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Novel Mechanisms of Some Traditional Chinese Medicine for the Therapy of Neurocognitive Disorders*

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Abstract This review summarizes recent progress of the anti-inflammatory effect of traditional Chinese medicine on neurocognitive disorders caused by Alzheimer's disease (AD) and Parkinson's disease (PD), and discusses some novel molecular mechanisms of traditional Chinese medicine (such as Xylocoside G, Formononetin, Honokiol, Sodium oligomannate and safflower flavonoid extract), including the regulation on Aβ generation and aggregation, tau phosphorylation, gut-brain axis and gut microbiota, autophagy, microglia polarization, extracellular space, neurogenesis and neurotransmission, for the treatment of AD and PD related neurocognitive disorders.

Key words Alzheimer's disease, inflammation, β-amyloid protein, tau, microglial polarization, extracellular space
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Neurocognitive disorder is generally described by decline in the mental functioning[1]. The presence of cognitive deficits is a key clinical feature of neurocognitive disorder related medical condition. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the cluster of neurocognitive disorder consists of three syndromes, namely delirium, mild neurocognitive disorder and major neurocognitive disorder[1]. Each syndrome may be induced by a variety of etiologies and display diverse clinical characteristics. Clinically, the diagnosis of neurocognitive disorders is based on both disease phenotypes and potential causative factors. Mild and major neurocognitive disorders therefore can be further classified into different subtypes according to their etiologies. For example, a range of neurodegenerative diseases (*e.g.* Alzheimer's disease, Frontotemporal lobar degeneration and Parkinson's disease) may impair the cognitive and behavioral abilities of individuals aged 65-year or older. Non-neurodegenerative factors such as cerebrovascular diseases, HIV infections or traumatic brain injuries could also lead to cognitive impairments. Identifying the causative factor in neurocognitive disorders could facilitate the diagnosis and treatment of the disease.

1 Neuroinflammation in Alzheimer's disease

Major neurocognitive disorder in the elderly is also termed as dementia[1]. The global prevalence of dementia has attracted public concern due to the

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increasing trend of ageing and the lack of effective interventions. It was estimated that there were 35.6 million people suffering from dementia worldwide in 2010[2]. China has the largest population in the world and is therefore facing the greatest challenge of population ageing and ageing related chronic diseases[3]. It has been estimated that patients with dementia in China accounts for about 25% of total dementia cases worldwide[4]. AD has been identified as one of the leading causes of neurodegenerative dementia in the elderly, contributing to more than 60% of all dementia cases[5]. The progressive decline in cognition and memory of Alzheimer's patients is accompanied by the accumulation of extracellular β-amyloid (Aβ) proteins in the form of diffusible species and amyloid plaques, and the presence of neurofibrillary tangles (NFTs) and neuropil threads derived from hyperphosphorylated tau proteins[6-7]. The amyloid cascade hypothesis proposes that the misfolding and aggregation of Aβ might be the initiating event of the pathogenesis and is able to trigger neuropathological changes including tau hyperphosphorylation, synaptic dysfunction and neuronal damages, finally leading to cognitive and memory impairments[8]. Although these two key pathological features of AD have been extensively investigated to understand the pathogenesis of the disease, as well as to develop therapeutical strategies, there are only four symptomatic treatments (three cholinesterase inhibitors and an NMDA receptor modulator) available for the management of cognitive dysfunction in AD patients[9]. Recent phase III clinical trials targeting Aβ via anti-Aβ antibodies or secretase modulators were not successful because of the lack of clinical efficacies on the cognitive function of participants and safety concerns[10]. This prompts the reconsideration of the role of Aβ aggregation in the progression of AD and the development of new disease-modifying targets.

