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Review

A Review of the Pathogenesis and Chinese Medicine Intervention of Alzheimer's Disease

Juanli Zhao[1,2], Jie Yang[1], Li Ding[2], Fang Wang[3,*], Li Lin[1,*]

[1]Laboratory of Medical Molecular and Cellular Biology, College of Basic Medical Sciences, Hubei University of Chinese Medicine, 430065 Wuhan, Hubei, China
[2]Department of Pharmacology, College of Pharmacy, Hubei University of Chinese Medicine, 430065 Wuhan, Hubei, China
[3]Department of Neurology, Fourth Hospital in Wuhan, 430034 Wuhan, Hubei, China
*Correspondence: maohuabing730630@ccnu.edu.cn (Fang Wang); linli@hbtcm.edu.cn (Li Lin)
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Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disease that is primary characterized as a cognitive disorder. Its pathology is characterized by the formation of senile plaques in the brain from amyloid-beta (Aβ) aggregation, neuronal fibrillary tangles from hyperphosphorylated tau protein aggregation, prolonged inflammatory responses, and neuronal death. The pathogenesis and clinical manifestations of AD are complex, but aging is generally accepted as one of the most important contributing factors. In addition, there are several hypotheses, including the Aβ hypothesis based on amyloid plaques, the tau hypothesis based on neuronal fiber entanglement, the inflammation hypothesis based on long-term inflammatory responses causing brain damage, and the neuroprotection hypothesis based on synaptic dysfunction and neuronal death. Although the pathogenesis of AD has been broadly classified into four major hypotheses, there are multiple forms of interactions, which is one of the reasons for its complex pathogenesis. Numerous epidemiological studies have shown the important role of genes in AD, followed by brain damage, hyperlipidemia, diabetes, hypertension, and obesity as risk factors for the disease. Despite years of research, several mysteries in AD remain unsolved. Drugs based on various pathogenetic hypotheses are being investigated in large numbers, but the effects are unsatisfactory. In recent years, traditional Chinese medicine (TCM) has made excellent progress and is expected to provide a new possibility for AD treatment. In this review, we focus on the latest developments in studies on the risk factors—Aβ aggregates and related factors such as apolipoprotein E, synaptic loss, and fatty acids, and then present the progress in the research of TCM based on the above pathogenesis, intended to provide a research reference and treatment for AD.

Keywords: Alzheimer's disease; amyloid-beta aggregation; inflammation; oxidative stress; fatty acids; traditional Chinese medicine

1. Introduction

Alzheimer's disease (AD), first described by German neuropathologist Alois Alzheimer in 1906 [1], is a neurodegenerative disease characterized by various degrees of memory impairment, cognitive dysfunction, and loss in daily living activities. According to medical statistics, approximately 50 million people are suffering from AD globally, accounting for 1/2–3/4 of all dementia cases. In fact, the majority of the population is over 65 years old. With the increase in the number of aging people around the world, the number of people affected will increase to 81.1 million by 2040 [2]. The reduction in the ability to perform daily life activities due to AD puts an unsupportable financial burden on the families of the patients and the government. Under these conditions, researchers are trying to find out more about the progression and pathogenesis of AD. To our great delight, the last decades have seen significant scientific progress in biochemistry, genetics, cell biology, and neuroscience. These findings have broadened our horizons and created more possibilities for AD research. Numerous epidemiological studies have shown that aging and genetics are the main factors contributing to AD, followed by brain damage, hyperlipidemia, diabetes, and obesity [3–6]. The primary pathogenesis of AD is extracellular amyloid plaque deposition and neurofibrillary tangles within neurons, both of which comprise highly insoluble and dense filaments [7]. Their complex pathogenesis has attracted the attention of scientists and researchers. Several challenges are faced when figuring out the exact pathogenesis of AD. At present, there are many hypotheses, including the amyloid cascade hypothesis based on amyloid plaques, the tau hypothesis based on neuronal fiber tangles, the inflammation hypothesis based on brain damage due to prolonged inflammatory responses, the cholinergic and oxidative stress hypothesis, and the neuroprotection hypothesis based on synaptic dysfunction and neuronal death [8–10]. Because the factors involved in AD are complex and influence a lot more than is known, currently, there are no satisfactory prevention and treatment methods, although AD was proposed more than a century ago. Here, we will discuss the risk factors and related mechanisms of AD pathogenesis, as well as the potential of Chinese Medicine in the management of Alzheimer's Disease. This will not only contribute to further research on AD, but also to the development of new drugs.

