-1β, and TNF-α in APP/PS1 mice. These findings suggested that SZRD may be able to improve cognitive deficits in AD mice by downregulating the JAK2/-STAT3 signal pathway to reduce Aβ deposition and neuroinflammation.

Cornel iridoid glycoside (CIG) is a terpenoid extracted from *Cornus officinalis* Sieb.et Zucc. (Shan Zhu Yu) [95], with neuroprotective effects [96,97]. Ma et al. [98] found that CIG reduced the protein expression of p-JAK2, p-STAT1, and STAT1 and increased the expression levels of N-methyl-D-aspartate receptor (NMDAR) subunits GluN1, GluN2A, and GluN2B and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) subunit GluA1 in the brain of P301S transgenic mice. This finding suggested that CIG could alleviate STAT1-induced inhibition of NMDAR expression by inhibiting the JAK2/STAT1 signal pathway, thereby increasing synaptic ultrastructure and number in the brain, improving synaptic plasticity, and ultimately effectively improving cognitive function in AD mice.

In addition, many herbal medicines and their active ingredients could delay the progression of AD pathology. For instance, ganoderic acid A significantly improved cognitive deficits in d-gal-treated mice by inhibiting the Th17 cell-induced JAK/STAT signal pathway and regulating Treg cells to enhance mitochondrial oxidative phosphorylation, thus improving brain mitochondrial dysfunction and reduce neuroinflammation [99]. Curcumin, a natural polyphenolic compound [100], has been proven to have a potential therapeutic effect in inhibiting neuroinflammation by a mechanism related to the regulation of the JAK/STAT/SOCS signal pathway [101].

2.5. Protein degradation systems

Pathogenic accumulation of proteins such as Aβ and Tau could lead to progressive neuronal loss and cognitive deficits, thus contributing to AD development [102]. The protein degradation pathway has been recognized as an important approach to combat AD. Because of its ability to degrade misfolded and easily aggregated abnormal proteins, this pathway plays an important role in maintaining normal cellular metabolism and avoiding protein dysfunction. The main pathways include the ubiquitin-proteasome pathway (UPP) and the autophagy-lysosome pathway (ALP) [103].

2.5.1. Ubiquitin-proteasome pathway

In eukaryotes, the vast majority of protein degradation takes place via UPP. UPP relies on ubiquitin (Ub) signals to target proteins to the proteasome and to achieve ubiquitination and degradation of target proteins in a highly coordinated manner [104]. Ubiquitination is tightly controlled by the enzymatic cascade reaction. The cascade reaction is initiated by Ub activation catalyzed by the Ub-activating enzyme (E1), followed by the formation of a high-energy thioester bond between the E1 enzyme and activated Ub, thus transferring Ub to the Ub-conjugating enzyme (E2). Next the Ub-ligase enzyme (E3) binds the E2 enzyme to the target protein and transfers Ub to the substrate, where the E3 enzyme determines the substrate specificity of the protein. Finally, the 26 S proteasome recognizes the target protein and undergoes degradation [105].

Due to the critical role of UPP in maintaining protein homeostasis, dysregulation of UPP is receiving sustained attention as an important factor in the pathogenesis of AD which is characterized by massive aggregation of harmful proteins [106]. Significant decreases in proteasome activity have been reported to be observed in the hippocampus, parahippocampal gyrus, superior temporal gyri, middle temporal gyri, and inferior parietal lobule in patients with AD compared to controls, indicating impaired proteasome function in AD [107]. The ubiquitination and proteasome-mediated receptor degradation in APP mutant transgenic mice were found to be affected to some extent, and the proteasome and deubiquitinating enzyme activities were also inhibited [108]. In addition, continued evidence suggests that abnormal ubiquitin-proteasome system (UPS) activity may lead to dysregulated

degradation of Aβ and Tau proteins. For example, in the triple transgenic (3xTg)-AD mouse model, blocking UPP by application of proteasome-specific inhibitors was found to result in a significant increase in the accumulation of Aβ and Tau proteins, while enhancing UPP specifically induced Tau protein degradation and reduced abnormal Tau protein levels in the brains of AD mice [109,110]. Another study pointed out that UPP is involved in the formation of abnormal aggregation of phosphorylated Tau proteins through stress granules, and it highlights the importance of activating UPP for alleviating AD pathology [111]. Therefore, the close association between UPP and the pathogenesis of AD may open new avenues for exploring therapeutic strategies for UPP-based treatment of AD in Chinese herbs, and numerous studies have been reported to support this view.

Iyaswamy et al. [112] found that Yuan-Hu Zhi Tong Prescription (YZT) significantly improved learning, memory function and motor deficits in P301S Tau and 3xTg-AD mice; reduced the load of phosphorylated Tau protein in the brain; and decreased ploy Ub protein levels. These findings suggested that YZT may exert anti-AD activity by modulating UPP to promote degradation of insoluble Tau aggregates. Sreenivasmurthy et al. [113] investigated the neuroprotective effects of protopine (PRO), a component of *Corydalis yanhusuo* W.T. Wang (Yan Hu Suo), on P301S Tau and 3xTg-AD mouse models. PRO was found to significantly improve learning and memory abilities; attenuate Tau pathology; inhibit histone deacetylase 6 activity; and enhance the molecular chaperones heat shock protein 70 (HSP70), HSP90, heat shock cognate 70 (HSC70), and acetylated HSP90 protein expression.

In addition, Li et al. [114] found that Yuan-zhi-san (YZS) improved memory deficits, restored neuronal numbers, reversed ultrastructural abnormalities and increased dendritic spine density in $A\beta_{1-40}$-induced AD rat model. The expression levels of UbE1a/b, UbE2a, carboxyl terminus of HSC70-interacting protein, ubiquitin C-236 terminal hydrolase L1, and 26 S proteasome proteins were significantly increased and the hyperphosphorylation of Tau proteins (Ser199 and Thr231) was effectively inhibited in AD rat brain after YZS intervention. These results suggested that YZS could restore UPP function in AD rats, thus promoting the degradation of phosphorylated Tau proteins and the recovery of normal neurological function and memory enhancement.