In addition to the abovementioned key neurological changes in the brain of AD patients, it has also been noted that sustained neuroinflammation can be observed throughout all stages of AD[11]. The inflammatory response is a complex cascade reaction of tissue toward injuries, toxins or infection. Human body uses a variety of inflammatory regulators to modulate the inflammatory response and maintain the balance between anti- and pro-inflammation, which is critical for the homeostasis and normal functioning of cells[11]. While in AD and other neurocognitive disorders, it has been demonstrated that the balance between anti- and pro-inflammatory effects is disrupted, probably owing to the dysregulation of the neuroimmune system during the progression of diseases[7,12]. The chronic inflammation in AD was first noticed by the co-localization of immune-related proteins with Aβ plaques in the brain, and was further supported by the presence of reactive astrogliosis and microgliosis surrounding amyloid plaques or tau tangles in the grey matter[13]. NLR family, pyrin domain containing 3 protein (NLRP3) inflammasome is an emerging protein complex that has been demonstrated to tightly participate in neuroinflammation in AD through modulating the generation of cytokines and active caspases[14-15]. The activation of NLRP3 inflammasome has been observed in cellular and animal models of AD[15]. Clinical evidence also demonstrated that AD patients have higher levels of cleaved caspase-1 and pro-inflammatory cytokines such as TNF-α or IL-6 in brain tissues than the control individuals do[16-17]. Recent genetic studies implicate a correlation between mutations in immune-related genes and increased risk of developing AD[18]. Microglia and astrocytes are important regulators of neuroimmune response in the brain. In the absence of toxins or stimuli, microglia stay in rest state and maintain the local environment and communications with neurons or other glial cells[19]. The activation of microglia in AD is thought to be initiated by Aβ aggregates, resulting in morphological changes and the migration of microglial cells[11]. Activated microglia have disparate roles in modulating the disease pathology. On the one hand, the activation of microglia enables the uptake and phagocytosis of Aβ aggregates through membrane receptors like the Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), to enhance the clearance of Aβ in the brain[7]. On the other hand, the prolonged activation of microglia might also stimulate the MAPK/NF-κB signaling pathway and up-regulate the expression of pro-inflammatory cytokines, further inducing neuroinflammation, oxidative damage and neuronal death[20]. Astrocytes comprise more than half of the total cells in the brain and are essential for the energy metabolism, synaptogenesis and neurogenesis in the central nervous system. It is shown that the release of pro-inflammatory cytokines could recruit and activate astrocytes, which will further exacerbate

the neuronal function by causing oxidative stress and excitotoxicity[21]. Mounting evidence also points out that neuroinflammation could deteriorate both Aβ and tau pathologies in the brain. Lee *et al*.[22] reported that intraperitoneal injection of LPS induced memory impairment in mouse models. Further research confirmed that inflammatory cytokines induced by the LPS treatment increase the expression of amyloid precursor protein (APP) and alter the amyloidogenic processing of APP by up-regulating both the protein level and enzymatic activity of β- and γ-secretases, thereby strongly elevating the generation of Aβ species. The vicious cycle between tau pathology and neuroinflammation was also established by findings showing that LPS induced neuroinflammation directly activated CDK5/p25 and increased tau phosphorylation independent of changing APP processing pathway[23-24]. Additional damages caused by neuroinflammation include the disruption of the blood brain barrier (BBB) integrity that is fundamental for the maintenance of a stable and toxin-free environment for the CNS[25]. Festoff *et al*. [26] found that pro-inflammatory mediators thrombin and high-mobility group box protein 1 (HMGB1) are significantly increased in the serum of AD patients compared with age-matched controls. Besides, this increase correlates well with the decrease in BBB integrity, suggesting a causative role of neuroinflammation in BBB dysfunction. Overall, neuroinflammation, as the third key pathological feature of AD, occurs in very early stage of disease progression and may represent a promising target for the early intervention of AD.

2 Anti−inflammatory effect of traditional Chinese medicine

The first evidence that anti-inflammatory agents might confer protective effects on AD came from several large epidemiological studies showing that individuals with a long history of non-steroidal anti-inflammatory drug (NSAID) usage have a significant reduction (~50%) in the risk of developing AD[27]. Since then continuous effort has been made to develop potential anti-inflammatory therapeutics to slow down or even prevent the progression of AD. China has a very long history of using medicinal herbs for the management of various medical conditions, including neurological diseases. The long practice of traditional Chinese medicine (TCM) has accumulated numerous experiences in dealing with neurocognitive disorders with different causes. An interesting property of TCM is that a lot of agents have been found to possess anti-inflammatory effect as demonstrated by experiments using different models and systems. In general, TCM-based treatments are either applied as extracts of total plants or as isolated active compounds, depending on whether it is possible to identify the effective components. TCM formulas have also been tested in clinical trials for the treatment of neurocognitive disorder in China[28-30]. A recent study by Li *et al*. [31] reported that decoctosomes, exosome-like nanoparticles found in TCM decoctions, exhibit excellent anti-inflammatory effects in mouse models. Many compounds, such as polyphenols, sterols, alkaloids, flavonoids, tannins, triterpenes and polysaccharides, have manifested beneficial effects against pathological changes in AD[32]. Natural polyphenols like resveratrol and Epigallocatechin-3-gallate (EGCG) are widely consumed in daily diets. These compounds contain multiple phenolic groups and are capable of scavenging reactive oxygen species (ROS), while studies have also shown that polyphenols are also able to inhibit inflammatory response simultaneously. For example, both resveratrol and EGCG could interfere with the signal transduction of NF-κB in cell and animal models through decreasing its nuclear translocation and reducing the phosphorylation process, respectively[33-34]. The clinical effect of resveratrol was also tested in a small clinical trial, showing that the compound modulated neuroinflammation response and may slow down the cognitive decline of AD patients[35]. Xylocoside G (XG) is a phenolic glycoside isolated from stems of *Itoa orientalis*. The plant has been used to treat rheumatism and hepatitis. By using cell models exposed to oligomeric Aβ species, Yu *et al*. in our lab[36] first reported that XG suppresses the phosphorylation of JNK and reduces the nuclear translocation of NF-κB/p65, consequently down-regulating the expression of inflammatory mediators COX-2, PGE2, TNF-α and IL-1β (Figure 1). XG further protects neuronal cells against Aβ induced apoptosis[36]. Guo *et al*. [37] showed that the ethyl acetate (EtOAc) extract of *Picrasma quassioides* strongly attenuated the generation of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) in