2. Amyloid Beta (Aβ): The Potential Target for AD

The senile plaques formed by excessive extracellular deposition of Aβ induces a series of pathological reactions, which are significant factors in the formation of AD.

2.1 The Generation of Amyloid Beta

Amyloid precursor protein (APP) is a transmembrane glycoprotein widely found in mammalian cells. The APP is spliced by the β-secretase and the γ-secretase, both aspartate hydrolases, to generate Aβ. The β-secretase is an intramembrane protein expressed in various tissues and is concentrated at the synaptic of neurons. APP can be broken down by α-, β-, and γ-secretases. When hydrolyzed by α-secretase, it forms the soluble fragment sAPPα with C38 at the carboxyl terminus; the C38 is hydrolyzed by γ-secretase to P3. The role of sAPPα is neuroprotective, so this pathway is not harmful to the organism. The β-secretase and γ-secretase splice APP successively, then APP is broken down to the Aβ; when Aβ is hydrolyzed by β-secretase, it forms the soluble fragment sAPPβ at the amino-terminal and βCTF at the carboxyl terminus. βCTF is then split by γ-secretase into amyloid precursor protein intracellular domain (AICD), and soluble Aβ_{40} and Aβ_{42}, which are associated with the deposition of powdery plaques [11]. Aβ is a polypeptide comprising 39 to 43 amino acids. It can be produced by various cells and circulates in the blood, cerebrospinal fluid, and interstitium. Most Aβ molecules bind to chaperonin molecules, and a few exist in a free state. APP is cleaved by the BACE-1 enzyme into β-APP and C99; simultaneously, C99 is catalyzed by γ-secretase to produce Aβ_{40} and Aβ_{42} (see Fig. 1), the most common Aβ isomers in humans. Aβ_{40} can easily enter the cerebral vasculature and induce cerebral amyloid angiopathy; similarly, Aβ_{42} is highly hydrophobic and easily aggregates into oligomers, which have a toxic effect on axons and synapses, leading to degenerative neuronal necrosis and synaptic dysfunction, which then induces AD pathological changes [12]. Compared to Aβ_{40}, Aβ_{42} is 1 to 1.5 times more in content, is more toxic, and is more likely to aggregate, forming a core of Aβ precipitates that can cause neurotoxicity [13,14].

2.2 The Amyloid-Beta Cascade Hypothesis

Numerous studies have shown that the pathology of AD is characterized by cortical atrophy, neuronal cell death, neuroinflammation, synaptic loss, and the accumulation of two well-defined pathological damages: neurofibrillary tangles (NFTs) and senile plaques [15,16]. NFTs are deposited within neurons and consist of hyperphosphorylated tau proteins, whereas senile plaques are generated extracellularly and are mainly composed of faulty autolysosomal acidification inducing autophagy of Aβ in neurons [17]. Excessive deposition of Aβ in the brain is considered a major pathogenic factor [18]. Under normal physiological conditions, Aβ produced by the body can be cleared by glial

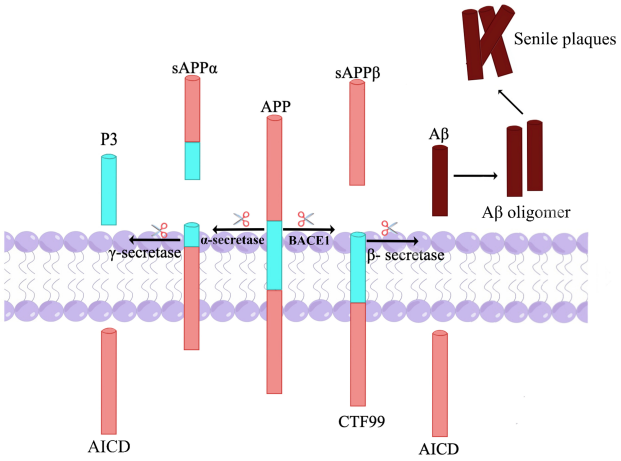

Fig. 1. Amyloid precursor protein (APP), a transmembrane protein be processed by both amyloid and non-amyloid pathways. Aβ is produced through the amyloid processing pathway. APP is cleaved by β-secretase into sAPPβ and CTFβ (C99) fragments, and then γ-secretase cleaves C99 into Aβ and amyloid precursor protein intracellular domain (AICD) fragments. In the non-amyloid processing pathway, α-secretase cleaves APP into soluble sAPPα and C83 fragments, followed by γ-secretase-mediated cleavage of C83 into non-toxic P3 and AICD fragments. Under pathological conditions, Aβ is abnormally increased, and Aβ oligomers are formed, causing senile plaques.