2.5.2. *Autophagy–lysosome pathway*

Although UPS has been recognized for decades as a key regulator of degradation of various aggregation-prone proteins, ALP has recently been shown to be an important pathway associated with neuronal health and related diseases [115]. This pathway is specifically responsible for the delivery and digestion of cellular contents, misfolded proteins, and damaged organelles produced during cellular catabolism, thus playing a protective role in maintaining cellular homeostasis, energy balance, and cellular defense [116].

In mammalian cells, autophagy could be classified into three main subtypes based on differences in target substrate recognition and delivery to lysosome: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [117]. Among them, macroautophagy (hereinafter referred to as “autophagy”) represents the majority of autophagic processes and is the main pathway for removing Aβ and abnormal Tau proteins [118]. Autophagy is a multistep process. Cytoplasmic cargoes are initially isolated by a phagophore that elongates to form the double-membrane structured vesicle called autophagosome [119]. During this phase, the Unc-51 like autophagy activating kinase (ULK) complex promotes phagophore initiation and elongation by recruiting and activating lipid kinase complexes [120]. This complex catalyzes the conversion of phosphatidylinositol to phosphatidylinositol 3-phosphate, allowing further recruitment of specific autophagy proteins necessary for phagophore formation and constituting the active complex autophagy-related gene (ATG) 5-ATG12-ATG12L1. These activities together lead to the binding of microtubule-associated proteins 1 A/1B Light Chain 3B (LC3) and Gamma-aminobutyric acid receptor-associated protein family members to phosphatidylethanolamine, resulting in the formation of LC3-II, a major marker of autophagy, which also leads to the formation of autophagosome by the extension and closure of phagophore membrane [121]. Finally, the outer membrane of the autophagosome fuses with the lysosomal membrane to form an autolysosome, allowing lysosomal hydrolases to degrade autophagic cargoes and release the recovered nutrients back into the cytoplasm for reuse [117].

In contrast to non-neuronal cells, neuronal cells are highly dependent on autophagy for their survival [122]. This is because neurons are post mitotic cells and are unable to dilute damaged organelles and abnormal proteins through mitosis. Thus neurons are in urgent need of efficient degradation of abnormal proteins such as Aβ and phosphorylated Tau proteins through the autophagic pathway [123]. Once the ALP pathway is defective and leads to a progressive accumulation of cellular waste, it will place a heavy burden on neurons [124]. Growing evidence showed that ALP dysfunction may play a critical role in the pathogenesis of AD. Impaired lysosomal protein degradation and excessive accumulation of autophagic vesicles were found in the brains of patients with AD and animal models of AD compared to normal brains [125,126127]; more severe memory impairment as well as more Aβ aggregation and SPs formation in the brain were seen in the offspring of autophagy-deficient mice [128].

ALP has a dual role in AD pathogenesis [129]. In the early stage of AD, autophagy gene expression is heavily upregulated, delivering misfolded proteins (including Aβ and Tau proteins) from neurons to lysosomes for efficient degradation, exerting an initial neuroprotective response [130]. However, it has been reported that the lysosomal degradation function has started to be significantly impaired by this time, with a progressive decrease in substrate lysosomal clearance [131]. As AD progresses, excessive autophagic activation beyond the lysosomal clearance capacity could lead to a massive accumulation of immature autophagosomes in neurons and impaired autophagosome-lysosome fusion, resulting in excessive organelle degradation, self-digestion, and neuronal death, thus accelerating AD pathology [130].

In the past decades, great progress has been made in the search for autophagy-lysosome modulators from TCM, providing new insights into the development of therapeutic strategies for AD targeting ALP. Tanscription factor EB (TFEB) is a key transcription factor that controls autophagy and lysosomal biogenesis [132]. Yang et al. [133] found that celastrol (Cel), a component of *Tripterygium wilfordii* Hook. f. (Lei Gong Teng), could improve memory impairment and cognitive deficits in P301S Tau and 3xTg-AD mice; reduce the aggregation of phosphorylated Tau protein in the brain; promote TFEB nuclear translocation; and increase the production of autophagy marker LC3B-II and decrease the expression of SQSTM1/p62. These findings suggested that Cel may promote the degradation of phosphorylated Tau proteins and enhance the cognitive performance of AD mice by activating TFEB-mediated autophagy and lysosomal biogenesis.

Furthermore, in vitro experiments also confirmed that Chinese medicine and its main active ingredients and derivatives, such as panax notoginseng saponins [134], β-asarone [135], and corynoxine B derivative CB6 [136], have certain autophagy-inducing and neuroprotective effects.

2.5.2.1. mTOR-dependent pathway. Autophagic signals can be regulated by the mammalian target of rapamycin (mTOR) signal pathway [137]. mTOR is a 289 kDa serine/threonine protein kinase in the PI3K-related protein kinase family [138]. It is present in mammals as two types of protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [139]. Among them, mTORC1 is the main controller of ALP that inhibits autophagosomes formation and could regulate autophagy by modulating the activity of the ULK1 complex [140,141]. Besides, mTORC1 inhibition could lead to dephosphorylation of TFEB and translocation of TFEB to the nucleus, where it binds to the promoter

region containing the CLEAR (coordinated lysosomal expression and regulation) sequence, thus upregulating the expression of lysosomal and autophagy-related genes and promoting lysosomal biogenesis and autophagy induction [142]. In contrast, mTORC2 is insensitive to rapamycin and has been found to regulate CMA activity in recent years [143]. Numerous studies have shown that upregulation of multiple components of the mTOR signal pathway and its association with Tau pathology could be observed in the brains of patients with AD [144, 145146].

Recent studies have shown that mTOR could coordinate or interact with various upstream signals, such as adenosine monophosphate-activated protein kinase (AMPK), glycogen synthase kinase-3 (GSK-3), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) [147].