mice treated with Aβ. They further identified several alkaloids as active components responsible for the neuroprotective effect of the extract on mouse models. Ginkgo biloba leaves are traditionally used for the treatment of memory impairments in aged population. The ginko biloba extract EGb 761 contains a number of active compounds including flavonoids, organic acids and terpenoid. Long term treatment with EGb761 not only inhibits microglial activation and neuroinflammation[38-39], but also eliminates reactive oxygen species in the brain of AD mice[40], suggesting a protective effect of the extract on Alzheimer's pathological changes. Flavonoids such as quercetin, scutellarein and anthocyanin could influence the MAPKs/NF- κB signaling pathway and reduce the level of inflammatory markers both *in vitro* and *in vivo*[41-43]. Generally, the anti-inflammatory effect of TCM on AD converges on regulating the NF- κB signaling pathway, the key regulator of inflammatory response in cells.

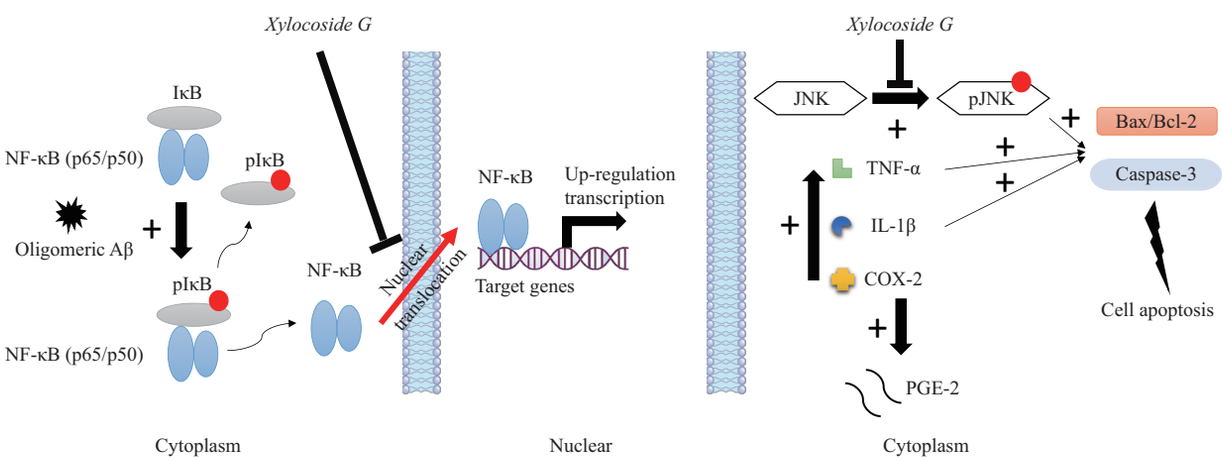

Fig. 1 The proposed mechanism of the anti−inflammatory effect of Xylocoside G（XG）on Aβ oligomer induced neurotoxicity

Xylocoside G is derived from stems of the traditional Chinese medicine *Itoa orientalis*. XG is able to suppress the nuclear translocation of NF-κB, therefore inhibiting the subsequent expression of genes involved in neuroinflammation (COX-2, TNF-α and IL-1β). Besides, it is also capable of inhibiting the phosphorylation of the JNK. All these effects contribute to the protective effect of XG against inflammatory response and apoptosis caused by Aβ oligomers. This mechanism may also apply to other Chinese medicines regarding the anti-inflammatory effect.