cells, the lymphatic system of the central nervous system (CNS), and receptor-mediated transport across the blood-brain barrier; in contrast, when Aβ is abnormally deposited in the brain, it induces glial cells to release large amounts of inflammatory factors, which then trigger inflammation, as a result, mediating the production of Aβ. The Aβ hypothesis was derived in the 1980s from Aβ peptides isolated from the brain of patients with AD, confirming that AD amyloid plaques are composed of Aβ peptides. When Aβ clearance is dysfunctional, the equilibrium between Aβ production and clearance is disrupted. For example, when Aβ acts on neurons, it can induce massive apoptosis through various cell signaling pathways [19,20]. Moreover, when Aβ accumulates at synapses, it impairs synaptic plasticity, blocks long-term potentiation (LTP) effects, and reduces learning memory in AD [21]. Then, excessive accumulation of Aβ activates glial cells, which on the one hand, can directly engulf the synapse, causing synaptic damage and loss. On the other hand, glial cells release large amounts of harmful substances such as inflammatory mediators and oxidative factors, which trigger inflammatory responses and oxidative stress and upregulate BACE-1 activity [22], inducing excessive production of Aβ, thus forming a vicious circle and promoting the development of AD suggesting that the main pathogenic mechanism of AD is the generation of amyloid plaques by Aβ aggregation, and multiple lines of evidence support the idea that alterations in amyloid pro-

cessing can support the hypothesis of AD. The pathophysiological model of AD proposes a temporal sequence in which the production, clearance, or disruption of both Aβ initiates a biological cascade leading to the formation of Aβ plaques that spread throughout the cerebral cortex, followed by tauopathy, neuronal dysfunction, neuronal death, and ultimately, dementia.

3. The Tau Hypothesis

One of the characteristics of AD is the development of neuronal fiber tangles (NFTs), which are protein aggregates of hyperphosphorylated tau that are generated in the brain. Tau's post-translational modifications are a major contributor to tau aggregation and neurodegeneration. The tau protein can transfer between neurons transsynaptically and transneuronally [23], and the abnormal aggregation of tau not only occurs intracellularly but also spreads to other areas of the brain through various forms, starting from the entorhinal cortex, which may result in diffusion-like pathological changes in adjacent brain areas or other brain areas with synaptic connections. There have six tau isoforms expressed in the adult human brain, including three isoforms have three microtubule-binding repeats (3R) and three isoforms have four repeats (4R) [24]. The tau protein is associated with microtubules and involved in microtubule assemble and stabilization. Abnormal phosphorylation of tau protein leads to dissociation of tau protein from microtubules, which reduces microtubule stability and promotes microtubule depolymerization, and the phosphorylated tau protein aggregates into a paired helical filament (PHF) structure, which further aggregates in neurons and leads to NFTs, affecting neuronal axoplasmic transport, synaptic plasticity, and cytoskeletal stability, ultimately leading to dementia. Phosphorylation of glycogen synthase kinase-3β (GSK-3β) causes tau filaments to coalesce into tangle-like aggregates, suggesting that GSK-3β phosphorylates tau to promote tangle-like filament formation [25]. Tau accumulation causes synaptic malfunction, endoplasmic reticulum (ER) stress, inflammation, and mitochondrial dysfunction, ultimately resulting in neurodegeneration [26]. However, ER stress and tau hyperphosphorylation stimulate each other, leading to the intensification of tau phosphorylation. The hyperphosphorylation associated with tau toxicity also predispositions tau filaments to coalescence into neurofibrillary tangles [27]. Post-translational modifications (PTM) are greatly altered in AD, and acetylation is an integral part of PTM, involved in protein regulation, metabolism and stress response. Acetylation modifications make tau protein insoluble by neutralizing the repulsive effect of positively charged lysine residues, promote tau aggregation, and inhibit pathological tau degradation. Acetylation neutralizes the repulsive reaction of positively charged lysine residues. Since the charge repulsion between the positively charged side chains is less, the charge neutralization of lysine by acetylation makes the stacking of β-chains in parallel registers more favorable [28,29]. Succinylation is a type of PTM, and increased succinylation at key sites of APP and microtubule-associated tau not only disrupts its normal protein hydrolysis process, but also promotes tau aggregation into tangles and impairs microtubule assembly [30]. Similarly, ubiquitination plays an important role in the pathogenesis of tau lesions, and in addition, ubiquitination can affect the physiological state and pathological transformation of tau in cellular condensates [31].