AMPK is a heterotrimeric complex consisting of α-catalytic subunit, β-regulatory subunit, and γ-regulatory subunit [148]. AMPK is a major regulator of cellular energy metabolism and could act as a pivotal sensor of relative energy status in the cell upstream of mTOR, activating autophagy during low energy states with high AMP/ATP ratio [149]. Activated AMPK has been found to inhibit mTOR activity by phosphorylating and activating tuberous sclerosis complex 2 (TSC2) function. TSC2 is a GTPase-activating protein that inhibits mTORC1 by converting the RAS homologue enriched in brain (RHEB) GTPase from the active GTP-bound form to the inactive GDP-bound form [150]. Additionally, activated AMPK could downregulate mTOR signal by directly phosphorylating regulatory-associated protein of mTOR (Raptor) [151] or directly phosphorylate ULK1, a downstream target of mTORC1, to enhance autophagy [152,153], thereby increasing Aβ clearance, alleviating Tau pathology, and improving cognitive function. However, some studies noted that AMPK activation had non-neuroprotective properties that might lead to deleterious outcomes such as Aβ production and abnormal phosphorylation of Tau proteins [154].

As a regulator of a wide variety of cellular processes, GSK-3 is central to cellular metabolism and signaling processes [155]. And it is considered to be a critical regulator involved in a number of neuronal processes including axonal transport, cholinergic function, and synaptic plasticity [156]. Moreover, GSK-3, one of the negative regulators of mTORC1, could regulate autophagy and lysosomal activity by phosphorylating TSC2 or directly phosphorylating Raptor at Ser859 to inhibit mTORC1 [155]. GSK-3 hyperactivity has been observed in the brains of patients with AD [157,158], and overexpression of GSK-3 has been shown to induce AD pathology, cognitive deficits, and gliosis in many animal models of AD [159,160161162163].

The PI3K/AKT signal pathway has significant roles in the brain in regulating cell proliferation, differentiation, and migration as well as establishing neuronal polarity, regulating neurotransmission and enhancing synaptic plasticity [164]. PI3K could convert phosphorylation of phosphatidylinositol 4,5-bisphosphate to phosphatidyl-inositol, 3,4,5 triphosphate by being activated by the input signal, which in turn leads to AKT activation. Activated AKT could prevent its negative regulation of Rheb by phosphorylating TSC1/2, thus activating mTORC1 [165]. The abnormal and sustained activation of neuronal PI3K/Akt/mTOR signal transduction has been reported to be an early feature of AD [166]. However, another study pointed out that while inhibition of PI3K/mTOR signal pathway activated autophagy to eliminate toxic proteins, activation of PI3K could promote neuronal cell survival [151].

Increasing evidence suggests the importance of mTOR-dependent autophagy in the pathogenesis of AD [167]. In-depth understanding of mTOR and its upstream signals may provide new ideas to explore the potential targets of TCM for the treatment of AD [168]. Rahman et al. [169] found that oxyresveratrol (OxyR) reduced the production of glucocorticoid-induced APP in mouse cortical astrocytes; increased the number of LC-3 puncta formation and LC3-II protein expression levels; increased the expression of p-AMPK, p-ULK1 (Ser757), and p-ULK1 (Ser555) proteins; and suppressed the expression of mTOR downstream phospho-S6 ribosomal protein (Ser240/244). These findings suggested that OxyR could activate autophagy by regulating the AMPK/ULK1/mTOR signal pathway, thereby reducing APP production in mouse cortical astrocytes and exerting anti-neurotoxic effects.

P. tenuifolia Willd. (Yuan Zhi) has been widely used in clinical treatment of insomnia, cognitive decline, and neurasthenia [170]. Studies have shown that it may induce autophagy through upregulation of AMPK/mTOR signal pathway, thus inhibiting the aggregation of Aβ and acting anti-AD effects [171]. Huang et al. [172] explored the neuroprotective effects of galangin (GA) on okadaic acid (OA)-induced PC12 cell injury. The results showed that GA treatment significantly increased OA-induced PC12 cell viability in a concentration-dependent manner; decreased the levels of p-Tau, $A\beta_{42}$, and β-secretase; increased the expression of p-Akt and p-mTOR; and attenuated the expression of p-GSK3β and Beclin-1. These findings suggested that GA could exert certain neuroprotective effects by regulating the Akt/GSK3β/mTOR--dependent autophagic pathway.

Curcumin (CUR) is the main polyphenol contained in *Curcuma longa* L.(Jiang Huang) [173]. Wang et al. [174] found that CUR could induce autophagy through downregulation of the PI3K/Akt/mTOR signal pathway, thus reducing the production of Aβ and improving cognitive impairment. Such effects correspond to the manifestations of excessive activation of PI3K/Akt/mTOR signal pathway and reduced autophagy observed in the brains of patients with advanced AD [175]. These findings suggested that Chinese herbs and their active ingredients may exert anti-AD effects by inducing autophagy to protect neurons.

Interestingly, other studies have indicated that upregulation of the PI3K/Akt/mTOR signal pathway could show neuroprotective effects under certain circumstances. For example, Deng et al. [176] used β-asarone, the active ingredient of *Acorus tatarinowii* Schott (Shi Chang Pu), to intervene in APP/PS1 mice and found that compared with the untreated group, the treated group showed increased expression of p-mTOR and p62 and decreased expression of p-Akt, Beclin-1, and LC3B. In addition, their learning and memory ability was significantly improved, suggesting that β-asarone could improve the cognitive ability of AD mice by upregulating the PI3K/Akt/mTOR signal pathway to inhibit Beclin-1-dependent autophagy. *In-vitro* studies have also demonstrated that β-asarone attenuated Aβ1–42-induced neuronal toxicity by activating the Akt/mTOR signal pathway to attenuate autophagy [177].