Neuroinflammation is closely associated with the pathological changes and progression of AD, and numerous studies have proved that TCM has excellent anti-inflammatory effects on AD and other neurological disease. Experimental evidence also suggests that TCM formulas or active components in TCM could affect AD pathologies *via* molecular mechanisms independent of inflammation related pathways[44]. These novel mechanisms complement the anti-inflammatory effect of TCM and could regulate pathological changes of AD comprehensively.

3 Regulating the biogenesis of Aβ

Aβ is the major component of amyloid plaques in the brain. It is generated by the successive proteolysis of the transmembrane amyloid precursor protein (APP) by β - and γ -secretases. Alternatively, APP could be processed by α -secretases (predominantly ADAM10), which cleaves the middle region of Aβ and abolishes the formation of the aggregation-prone Aβ[45]. Interestingly, although the amyloidogenic processing pathway is widely recognized to be toxic to the CNS, the non-amyloidogenic processing pathway is thought to be beneficial and neuroprotective through different mechanisms. The soluble-APPα (sAPPα), the extracellular fragments of APP after the α-secretase cleavage, is able to maintain the normal neuronal function and survival and preserve the mitochondrial energy metabolism[46-48]. It could also promote the axonal outgrowth and neuritogenesis in cellular and animal experiments[49]. Obregon *et al.*[50] showed in their studies that sAPPα

is also capable of directly interacting with the β-secretase and inhibiting the production of Aβ in the brain, indicating an auto-regulation mechanism of APP processing in modulating the equilibrium of Aβ generation. The neurotrophic and neuroprotective role of sAPPα might be an important approach for disease intervention. Formononetin is a soy isoflavonoid mostly found in *Astragalus mongholicus* (Bunge) and *Trifolium pretense* L. (red clover). Sun *et al*. [51] demonstrated that Formononetin promotes the expression of the α-secretase ADAM10 at transcriptional level by modulating the activity of SIRT1, thus enhancing the non-amyloidogenic processing of APP and up-regulating the production of the neuroprotective sAPPα. Ginsenoside Rh2 is a derivative from ginseng. Qiu *et al*. [52] reported that Rh2 treatment could reduce the endocytosis of APP and increase the level of sAPPα, finally improving the cognitive ability of AD mouse models. Another Ginsenoside Rg1 is also able to enhance the activity of α-secretase and promote the generation of sAPPα by the estrogen receptor signaling pathway[53]. Berberine is the main active component of *Coptidis rhizome*. Zhang *et al*. [54] showed that berberine activates the AMP-activated protein kinase (AMPK) in cells and reduces the expression of the β-secretase BACE1 in neurons, therefore reducing Aβ levels in cell models of AD. Up-regulating the non-amyloidogenic processing of APP has several advantages over a direct inhibition of Aβ generation *via* applying secretase inhibitors. First of all, this strategy avoids the interference with the normal physiological functions of β- and γ- secretases in the CNS, which has been an important concern of the safety of secretase inhibitors in clinical trials so far[55]. Second, this strategy could be applied as a preventive intervention rather than a curative treatment for AD. Nevertheless, it should be mentioned that although sAPPα is generally thought to be neuroprotective, the protein has also been found to play a role in regulating immune response as it is also secreted by lymphocytes[49]. The finding that sAPPα could stimulate microglia and induce the release of neurotoxic cytokines[56] implies that enhancing the generation of sAPPα should take place prior to the occurrence of chronic neuroinflammation in AD, otherwise it might further exacerbate the pathological changes in AD.

4 Regulating the aggregation of Aβ and the hyperphosphorylation of tau

Aβ aggregation and tau hyperphosphorylation are early pathological features of AD and are therefore important interventional targets for the early prevention of AD. Aβ monomer is an intrinsically disordered protein and lacks defined secondary structure in aqueous conditions. The aggregation of Aβ starts from the oligomerization of several monomeric species into soluble oligomers that are diffusible and highly toxic to neurons[57]. With the addition of Aβ monomers and the accumulation of β-sheet structures, oligomers grow into protofilaments and protofibrils. Finally, several protofilaments associate together to form elongated fibrils with ordered cross- β structures[57-58]. Recent evidence suggests that oligomers rather than Aβ monomers and fibrillar species are the main culprit of Aβ related neurotoxicity[59]. Aβ oligomers disrupt the membrane integrity of organelles and cells, and cause calcium overload in neurons. They are also able to interact with membrane receptors and initiate signaling pathways responsible for tau hyperphosphorylation, synaptotoxicity, inflammation and cell apoptosis[60]. The impact of TCM on the aggregation of Aβ could be assessed by using the thioflavin T (ThT) assay and atomic force microscopy imaging (AFM) *in vitro*. Liu et al. [61] examined how a *Lonicera japonica Thunb.* derived pectic polysaccharide LFA03-a influenced the aggregation of Aβ *in vitro*. LFA03-a impedes the oligomerization and fibrillation of Aβ in a dose dependent manner. Phenylethanoid glycosides extracted from *Cistanche tubulosa* chelate metal ions like iron and remodel the aggregation as well as the deposition of Aβ in an animal study[62]. Smart soup is a TCM formula against memory impairments in China. Hou *et al*. [63] studied the effects of the total formula and single component of smart soup on the aggregation of Aβ. They found that *Rhizoma Acori Tatarinowii* and *Poria cum Radix Pini* in the smart soup significantly suppress the aggregation of Aβ in a concentration dependent manner. They could also protect neurons from Aβ oligomers induced toxicities. The polyphenolic flavonoid EGCG was found to be capable of blocking the formation of toxic Aβ oligomers and strongly inhibiting the fibrillation of Aβ[64]. Honokiol, the active lignin compound isolated