4. Inflammatory Hypothesis

Neuroinflammation, a hallmark of AD, is an inflammatory response in the CNS caused by a variety of factors, including brain injury, infection, aging, and neurodegenerative diseases [32]. Aβ-mediated glial cell activation is a key factor in triggering the inflammatory response. Glial cells are the most numerous cells in the CNS, and interact with neurons and immune cells [33]. In the early stages of AD, glial cells activate a neuroinflammatory response, leading to a decrease in metabolism, blood-brain barrier dysfunction, and energy impairment, which accelerates neuronal death [34]. Although inflammation is a normal response of the body and the process is important for protection under normal conditions, excessive production of inflammatory factors can be damaging to some extent, more so in the extremely sensitive CNS. Neuroinflammation causes neurodegenerative disease, which is difficult to control and progressively deteriorates into a chronic disease. There is growing evidence that the pathogenesis of AD extends beyond the neuronal compartment and interacts closely with the immune mechanisms of the brain [35,36]. Microglia are widely distributed in the brain. As immune sentinel cells in the brain, microglia play an immune role in the CNS. Microglia are highly active in designated brain regions [37]. They search for pathogens and cellular debris in specific areas, respond to unfamiliar and dangerous signals, remove cellular and extracellular debris, and regulate synaptic plasticity [38–40]. Microglia can differentiate into two morphologically similar and functionally distinct cell subtypes, M1 and M2, which play different roles in the inflammatory response depending on signals from different injury environments. The M1 type, the classically activated microglia, produce high levels of oxidative metabolites and pro-inflammatory cytokines, such as IL-12, IL-1β, IL-6, inducible nitric oxide synthase (iNOS), and tumor necrosis factor-α (TNF-α), which contribute to local antigen delivery, destroy invading pathogens, increase oligodendrocyte death, and promote inflammatory responses and neuronal damage. The M2 type, the selectively activated microglia are categorized as M2a, M2b, M2c, Mox, and so on, which can secrete a multitude of anti-inflammatory cytokines, such as IL-4, IL-10, vascular endothelial growth factor, transforming growth factor-β, and brain-derived neurotrophic factor. They have the ability to repair arginase activity, inhibit inflammatory responses,

and promote tissue repair and functional remodeling [41]. When pathogens or apoptotic debris are present in the organism, microglia are activated into an amoeboid phagocytic form with large cell bodies and sparse, thick branches. They rapidly migrate to the site of injury to exert phagocytosis and release tumor necrosis factors. At the same time, microglia help protect and remodel synapses [42], allowing neuronal circuits to be maintained. Microglia in the brain are highly activated and can release various immune and cytotoxic factors such as inflammatory cytokines (TNF-α and NO) as well as reactive oxygen radicals [43]. The overproduction of these substances induces neuronal death, especially TNF-α, which has a dual nature: low levels are protective for the body, but excessive levels cause inflammatory damage. TNF-α mediates neurotoxicity by binding directly to neuronal receptors on the one hand and expresses more inflammatory cytokines by activating glial cells on the other. In turn, the entry of TNF-α into the brain activates the relevant receptors on microglia, initiating a cascade reaction that leads to increased production of TNF-α and other pro-inflammatory factors [44]. Meanwhile, Aβ aggregates can induce the release of inflammatory mediators such as reactive oxygen species (ROS), NO, and leukocyte mediators by activating microglia, which ultimately leads to neuronal death. On the contrary, as the most numerous and functional class of glial cells, astrocytes regulate ions and neurotransmitters in the CNS environment by controlling neuronal metabolism. Under normal physiological conditions, astrocytes rely on apolipoprotein E (*APOE*) lipidation to enhance the ability of microglia to clear Aβ. Increasing evidence suggests that besides microglia and astrocytes, T cells are also involved in the regulation of the inflammatory response in AD. With the development of AD, the infiltration of T cells into the brain increases, and a large number of T-cell-derived inflammatory cytokines from the peripheral blood enter the brain, which ultimately increases neuroinflammation and accelerates neuronal death [45].

5. Synaptic Deficiency

Dendritic spines are the protrusions at the synapse ends of neurons which consist of cytoskeletal networks, scaffolding proteins, and surface receptors; these receptors contain both N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Actin is the main factor affecting the shape and number of dendritic spines, and the actin content of dendritic spines is about 6 times higher than that of dendrites. The cross-linkage between F-actin and G-actin causes the dendrites to change morphologically. Dendritic spines are divided into three categories according to their shape: mushroom-shaped, stubby spines, and thin spines [46]. To study the effects on the presynaptic and postsynaptic neuronal compartments in AD patients, Reddy *et al*. [47] quantified the number of synapses and showed that there were 25–30% fewer synapses in AD brains than in controls and that there were 25–30% fewer synapses in the cerebral cortex and 15–35% fewer synapses per cortical nerve than in controls. At the same time, they studied and compared the protein levels in frontal and parietal cortices of a large number of AD subjects and healthy controls by immunoblot analysis, which showed that all brain specimens from AD patients lost presynaptic vesicle proteins and postsynaptic proteins, showing that postsynaptic and presynaptic proteins are important for synaptic function in AD [47].