The above studies suggested that the potential pathways regulating mTOR-dependent autophagy are intricate and complex. Therefore, clinical treatment of AD should pay due attention to the central role of the mTOR signal pathway in ALP regulation, while dynamically coordinating the balance between mTOR and its upstream signals. Compared with simple mTOR inhibitors or agonists, the advantage of TCM is that it can play a synergistic role between drugs, or can play a role in dynamically regulating mTOR and its related signal pathways and autophagic activity, which is more in line with the rule of AD pathological transformation.

2.5.2.2. mTOR-independent signal pathway. Although current research on autophagy-related signal pathways has been mainly focused on the classical mTOR signal pathway, autophagy could also be regulated by other mTOR-independent signal pathways, such as the silent information-regulated transcription factor 1 (SIRT1) signal pathway and the peroxisome proliferator activated receptor alpha (PPAR-α) signal pathway [178].

SIRT1, a nicotinamide adenosine dinucleotide-dependent class-III protein deacetylase, is widely expressed in the brain and is involved in regulating important processes such as neurogenesis, neuroprotection, synaptic plasticity, and memory formation [179]. SIRT1 expression has been reported to be significantly downregulated in the brains of patients with AD [180]. *In vivo* experiments showed that inhibition or knockdown of SIRT1 exacerbated synaptic loss and impaired the ability of

Table 1
Effects of TCM and its active ingredients on preventing and treating AD.

Active ingredients	Herb source	Experiments of the TCM Group		Molecular mechanisms and outcomes	Signal pathways	Ref.
		In-Vivo model	*In-Vitro* model			
Baicalin (BAI)	Huang Qin (*Scutellaria baicalensis* Georgi)	APP/PS1 double transgenic AD mice	–	↓: TLR4, p-NF-κB p65, p-IκBα, NLRP3, iNOS, IL-1β, IL-18	TLR4/NF-κB NLRP3	[30]
Sesame oil (SO)	Zhi Ma (*Sesamum indicum* L.)	$AlCl_3$-induced AD mice	–	↑: BDNF, PPAR-γ ↓: NF-κB, p38MAPK, Aβ, TNF-α, IL-1β, AChE	NF-κB/p38MAPK/ BDNF/PPAR-γ	[33]
Tanshinone IIA	Dan Shen (*Salvia miltiorrhiza* Bge.)	APP/PS1 double transgenic AD mice	$Aβ_{1–42}$-induced BV2 cells, U87 cells	↓: RAGE, p-IκBα, p-NF-κB/p65, Aβ, TNF-α, IL-6, IL-1β	RAGE/NF-κB	[36]
Forsythoside B (FTS•B)	Lian Qiao (*Forsythia suspensa* (Thunb.) Vahl)	APP/PS1 double transgenic AD mice	–	↑: WDFY1, TLR3, p-IRF3 ↓: ELKS, p-IKK(α + β), p-IκBα, p-NF-κB (Ser536), Aβ, p-Tau, 4-HNE, GFAP	NF-κB	[37]
Corydalis edulis total alkaloid (CETA)	Yan Hu Suo (*Corydalis yanhusuo* W.T.Wang)	D-gal-induced AD rats	–	↑: MAP2, SOD, CAT ↓: NF-κB, Aβ, ROS, MDA, L-1β, TNF-α	MAP2/NF-κB	[38]
Rhynchophylline (Rhy)	Gou Teng (*Uncaria rhynchophylla* (Miq.) Jacks.)	$Aβ_{1–42}$-induced AD mice	–	↑:Nrf2, HO-1, NOQ1, GCLM, GSH ↓: ROS, MDA	Nrf2/ARE	[51]
Astragalus polysaccharide (APS)	Huang Qi (*Astragalus membranaceus* (Fisch.)	APP/PS1 double transgenic AD mice	–	↑: Nrf2, SOD, GSH-Px ↓: MDA	Nrf2	[52]
Oxyphylla A	Yi Zhi (*Alpinia oxyphylla* Miq.)	SAMP8 mice	–	↑: Nrf2, HO-1, NQO1 ↓: Keap1, APP, $Aβ_{1–40}$, $Aβ_{1–42}$	Nrf2/Keap1/HO-1	[53]
Centella asiatica water extract (CAW)	Ji Xue Cao (*Centella asiatica* (L.) Urb.)	5xFAD mice	–	↑: Nrf2, HO-1, NQO1, GCLC ↓: Aβ	Nrf2	[54, 55]
Hydroxy-α-sanshool (HAS)	Hua Jiao (*Zanthoxylum schinifolium* Sieb. et Zucc.)	D-gal/$AlCl_3$-induced AD mice	–	↑: Nrf2, HO-1, SOD, GSH-Px, CAT, Bcl-2 ↓: MDA, Cyt-C, Bax, Caspase 3	Nrf2/HO-1	[56]
Curcumin (CUR)	Jiang Huang (*Curcuma longa* L.)	APP/PS1 double transgenic AD mice	–	↓: HMGB1, RAGE, TLR4, NF-κB/p65	HMGB1/RAGE/ TLR4/NF-κB	[70]
Hesperidin (HP)	Chen Pi (*Citrus reticulata* Blanco)	APP/PS1 double transgenic AD mice	–	↑: Nrf2, HO-1, SOD, GSH-Px, CAT ↓: NF-κB/p65, p-IκBα, TNF-α, CRP, MCP-1	Nrf2 NF-κB	[79]
Pinoresinol diglucoside (PDG)	Du Zhong (*Eucommia ulmoides* Oliv.)	$Aβ_{1–42}$-induced AD mice	–	↑: Nrf2, HO-1, SOD, CAT, Bcl-2/Bax ↓: NF-κB/p65, IL-1β, TNF-α, ROS, MDA, Cyt-C, cleaved caspase-3	Nrf2/NF-κB	[80]
Isoliquiritigenin (ISL)	Gan Cao (*Glycyrrhiza uralensis* Fisch.)	–	AβO-induced BV2 cells, N2a cells	↑: Nrf2, HO-1, NQO1 ↓: NF-κB, iNOS, COX-2, IL-1β, IL-6, TNF-α, NO	Nrf2/NF-κB	[81]
Platycodin D (PLD)	Jie Geng (*Platycodon grandiflorum* (Jacq.) A.DC.)	–	$Aβ_{1–42}$-induced BV2 cells	↑: IκBα, Nrf2, HO-1, NQO1, SOD ↓: TLR4, p-NF-κB/p65, TNF-α, IL-1β, IL-6, ROS, MDA	TLR4/NF-κB Nrf2/HO-1	[82]
Higenamine (HIG)	Fu Zi (*Aconitum carmichaelii* Debx.)	–	LPS-induced BV2 cells	↑: Nrf2, HO-1, cytoplasmic IκBα ↓: Nuclear NF-κB/p65, cytoplasmic p-IκBα, ROS, iNOS, NO, COX2, IL-6, TNF-α	Nrf2/HO-1 NF-κB	[83]
α-Cyperone	Xiang Fu (*Cyperus rotundus* L.)	–	LPS-induced BV2 cells	↑: Nuclear Nrf2, HO-1, p-Akt, IκBα ↓: p-NF-κB/p65, p-IκBα, TNF-α, IL-6, IL-1β	Akt/Nrf2/HO-1 NF-κB	[84]
Cornel iridoid glycoside (CIG)	Shan Zhu Yu (*Cornus officinalis* Sieb.et Zucc.)	P301S transgenic mice	–	↑: NMDAR subunits GluN1, GluN2A, GluN2B, AMPAR subunit GluA1 ↓: p-JAK2, p-STAT1, STAT1	JAK2/STAT1	[98]
Ganoderic acid A (GAA)	Ling Zhi (*Ganoderma lucidum* (Leyss.ex Fr.) Karst.)	D-gal-induced AD mice	–	↑: IL-10, TGF-β1, IL-35, Foxp3 ↓: p-JAK, p-STAT, ROR-γt, IL-17A, IL-17 F, IL-6, IL-21, IL-22	JAK/STAT	[99]
β-Asarone	Shi Chang Pu (*Acorus tatarinowii* Schott)	APP/PS1 double transgenic AD mice	–	↑: p-mTOR, p62 ↓: p-Akt、Beclin-1, LC3B, APP, $Aβ_{42}$, AChE	PI3K/Akt/mTOR	[176]
β-Asarone	Shi Chang Pu (*A. tatarinowii* Schott)	–	$Aβ_{1–42}$-induced PC12 cells	↑: p-Akt, p-mTOR ↓: Beclin-1, NSE	Akt/mTOR	[177]
Protopine (PRO)	Yan Hu Suo (*C. yanhusuo* W. T.Wang)	3xTg-AD mice, P301S tau mice	SHSYP301L cells, N2A cells,	↑: Acα-tubulin, HSP70, HSP90, HSC70, acetylated HSP90 ↓: PHF1, AT8, CP13, ALZ50, MC1, HT7, TAU5, ubiquitin	Ubiquitin-proteasomal pathway	[113]
Celastrol (Cel)	Lei Gong Teng (*Tripterygium wilfordii* Hook. f.)	3xTg-AD mice, P301S tau mice	CF-7 cells, N2a cells	↑: LC3B-II, LAMP1, nucleus TFEB ↓: AT8, PHF1, CP13, MC1, Total Tau proteins, SQSTM1/p62	Autophagy-lysosome pathway	[133]
Panax notoginseng saponins (PNS)	San Qi (*Panax notoginseng* (Burk.) F. H. Chen)	–	Aβ-induced PC12 cells	↑: LC3II/I, PINK1, parkin, NDP52 ↓: p62, OPTN	Autophagy-lysosome pathway	[134]
β-Asarone	Shi Chang Pu (*A. tatarinowii* Schott)	–	APPswe-overexpressing PC12 cells	↓: Beclin-1, p62, LC3-II, $Aβ_{1–42}$	Autophagy-lysosome pathway	[135]
Oxyresveratrol (OxyR)	Sang Zhi (*Morus alba* L.)	–	cortical astrocytes	↑: LC3-II, p-AMPK, p-ULK1 (Ser757), p-ULK1 (Ser555), LAMP1	AMPK/ULK1/ mTOR	[169]