from *Magnolia officinalis*, shows strong binding to the hydrophobic region of Aβ pentamers and remarkably inhibits the on-pathway aggregation of Aβ[65-66]. Although *in vitro* evidence demonstrates that some TCM formula or active components in TCM could modulate the aggregation of Aβ, it is not fully clear how this may be translated into *in vivo* environment, *e. g.* in the brain. Besides, increasing effort has been shifted toward investigating Aβ oligomers instead of the whole aggregation process of Aβ for disease intervention. Whether and how directly modulating the aggregation of Aβ by TCM could contribute to the overall pathology of AD remains to be clarified.

Tau protein is a microtubule-associated protein (MAP) that is crucial for the stability of microtubules. The phosphorylation and dephosphorylation of tau regulate the polymerization of tubulin that is important for physiological events like axonal transport and neurite outgrowth[67]. In the case of hyperphosphorylation of tau by protein kinases, these abnormal tau proteins will aggregate into paired helical filaments (PHF), leading to the formation of neurofibrillary tangles (NFT) and disrupting the normal function of microtubules in neurons in AD patients[68]. The phosphorylation of tau is modulated by tau kinases and phosphatase. GSK-3β and CDK5 are the main kinases involved in the phosphorylation process, while protein phosphatase 2 (PP2A) plays a major role in dephosphorylating tau protein[69]. In order to reduce the hyperphosphorylation of tau protein, compounds that can either down-regulate tau kinases or up-regulate phosphatase, or have dual effects, have to be identified and applied. A lot of components from TCM are reported to have such properties based on cellular and animal studies. For instance, Cornel iridoid glycoside from *Cornus officinalis* regulates the cross-talk between GSK-3β and PP2A signaling pathways and significantly reduces tau hyperphosphorylation in a rat model of tau pathology[70]. Tanshinone IIA is abundant in *Salvia miltiorrhiza,* a common treatment for cardiovascular disease in TCM. Lin *et al*. [71] demonstrated that Tanshinone IIA attenuated Aβ induced tau phosphorylation by down-regulating the activity of GSK-3β in rat models treated with Aβ. Codonopsis pilosula polysaccharide could improve the activity of PP2A and reduce the phosphorylation level of tau proteins in a mouse model. This effect could result in improved synaptic plasticity and function as well as restored learning and memory abilities in mouse models with tau pathologies[71]. It should be noted that some TCM such as the rhizome of *Salvia miltiorrhiza* might be able to modulate Aβ aggregation and tau phosphorylation concomitantly[72], implicating a promising application of these TCM in the treatment of AD.

5 Regulating the gut−brain axis

The gut-brain axis describes the communication between the central nervous system, the enteric nervous system and gastrointestinal functions[73]. The gastrointestinal tract has the biggest population of microbes in the human body. There is a dynamic interaction between the gut microbiota, nutrient metabolism and the immune system. Recent studies also demonstrated that this dynamic interaction is also linked with the pathophysiology of some neurological disorders including autism spectral disorders, Parkinson's disease (PD), depression and chronic pain[74]. Clinical data suggests that there is an alteration in the composition of the gut microbiota in patients with Alzheimer's disease compared with the normal controls[75], and this alteration is even evident in the mild cognitive impairment stage[76]. Kim *et al*. [77] found that an AD transgenic mouse model manifests a different gut microbiota pattern compared with that of the wild type mouse. Besides, the AD mouse model also displayed impaired epithelial barrier integrity and chronic intestinal and systemic inflammation. By transferring the fecal microbiota of healthy mice to the AD mice, the authors successfully reversed the AD-like pathologies and cognitive impairments in AD mice. Similarly, fecal microbiota transplantation alleviates pathological changes of APP/PS1 transgenic mice by reducing the amyloid deposition and tau hyperphosphorylation, and improving synaptic functions. Besides, the transplantation seems to be effective in ameliorating neuroinflammation in the brain of AD mice[78]. These findings indicate that the gut-brain axis could be a potential target for the management of AD. Sodium oligomannate (GV-971) is a mixture of acidic linear oligosaccharides derived from brown algae *Echlonia kurome*. Previous experiments revealed that GV-971 directly binds to multiple areas of Aβ. The binding not only suppresses the fibril formation of Aβ, but also