Synaptic loss is one of the most important factors in cognitive decline in AD, and there is evidence that AD is primarily a disease of synaptic dysfunction [48,49], with Aβ and tau oligomers contributing to synaptic loss [50]. In addition to plaques and amyloid angiopathy, Aβ is multimerized into a series of oligomers [51]; soluble oligomeric forms of Aβ, a peptide that aggregates in the brains of AD patients to form senile plaques, have been shown *in vitro* and *in vivo* to be toxic to neuronal synapses. Aβ oligomers inhibit long-term dementia (LTP) and promote long-term depression (LTD), a memory formation electrophysiologically relevant, thus functioning as a memory formation. In addition, oligomeric Aβ has been shown to cause synaptic loss and cognitive impairment in animals [52]. Massive loss of synapses in the temporal region of the brain of the patient is one of the features of AD [53], and synaptic loss is one of the most important causal mechanisms of cognitive dysfunction in AD [54], with the most severe areas of synaptic loss being in the vicinity of senile plaques, suggesting that plaques may be a reservoir of synaptotoxic molecules such as Aβ [55–58]. When testing the hypothesis that oligomeric Aβ around plaques causes synaptic loss in a mouse model of AD, Koffie RM *et al*. [59] found that senile plaques are surrounded by an oligomeric Aβ halo. Analysis of over 14,000 synapses revealed a 60% loss of excitatory synapses in the oligomeric Aβ halo surrounding senile plaques. This suggests that oligomeric Aβ may be present in AD in balance with plaques [59]. Moreover, one of the functions of microglia is to maintain the homeostasis of the brain and eliminates inflammation caused by injury or infectious microorganisms through phagocytosis. Although a small amount of inflammatory response can protect the brain neurologically, once this homeostasis is disrupted, continuous stimulation activates microglia to convert them into harmful responses, leading to prominent dysfunction and neuronal death [60] (See Fig. 2). A recent study that age affects the brain's ability to activate asparagine endopeptidase. Synapsin I is broken down by active AEP into the synapsin I C83 fragment, which alters synaptic vesicle recycling, results in synaptic dysfunction, impairs cognitive function, and aids in the development of AD [61].

6. Oxidative Stress and Apoptosis

The accumulation of Aβ in the brain is an important factor contributing to neuronal apoptosis, and Aβ can mediate the mitochondrial apoptotic pathway, the death re-

Fig. 2. Structural differences between the brain of a person with Alzheimer's disease and a normal brain. When synapses are lost, the structure of the brain changes significantly. Compared with the normal brain, the neuronal cell in the AD brain dies, and the volume is reduced.