(*continued on next page*)

Table 1 (*continued*)

Active ingredients	Herb source	Experiments of the TCM Group		Molecular mechanisms and outcomes	Signal pathways	Ref.
		In-Vivo model	*In-Vitro* model			
				↓: APP, p62/SQSTM1, p-S6 (Ser240/244)		
Polygala tenuifolia extract	Yuan Zhi (*Polygala tenuifolia* Willd.)	–	SH-SY5Y cells	↑: LC3II /LC3I, p-AMPK (Thr172), Raptor (Ser792) ↓: Aβ, p-mTOR (Ser2448), p70s6k (Thr389),	AMPK/mTOR	[171]
Galangin (GA)	Gao Liang Jiang (*Alpinia officinarum* Hance)	–	okadaic acid-induced PC12 cells	↑: p-Akt, p-mTOR ↓: β-secretase, $A\beta_{42}$, p-tau, p-GSK3β, Beclin-1	Akt/GSK3β/mTOR	[172]
Curcumin (CUR)	Jiang Huang (*C.longa* L.)	APP/PS1 double transgenic AD mice	–	↑: Beclin-1, LC3 I/II ↓: PI3K, p-AKT, p-mTOR	PI3K/Akt/mTOR	[174]
β-Asarone	Shi Chang Pu (*A.tatarinowii* Schott)	APP/PS1 double transgenic AD mice	–	↓: AChE, $A\beta_{42,}$ p-Akt, Beclin-1, LC3B, APP,	PI3K/Akt/mTOR	[176]
β-Asarone	Shi Chang Pu (*A. tatarinowii* Schott)	–	$A\beta_{1-42}$-induced PC12 cells	↑: p-Akt, p-mTOR ↓: NSE, Beclin-1	Akt/mTOR	[177]
Resveratrol (RSV)	Hu Zhang (*Polygonum cuspidatum* Sieb. et Zucc.)	–	$A\beta_{25-35}$-induced PC12 cells	↑: SIRT1, PARP1, TyrRS, LC3-II ↓: p62	TyrRS-PARP1-SIRT1	[198]
fisetin	Zao Jiao Ci (*Gleditsia sinensis* Lam.)	Pb-treated mice	–	↑: LC3-II, Beclin-1, SNAP-25, PSD-95, p-CREB, p-CaMKII, p-AMPK, SIRT1	AMPK/SIRT1	[199]
Cynanchum otophyllum extract	Qing Yang Shen (*Cynanchum otophyllum* Schneid.)	3xTg-AD mice	–	↑: PPARα, TFEB, LC3B-II, LAMP1, Mature CTSD ↓: $A\beta_{1-42}$, $A\beta_{1-40}$, APP, CTF, p-APP, p-CTF, PHF1, CP13, MC1, AT8, HT7	PPARα-TFEB	[200]
Cinnamic acid (CA)	Rou Gui (*Cinnamomum cassia* Presl)	5XFAD mice	–	↑: LC3B-II, LAMP2, Cln2, TPP1, Cathepsin B, PPARα, TFEB ↓: Aβ	PPARα	[201]