destabilizes already existing fibrils into monomeric species. Besides, the drug candidate promotes the clearance of Aβ *via* microglia-mediated Aβ phagocytosis[79]. By using the 5×FAD transgenic AD mouse model, Wang *et al*. [79] observed that gut microbiota alteration induced changes in the amino acid metabolism plays a role in immune cell infiltration and microglial activation in the brain of AD mice. GV-971 is able to suppress gut dysbiosis and the accumulation of phenylalanine and isoleucine, consequently restoring the balance of the immune system and the cognitive function of AD mouse models. Another group of oligosaccharides from *Morinda officinalis* (OMO) is also capable of maintaining the microbiota in APP/PS1 mice. Furthermore, it is able to decrease the level of intracellular Aβ42, thus improving the pathological swelling and neuronal apoptosis in the brain[80]. The link between the central nervous system and the peripheral system has always been a fundamental aspect for understanding the CNS functions and the development of drugs for CNS diseases. Since the brain is protected by the blood-brain barrier, drug candidates might have limited access to the expected brain regions. The development of treatments that target peripheral systems and have profound and consistent positive effects on the brain would be very desirable for a series of neurological disorders. Another aspect derived from modulating the gut-brain axis would be to harness the immune regulation effect of TCM[81], such that a positive regulation of the peripheral immune systems by TCM treatment could also influence the immune function in the brain.

6 Regulating the autophagy function

Autophagy is an important intracellular quality control system of the cell to degrade aggregated/misfolded proteins and damaged organelles. It has been shown that the autophagy function undergoes gradual decline with the process of ageing. The loss of autophagy function is much more significant in brains of AD patients than that in cognitively normal control. For example, there are more autophagosomes in the frontoparietal cortex of AD patients compared with control individuals[82]. Additionally, proteins which regulate the autophagy pathway are also down-regulated in the brain of AD patients[83]. These results suggest that the normal autophagy function is impaired during the progression of AD. As a protective mechanism of the cell against cellular stress, the autophagy system could be activated in the presence of Aβ aggregates and hyperphosphorylated tau proteins, while it seems that neurons are not able to complete the full autophagy process and are stuck somewhere in the middle, leading to the aberrant accumulation of autophagosomes[84]. Therefore, neurons are not able to eliminate the toxic Aβ and tau aggregates, contributing to neuronal damages in AD. The core upstream regulator of the autophagy function is the mammalian target of rapamycin (mTOR) complex protein. Down-regulation of the PI3K/Akt/mTOR signaling pathway induces the enhancement of autophagy function and subsequent Aβ degradation[85-86]. Other important regulators of autophagy include the AMPK/ULK1 pathway and the Bcl-2/Beclin-1 pathway. Therefore, molecules that could influence either pathway might have an impact on the autophagy function. As an example, resveratrol was reported to be capable of activating AMPK and inducing the autophagy and lysosomal degradation of Aβ[87]. Piperlongumine, an alkaloid extract from *Piper longum* L., promotes the phosphorylation of Bcl-2 at Ser70. This in turn facilitates its dissociation from the Beclin-1 complex and enhances the autophagy function[88]. Meng *et al*. [89] characterized how the saponin component gypenoside XVII from ginseng and Panax notoginseng affect the autophagy function using different models. The compound activates transcription factor EB (TFEB) and induces autophagy as well as lysosome biogenesis, thereby removing accumulated Aβ species and preventing the deposition of Aβ plaques. A very comprehensive summary of the effects of herbal medicine on the autophagy function in AD can be found in the review of Zeng *et al*.[85]. Although autophagy enhancement is generally thought to be protective in AD, over-activation of autophagy might cause detrimental effects in the brain. The accumulation of Aβ -containing autophagosomes in neurons may overwhelm the degradation capacity of cells, thus leading to intracellular toxicity and probably the release of Aβ into extracellular space[85,90]. Considering the contrasting roles of autophagy function in AD, it would make sense to select molecules that could direct autophagy toward Aβ and tau clearance for disease intervention.