ceptor pathway, and the endoplasmic reticulum apoptotic pathway, which together induce apoptosis in neuronal cells. There is substantial evidence that Aβ disrupts the electron transport chain by decreasing the activity of key enzymes [62]. Aβ is the largest contributor to mitochondrial dysfunction, disrupting mitochondrial dynamics and participating in ROS production. Metal ions such as Cu and Fe play an important role in oxidative stress and are also involved in ROS production. Cu and Fe can produce a complex with Aβ, and this complex is directly involved in ROS production; because the redox activity of Fe-Aβ is low, the production of ROS is mainly analyzed by examining Cu-Aβ. During ROS production, the Aβ peptide is damaged by oxidation [63]. Mitochondria are the refueling stations of cells, and their core function is to provide cells with the required energy, participate in the process of cell generation up to apoptosis, and play an important role in the regulation of apoptosis, calcium handling, and innate immunity [64]. Oxidative stress is a cascade response resulting from an imbalance between oxidative and antioxidant systems. When oxidative stress begins, free radicals such as ROS and reactive nitrogen species are significantly elevated in the body. Free radicals are continuously produced during the body's metabolic processes; therefore, antioxidant enzymes and antioxidant proteases are required to maintain redox homeostasis by scavenging free radicals [65]. Although the brain is an extremely oxygen-consuming organ, it has a relatively weak antioxidant capacity and is therefore vulnerable to damage from oxidative stress. Oxidative damage is caused to biomolecules during oxidative stress [66]. Oxidative stress can lead to increased secretion of neutrophil inflammatory infiltrative proteases and the production of large amounts of oxidative intermediates, ROS. ROS not only directly damage the cells but also activates various oxidative and anti-oxidative stress pathways. Oxidative stress is a negative effect of free radicals in the body, which is an important factor in inflammation and aging. It has been shown that APP undergoes cleavage to produce a large number of Aβ molecules, some of which remain in the neuronal lipid bilayer and evolve into Aβ oligomers through a series of reactions that cause channel-like active pores in the neuronal membrane, which in turn contribute to increased calcium inward flow [67]. Simultaneously, Aβ can regulate calcium/calmodulin-dependent protein kinase II, calcium phosphatase, protein phosphatase 1, and cyclic AMP response element-binding protein (CREB) through N-methyl-D-aspartate receptor-mediated regulation of calcium channels. CREB induces intracellular calcium overload [68], and excess calcium and other metal ions increase mitochondrial dysfunction, affecting various apoptotic signaling pathways and even neuronal apoptosis. If calcium ion stabilization is dysregulated, it also leads to increased levels of the pro-apoptotic protein Bax and decreased expression of the anti-apoptotic protein Bcl-2 in the mitochondrial membrane. Ultimately, the outer mitochondrial membrane is permeabilized, and neuronal cytochrome c oxidase activity is reduced, allowing it to bind to apoptotic protease activator-1, cysteine aspartate-specific protease 9 (caspase-9), forming an apoptosome complex that activates caspase-3 and initiates the caspase protease cascade reaction that mediates apoptosis [69]. When stimulated by Aβ, mitochondrial fusion proteins 1 (mitofusins, Mfn1) and Mfn2 are significantly reduced, while division-related factors are highly upregulated, leading to increased permeability of the outer mitochondrial membrane and massive release of cytochrome c, which activates caspase-3 and ultimately triggers the apoptotic pathway [70]. This suggests that Aβ is highly susceptible to damage to intracellular neuronal mitochondria, which induces oxidative stress and mediates apoptosis.

7. The Apolipoprotein E (APOE) Family

AD is inherited as an autosomal dominant gene, and its lipoprotein e4 genotype (*APOE4*) on chromosome 19 is the highest genetic risk. *APOE* is part of the large lipoprotein (lipoprotein) family and plays a key role in lipid metabolism [71]. *APOE*, a 34 kDa glycoprotein, is a plasma lipoprotein, synthesized mainly by the liver and involved in systemic lipid transport [72]. *APOE* production and secretion have distinct cellular and tissue properties [73]. *APOE* is abundant in the brain, is a chaperone of lipoproteins, is mainly expressed by astrocytes, and can be transported to neurons. Compared with astrocytes, microglia can take up ApoE from other cellular sources. In addition *APOE* expressed by microglia may contribute to neuronal damage in AD [74]. There are three allelic variants of *APOE*, namely *APOE2*, *APOE*3, and *APOE*4, which differ in amino acid composition, *APOE*2 (Cys112, Cys158), *APOE*3 (Cys112, Arg158), and *APOE*4 (Arg112, Arg158) [75]. The difference in amino acid sequences between these isoforms leads to different conformations.

Patients carrying the *APOE4* gene differ significantly in the interaction of *APOE*4 and Aβ. A study spanning more than 6 years showed that the interaction of the *APOE* isoform with Aβ increases the risk of AD. Mishra S and Blazey TM *et al*. [76] analyzed dates from a dominantly inherited Alzheimer's network regarding mutation non-carriers, asymptomatic carriers, and symptomatic carriers from families with mutations in the preset protein 1 (PS1), preset protein 2 (PS2), or amyloid precursor protein (APP) genes, and then, using linear mixed-effects models, estimated the risk of 11C-Pittsburgh compound B and 18F-deoxyglucose by positron emission tomography (PET) and structural magnetic resonance imaging (MRI). PET and MRI can be used to assess the number and location of Aβ plaques. Finally, it was found that the rate of Aβ deposition was significantly different in mutation carriers compared to non-carriers, with elevated Aβ deposition in mutation carriers than in non-carriers, followed by a decrease in metabolism, and finally, structural atrophy [76].