learning and memory in AD mice [181,182]. In contrast, overexpression of SIRT1 reduced Aβ aggregation, promoted Tau protein deacetylation and improved Tau pathological propagation, thus improving cognitive function and reducing mortality [183,184]. In addition, SIRT1 has an important role in autophagy regulation and could activate autophagy through deacetylation of some Atg proteins [185]. From these, it is clear that SIRT1 is closely related to autophagy regulation and AD progression.

PPARα, PPARδ, and PPARγ are transcription factors that regulate gene expression upon ligand activation [186]. Among them, PPARα is responsible for the regulation of cellular metabolism and energy homeostasis [187], including the fatty acid β-oxidation pathway, glucose metabolism, and glutamatergic and cholinergic/dopaminergic neurotransmission in the brain [188]. Cumulative evidence suggested strong association between PPARα and AD. For instance, PPARα-null mice were found to have deficits in spatial learning and memory abilities [189]. Moreover, activation of PPARα-mediated autophagy and lysosomal pathway could inhibit the accumulation of Aβ in hippocampal and cortical tissues of APPswe/PSEN1dE9 mice and ameliorate their spatial learning deficits, memory deficits, and anxiety symptoms [190], suggesting that PPARα is required for the maintenance of normal cognitive performance [191]. In addition, it has been reported that PPARα could induce the expression of ADAM10 (a disintegrin and metalloproteinase 10) in the brain of flag-TFEB transgenic mice in an autophagy-dependent manner and stimulate APP processing toward the alpha-secretase pathway, thus increasing soluble amyloid precursor protein alpha production and reducing c-terminal fragment-β (CTF-β) level, thereby exerting definite neuroprotective effects [192].

Resveratrol (RSV) is a natural phenolic compound widely found in *Polygonum cuspidatum* Sieb. et Zucc. (Hu Zhang), *Morus alba* L. (Sang Bai Pi), *Magnolia officinalis* Rehd. Et Wils. (Hou Po), and other Chinese herbs [193]. Recent studies have identified RSV as a natural autophagy modulator against AD [194], which could inhibit inflammatory cytokine release, modulate mitochondrial function, reduce Aβ deposition, and improve impaired cognitive performance [195–197]. RSV was found to inhibit the $A\beta_{25-35}$-induced decrease in viability of PC12 cells; upregulate LC3-II expression; promote autophagosome formation and p62 degradation; and increase the expression of SIRT1, auto-poly-ADP-ribosylation of poly polymerase 1 (PARP1), and tyrosyl transfer-RNA synthetase (TyrRS) proteins [198]. These findings suggested that RSV may induce autophagy through activation of the TyrRS-PARP1-SIRT1 signal pathway, thus attenuating $A\beta_{25-35}$-induced neurotoxicity. Furthermore, Yang et al. [199] found that fisetin could attenuate Pb-induced synaptic dysfunction and cognitive impairment by regulating AMPK/SIRT1 signal pathway and autophagy pathway.

Iyaswamy et al. [200] found that *Cynanchum otophyllum* Schneid. (Qing Yang Shen, QYS) could significantly improve spatial memory and learning ability in 3xTg-AD mice; reduce the accumulation of insoluble Aβ aggregates and phosphorylated Tau aggregates; downregulate the expression of APP, CTF, p-APP, p-CTF, and Sarcosyl-insoluble fractions of phosphorylated Tau proteins (PHF1, CP13, MC1, AT8, and HT7); and increase expression levels of PPARα, TFEB, LC3B-II, LAMP1, and mature CTSD. These findings suggested that QYS could promote ALP through activation of the PPARα-TFEB signal pathway, thus alleviating AD pathology and promoting recovery of cognitive function. In addition, in 5XFAD mice, cinnamic acid also could activate PPARα, upregulate TFEB, and increase lysosome biosynthesis, thus inhibiting the production of SPs and improving memory function in AD mice [201].

3. Conclusion

Intracellular signal pathways mediate significant events in cellular life cycle, and they are closely associated with AD development. Simultaneously, during the evolution of organisms, complex and close connections have been established between major signal pathways [202]. In the present study, the action mechanisms and potentials of TCM against AD were synthesized and summarized from the perspective of signal pathways (Tables 1 and 2). Chinese herbs could regulate signal pathways related to AD pathological progression, such as NF-κB, Nrf2, JAK/STAT, ubiquitin-proteasome pathway, autophagy-lysosome pathway-related AMPK/mTOR, GSK-3/mTOR, and PI3K/Akt/mTOR, as well as SIRT1 and PPARα pathway. They could regulate crosstalk between pathways through multitarget synergy, thus maintaining chronic inflammatory interaction balance, inhibiting oxidative stress damage,

Table 2
Effects of Chinese herbal formulas on preventing and treating AD.