7 Regulating the interstitial fluid （ISF） in the brain

The extracellular space (ECS) accounts for almost a quarter of the volume of the brain[91]. The interstitial fluid (ISF) in the ECS is essential for the survival of neurons due to its critical role in mediating substance exchange in the brain. It has been recognized that a smooth ISF flow is important for maintaining the normal function of the brain due to its role in delivering neuroactive molecules and eliminating toxic substances or metabolic wastes[92]. For instance, the clearance of Aβ through the ISF drainage contributes to the elimination of brain Aβ[93]. The normal ISF flow has been found to be disrupted in ageing and neurodegenerative diseases such as AD and PD. Arbel-Ornath *et al*.[92] showed that mice with significant vascular Aβ deposition have reduced ISF solute clearance, which in turn may worsen brain Aβ deposition by affecting its clearance. A recent study further demonstrated that Aβ deposition in the ECS obstructs the ISF flow and disturbs the ISF-CSF cycle in APP/PS1 mice, therefore affecting the transportation of medicine to the deep brain regions. This may offer some clues to understand the ineffectiveness of recent drug candidates in clinical trials of AD[94].

Parkinson's disease is the second most common disorder of the central nervous system (CNS). We previously investigated a standardized safflower flavonoid extract (SAFE) isolated from safflower. Kaempferol 3-O-rutinoside and anhydrosafflor yellow B, the major active components in the extract, were able to suppress the destabilization of microtubule in neurons[95]. Using a rat PD model induced by 6-hydroxydopamine (6-OHDA) treatment, we observed that the extract not only inhibits the expression and aggregation of α-synuclein, but also attenuates reactive astrogliosis[96]. MRI tracer-based analysis showed that 6-OHDA could change extracellular space (ECS) diffusion parameters by decreasing the tortuosity and the rate constant of clearance. In addition, the 6-OHDA-lesioned substantia nigra also had increased elimination half-life of the tracer. However, SAFE treatment could partially inhibit the changes in ECS diffusion parameters caused by 6-OHDA, indicating that SAFE could be a potential therapeutic herbal product for treatment of PDD[95].

8 Other mechanisms of traditional Chinese medicine for the intervention of AD

The activation of microglia has an essential role in regulating the CNS repair and recovery after brain damage. It has been shown that there are two typical states of activation for microglia in the brain, which is termed as M1/M2 dichotomy[19]. Microglia respond acutely to CNS injuries by migrating to the injury site and expressing M2 signature genes. This phenotype has been found to be beneficial for the CNS because it not only helps to resolve inflammation, but also could maintain the normal neuronal function and the local microenvironment. However, if microglia remain activated in M1 state in chronic inflammation, this would cause the release of pro-inflammatory cytokines and incompetent phagocytosis[97]. Besides, recent studies also demonstrate that the activation of inflammasomes, the multi-protein complexes closely involved in innate immune response and inflammation, might be an important regulator of neuroinflammatory processes in AD[98]. For instance, the NLRP3 inflammasome is widely found in macrophages and microglia. Aβ has been shown to be able to activate the assembly of NLRP3 inflammasomes in microglia, leading to the generation of active caspase-1 and the release of proinflammatory cytokines such as IL-1β[99-100]. Inhibiting the function of NLRP3 inflammasome could not only ameliorate inflammatory responses by changing microglia to M2 phenotype, but also promote the clearance of Aβ species in brains of AD mouse models[100]. Additionally, NLRP3 seems to mediate Aβ induced tau pathologies and its deactivation protects neurons against tau hyperphosphorylation and aggregation, according to the recent report from Ising *et al*. [101]. There is evidence that shifting the activation state of microglia could be a possible strategy for the treatment of AD related inflammation. For instance, the activation of PPARγ by Rosiglitazone could induce the polarization of M2 microglia and reduce the amyloid and tau pathologies in AD mouse models[102]. Several researches have investigated how TCM may modulate the polarization of microglia and affect the subsequent inflammatory response. Salvianolic acid is able to inhibit LPS induced M1 microglia activation but promote the activation of M2 phenotype, which leads

to reduced inflammation and elevated neurogenesis in stress-exposed mice[103]. Astragaloside IV from astragalus could also shift the polarization of microglia toward neuroprotective M2 phenotype[104]. The promising immune-modulating activity of TCM envisions its application in regulating the polarization of microglia for the intervention of neuroinflammation in AD. Celastrol is a triterpene extracted from Thunder God Vine. Sang *et al*. [105] reported that celastrol suppresses the assembly of NLRP3 and its activation, thereby reducing the production of IL-1β and active capase-1 in cell models. These results implicate that TCM may exert anti-inflammatory effects through novel molecular mechanisms such as altering microglial phenotypes and inhibiting NLRP3 inflammasoomes.