8. The Effect of Fatty Acids on Alzheimer's Disease

Fatty acids (FAs) can be broadly classified into three categories, saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids, based on the saturation and unsaturation of the hydrocarbon chain. Studies have shown that fatty acids can affect gene expression and metabolic responses not only by altering intracellular and extracellular signaling pathways but also by altering intracellular and extracellular signaling pathways in many different cells and tissue types [77]. The recent study found Stearoyl-CoA desaturase (SCD) which is a key regulator of fatty acid desaturation, inhibition of its activity in the 3xTg mouse model of AD brain alters core transcriptomic pathways associated with AD in the hippocampus [78]. With the improvement of quality of life and lifestyle changes, high sugar and high-fat diets (HFDs) have become an important part of the contemporary diet. It has been found that the cerebral glucose metabolism of AD patients is lower than normal, and the altered cerebral energy metabolism increases the risk of AD [79]. The main pathological process of AD is the aggregation of Aβ, and the protein plaques in the AD brain are mainly formed by the aggregation of Aβ fibers, which are mainly formed by the aggregation of monomeric Aβ peptides. Fatty acids and anionic surfactants such as lipids are important factors affecting Aβ nucleation kinetics [80], where polyunsaturated fatty acids (PUFA) affect the interaction between amyloid precursor protein (APP) and β-secretase. A diet high in unsaturated fatty acids can reduce amyloid accumulation and mitigate glial cell activation, as well as affect mitochondrial energy homeostasis and the production of inflammatory or prolysis immune factors, the production of mitochondrial energy homeostasis and inflammatory or pro-soluble and immune regulators [81]. Simultaneously, short-chain fatty acids can inhibit NF-κB transactivation through GPR43-mediated oxidative stress, thereby reducing the inflammatory response [82]. But lipid droplet accumulation in astrocytes and microglia promotes inflammatory responses [83].

APP is a transmembrane protein, and its membrane-bound proteins are influenced by membrane lipids, of which fatty acyl is a major component; on cell membranes, fatty acyl enhances the activity of transmembrane proteins in cells. Lipids are central in central metabolism and can directly initiate aging. Fatty acids can enhance brain cell activity and memory, and thinking ability, and they are present in large amounts in brain tissue and cerebrospinal fluid.

Alfred N. Fonteh *et al*. [84] found that lipid metabolism leads to abnormal processing of Aβ_{42}. Neuropsychological measurements of Aβ_{42} in the cerebrospinal fluid showed that PUFA metabolism is associated with amyloid and tau processing and that unsaturated fatty acids improve memory and restore cognition.

9. Traditional Chinese Medicine (TCM) for the Treatment of Alzheimer's Disease

The drugs currently in clinical trials and approved for the treatment of AD are all based on the regulation of excitatory neurotransmitter transmission pathways, and they are all agonists or antagonists of neurotransmitter production or neurotransmitter receptors. All these drugs have different degrees of side effects in clinical use. For example, tacrine, the first reversible acetylcholinesterase inhibitor approved for clinical treatment of AD, was discontinued due to hepatotoxicity. The most common adverse effects of donepezil, a reversible acetylcholinesterase inhibitor, are diarrhea, nausea, vomiting, insomnia, fatigue, urinary incontinence, etc. So far, even though a large number of clinical trials of AD drugs have ended in failure and the efficacy of the drugs that have been approved for clinical use is unsatisfactory, the search for a TCM to treat AD has never stopped.

TCM has long been a valuable source of medication, and research on herbal medicine has developed rapidly in recent years. Many herbal medicines and combinations have been shown to be effective in treating AD, with significant improvements in cognitive function in clinical trials (Fig. 3). It is effective in reducing Aβ deposition and inflammation, maybe is a potential drug for AD treatment.

9.1 Based on the Amyloid-Beta Hypothesis

The amyloid senile plaques in the brain of AD patients are caused by Aβ aggregation [85]; therefore, we can treat AD by re-establishing the dynamic balance of Aβ production and clearance, wherein reducing Aβ production and increasing Aβ clearance are both useful measures. Aβ is derived from β-secretase and γ-secretase cleavage APP, so reducing the activity of β-secretase and γ-secretase can effectively inhibit the production of Aβ. β-secretase, also