Herbal formula	Ingredients	Experiments of the TCM Group		Molecular mechanisms and outcomes	Signal pathways	Ref.
		In-Vivo model	*In-Vitro* model			
Modified Huanglian-Jie-Tu-Tang (HLJDT-M)	Huang Lian (*Coptis chinensis* Franch.), Huang Qin (*Scutellaria baicalensis* Georgi), Huang Bo (*Phellodendron amurense* Rupr.), Zhi Zi (*Gardenia jasminoides* Ellis)	3XTg-AD mice	N2a-SwedAPP cells	↓: $A\beta_{1-42}$, FL-APP, CTFs, pAPP, PHF-1 Tau, total Tau, pCTFs	–	[19]
NaoXinTong Capsule (NXT)	Huang Qi (*Astragalus membranaceus* (Fisch.), Chi Shao (*Paeonia lactiflora* Pall.), Dan Shen (*Salvia miltiorrhiza* Bge.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Chuan Xiong (*Ligusticum chuanxiong* Hort.), Tao Ren (*Prunus persica* (L.) Batsch), Hong Hua (*Carthamus tinctorius* L.), Ru Xiang (*Boswellia carterii* Birdw.), Mo Yao (*Commiphora myrrha* Engl.), Ji Xue Teng (*Spatholobus suberectus* Dunn), Niu Xi (*Achyranthes bidentata* Bl.), Gui Zhi (*Cinnamomum cassia* Presl), Sang Zhi (*Morus alba* L.), Di Long (*Pheretima aspergillum* (E. Perrier), Quan Xie (Buthus martensii Karsch), Shui Zhi (*Whitmania pigra* Whitman)	APP/PS1 double transgenic AD mice	–	↓: NF-κB, TLR4, Aβ, p-Tau, IL-1β, IL-6, TNF-α	TLR4/NF-κB/IL-1β	[31]
Sanweidoukou decoction (DK-3)	Bai Dou Kou (*Amomun kravak* Pierre ex Gagnep), Bai Ju Sheng (*Lactuca satica* L.), Bi Ba (*Piper longum* L.)	$A\beta_{25-35}$-induced AD rats	$A\beta_{25-35}$-induced PC12 cells	↓: p-NF-κB, nuclear NF-κB/p65, p-p38, p-ERK1/2, p-JNK, IL-6, COX-2, IL-1β	MAPK/NF-κB	[34]
Qifu-Yin (QFY)	Ren Shen (*Panax ginseng* C. A. Mey.), Shu Di (*Rehmannia glutinosa* Libosch.), Dang Gui (*A. sinensis* (Oliv.) Diels), Bai Zhu (*Atractylodes macrocephala* Koidz.), Suan Zao Ren (*Ziziphus jujuba* Mill. var. spinosa(Bunge) Hu ex H. F. Chou), Yuan Zhi (*Polygala tenuifolia* Willd.), Gan Cao (*Glycyrrhiza uralensis* Fisch.)	AGE-induced AD rats	–	↓: RAGE, NF-κB, Aβ, TNF-α, IL-1β	RAGE/NF-κB	[35]
Yizhiqingxin Formula (YQF)	Ren Shen (*P. ginseng* C. A. Mey.), Huang Lian (*C. chinensis* Franch.), Chuan Xiong (*L. chuanxiong* Hort.)	APP/PS1 double transgenic AD mice	–	↑: Beclin 1, LC3II/LC3I, cathepsin D, V-ATPase ↓: mTOR, Aβ	mTOR	[205]
Shenzhiling oral liquid (SZL)	Gui Zhi (*C. cassia* Presl), Bai Shao (*Raeonia lactiflora* Pall.), Fu Ling (*Poria cocos* (Schw.) Wolf), Shi Chang Pu (*Acorus tatarinowii* Schott), Yuan Zhi (*P. tenuifolia* Willd.), Long Gu (*Dragon bone* Fossil), Mu Li (Ostrea gigas Thunberg), Gan Cao (*Gl. uralensis* Fisch.), Gan Jiang (*Zingiber officinale* Rosc.)	APP/PS1 double transgenic AD mice	–	↑: p-PI3K, PI3K, p-Akt, Akt, p-mTOR, and mTOR, MBP, PLP, MAG ↓: $A\beta_{42}$, $A\beta_{40}$, G-ratio (d_{axon}/d_{fiber})	PI3K/Akt/mTOR	[206]
Suan-Zao-Ren decoction (SZRD)	Suan Zao Ren (*Z. jujuba* Mill. var. spinosa(Bunge) Hu ex H. F. Chou), Fu Ling (*P. cocos* (Schw.) Wolf), Chuan Xiong (*L. chuanxiong* Hort.), Zhi Mu (*Anemarrhena asphodeloides* Bge.), Gan Cao (*G. uralensis* Fisch.)	APP/PS1 double transgenic AD mice	–	↓: p-JAK2-Tyr1007, p-STAT3-Tyr705, $A\beta_{1-42}$, $A\beta_{1-40}$, IL-6, IL-1β, TNF-α	JAK2/STAT3	[94]
Yuan-Hu Zhi Tong Prescription (YZT)	Yan Hu Suo (*Corydalis yanhusuo* W. T. Wang), Bai Zhi (*Angelica dahurica* (Fisch.ex Hoffm.) Benth.et Hook.f.)	P301S tau mice, 3XTg-AD mice	SH-SY5Y-P301L cells, 7PA2 cells	↓: AT8, AT100, AT180, MC1, PHF1, HT7, TAU5, poly ubiquitin, ubiquitin K48	Ubiquitin-proteasomal pathway	[112]
Yuan-zhi-san (YZS)	Yuan Zhi (*P.tenuifolia* Willd.), Huang Lian (*C. chinensis* Franch.), Ren Shen (*P. ginseng* C. A. Mey.), Fu Ling (*P. cocos* (Schw.) Wolf), Shi Chang Pu (*A. tatarinowii* Schott)	$A\beta_{1-40}$-induced AD rats	–	↑: UbE1a/b, UbE2a, CHIP, UCH-L1, 26 S proteasome ↓: p-S199, p-T231	Ubiquitin-proteasomal pathway	[114]