A significant pathological change in AD is the loss of neurons in brain regions responsible for learning and memory. The neuronal loss is especially evident in middle and late stages of the disease. Yang *et al*. [106] carried out a systematic review on whether Chinese herbal medicine is able to retard the progression of AD by promoting hippocampal neurogenesis. Their study showed that TCM has additive benefits for AD when consumed together with other anti-AD drugs such as cholinesterase inhibitors, probably *via* enhancing the hippocampal neurogenesis with several signaling pathways. Xanthoceras sorbifolia extracts up-regulates the BDNF/TrkB pathway and the dendritic spine density in a rat model of AD[107].

The disturbance in the normal neurotransmission is a downstream pathological change in AD resulted from Aβ aggregation and tau hyperphosphorylation. In addition to the cholinergic dysfunction that has been utilized for symptomatic treatments, neurotransmissions including the glutamate, serotonin and histamine are also reported to be dysregulated in AD[108]. The homeostasis of neurotransmission is directly associated with the neural function and activity in the CNS. Zhao *et al*. [95] observed that Geniposide, the main active component of *Gardenia jasminoides Ellis*, rescues hippocampal neurons from Aβ oligomers induced cholinergic deficit by increasing the level and activity of Choline acetyltransferase and reducing AChE activity. Ginsenosides was also revealed to be able to increase the content of γ-aminobutyric acid, acetylcholine, and dopamine while decrease glutamate and aspartic acid levels in the hippocampus and cortex in a rat model of AD[109].

9 Conclusion

In addition to the well-recognized anti-inflammatory effects of TCM on neurodegenerative diseases, accumulating evidence indicates that TCM has diverse benefits in the treatment of AD and PD induced cognitive disorders through multiple molecular pathways (Figure 2). TCM could be used as a monotherapy or combined with other therapeutics to achieve disease intervention in neurocognitive disorders. The multifaceted pharmacological effects

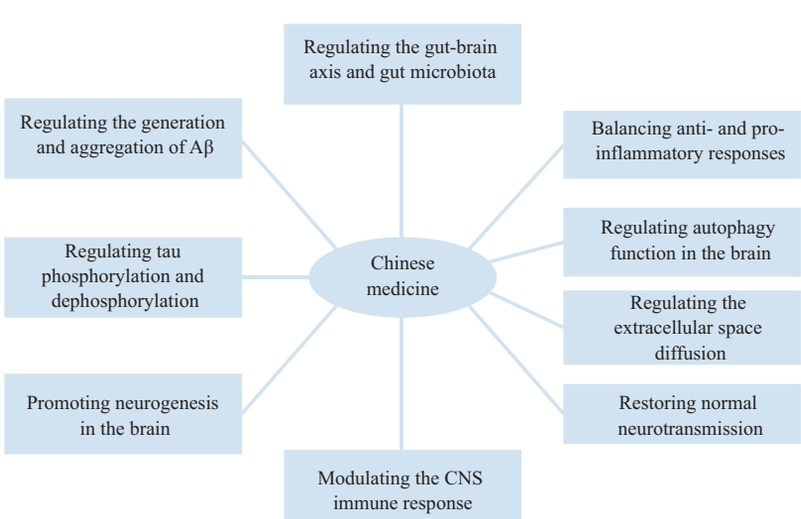

Fig. 2 A summary of molecular mechanisms of traditional Chinese medicine for the intervention of Alzheimer's disease based on literature review

of TCM could provide new insight for the development of multi-target treatments for AD and PD. Combining the promising potential of TCM with their molecular mechanisms and techniques could remarkably aid to the development of new treatments for neurocognitive disorders.

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中医药干预神经退行性疾病引起的认知功能障碍的分子机制*

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摘要　本文综述了中医药对阿尔茨海默病（Alzheimer's disease，AD）和帕金森病（Parkinson's disease，PD）引起的认知功能障碍抗炎作用分子机制的研究进展，并讨论了中医药（如伊桐苷、芒柄花素、和厚朴酚、甘露寡糖二酸和红花类黄酮提取物等）在干预神经退行性疾病中的作用机制，具体包括中医药影响Aβ的生成及聚集、tau磷酸化、肠-脑轴和肠道菌群的调节、自噬功能、小胶质细胞极化、细胞外间隙、神经发生和神经递质传递等.

关键词　阿尔茨海默病，炎症，β-淀粉样蛋白，tau蛋白，小胶质细胞极化，细胞外间隙

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