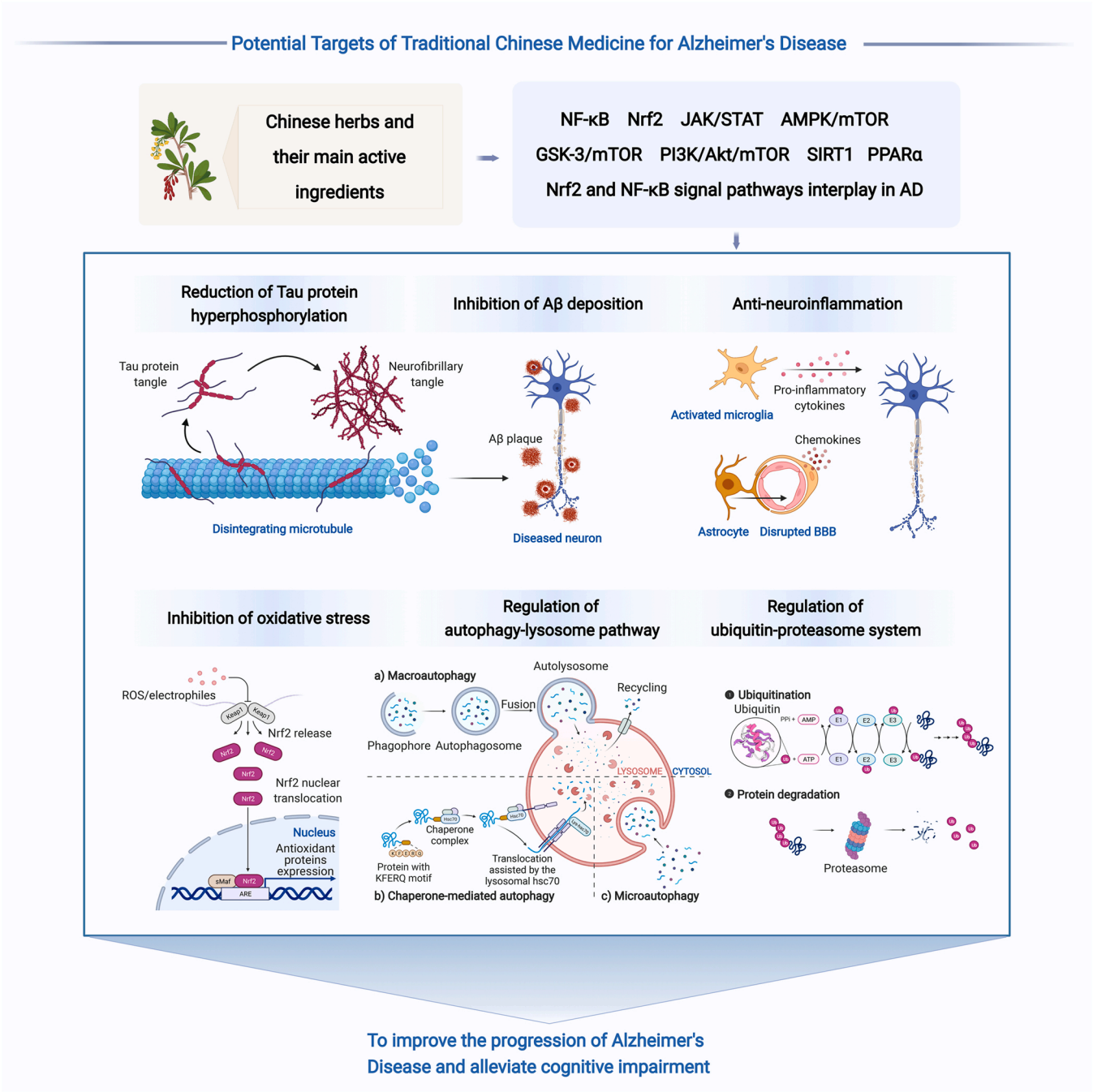

Fig. 1. Potential targets of TCM for treating AD. TCM could regulate signal pathways related to AD pathological progression, including NF-κB, Nrf2, JAK/STAT, ubiquitin-proteasome pathway, autophagy-lysosome pathway-related AMPK/mTOR, GSK-3/mTOR, and PI3K/Akt/mTOR, as well as SIRT1 and PPARα pathway. These signal pathways involved in Aβ deposition, Tau protein hyperphosphorylation, oxidative stress, neuroinflammation, protein degradation and autophagy. TCM are therefore alleviating the AD progression and improving cognitive impairment. This figure was created with BioRender (https://biorender.com/).

regulating ubiquitin-proteasome system function, modulating autophagy, and ultimately improving cognitive impairment in patients with AD (Fig. 1). Considering the complexity of AD pathological mechanisms, TCM with multilevel and multitarget potential may become a breakthrough for AD therapeutic drug development. The prospects for exploring and developing potential novel anti-AD drugs from TCM and its active ingredients are broad. Besides, signal pathways such as HIPPO [203] and Notch [204] are closely related to delaying AD development. However, relatively few studies have reported on the prevention and treatment of AD through these pathways, and this could be one of the directions to be further explored in the future. To sum up, future research on the prevention and treatment of AD in TCM should be carried out in depth to provide new ideas for exploring the pathogenesis of AD and screening potential targets for the treatment of AD, and to lay a certain foundation for further development of novel AD therapeutic drugs.

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CRediT authorship contribution statement

Minrui Ding: Software, Writing – original draft, Writing – review & editing. **Yanjie Qu:** Writing – review & editing. **Bing Hu:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Hongmei An:** Conceptualization, Methodology, Project administration.

Authors' contributions

HMA and BH designed the study, coordinated technical support and funding. BH revised the manuscript. MRD performed the study and drafted the manuscript. YJQ participated the study. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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