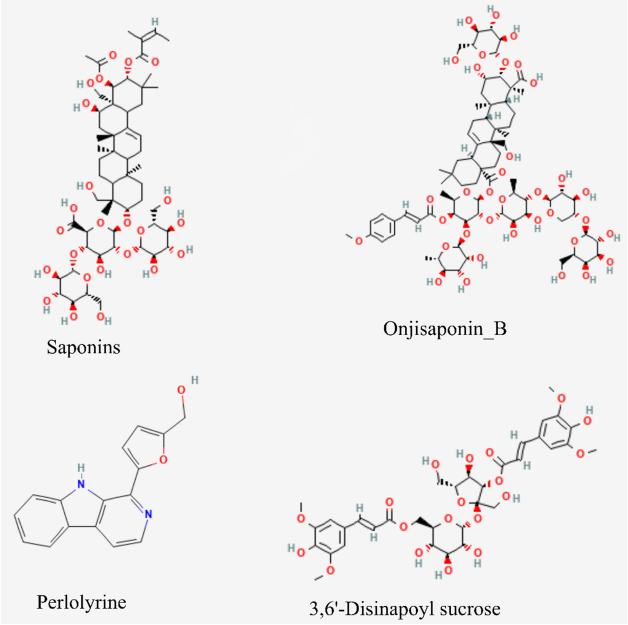

Fig. 3. Chemical structures of the active ingredients of Polygala tenuifolia. Chemical structure downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/).

known as β-site amyloid cleavage enzyme 1 (BACE1), is composed of 501 amino acid residues, The protein amount and enzyme activity of BACE1 are higher in AD brains than in normal brains, and the hydrolysis of APP can be inhibited by decreasing the activity of BACE1, thus reducing the production of Aβ [86]. Severin Filser *et al.* [87] studied the effects of BACE1 inhibition on dendritic spine dynamics, synaptic function, and cognitive performance and demonstrated that low doses of BACE1 inhibitors promoted the reduction of Aβ production, and consequently, high doses of BACE1 inhibitors caused synaptic damage as well as memory loss. Jiannao Yizhi Formula (JYF) is commonly used in TCM clinics for the treatment of AD. To investigate the long-term efficacy of JYF in treating AD, Hui-Chan Wang *et al.* [88] recruited 60 patients aged 50–80 years with mild to moderate AD and randomly assigned them to the treatment group (n = 30) and the control group (n = 30). The treatment group was given 5 g of JYF orally twice daily and 5 mg of donepezil placebo once daily, while the control group was given 5 mg of donepezil once daily and 5 g of JYF placebo twice daily. After 6 months of treatment, the scores of the AD Rating Scale-Cognitive (ADAS-Cog) and Chinese Medicine Symptom Scale (CM-SS) were tested. Compared with baseline, both JYF and donepezil decreased the ADAS-Cog and CM-SS scores ($p < 0.05$ or $p < 0.01$). Acetylcholine (Ach), Aβ_{42}, and the microtubule-associated protein tau were measured in the serum of patients by enzyme linked immunosorbent assay. The results demonstrated that both drugs increased the serum levels of Ach and decreased the serum levels of Aβ_{42} and tau ($p < 0.05$). These results suggest that the effect and safety of JYF for the treatment of AD were not inferior to those of donepezil and the mechanisms were related to regulating the levels of Ach, Aβ_{42} and tau in serum [88]. γ-secretase is a complex consisting of PS1, PS2, and dull protein, and mutation in PS1 and PS2 genes increases the production of the highly amyloidogenic 42-residue form of amyloid-beta protein (Aβ_{42}) [89]. Phytochemical studies reveal that inhibition of Aβ aggregation is also important. More than 140 compounds, including saponins, xanthones, oligosaccharide esters, 3,6′-disinapoyl sucrose (DISS), onjisaponin B (OB), etc. have been isolated from Polygala tenuifolia [90–92] (Fig. 3). These components have a wide range of pharmacological activities; among them, farcicin saponins can reduce the aggregation of Aβ, and DISS can improve the cognitive deficits and pathological defects of hippocampal neurons in adult APP/PS1 mice and increase the number of neurons [93]. CA-30, an oligosaccharide extracted from LiuweiDihuang decoction (LW), consists of stachyose and mannotriose. Jianhui Wang *et al.* [94] investigated the effects of CA-30 on senescence-accelerated mouse prone 8 (SAMP8) mice. The behavioral assessments showed that CA-30 slowed down the aging of SAMP8 mice and also alleviated their cognitive impairment; further radioimmunoassays showed that CA-30 balanced the neuroendocrine system of SAMP8 mice. Long-term administration of LW or its active ingredient has restorative and regulatory effects on the neuroendocrine-immune system and intestinal microbiota in AD animal models and can reduce the accumulation of Aβ in model mice [94]. Danggui-Shaoyao-San (DSS), a classic herbal formula, has been widely used in gynecological treatment [95]. There is substantial clinical evidence that DSS affects free radical-mediated neurological disorders and has multiple effects on neurons. Previous studies have shown that DSS has an antioxidant capacity, reduces inflammatory responses, and attenuates apoptosis in the hippocampus [96]. Nobuaki Egashira *et al.* [97] found that DSS could significantly reduce neuronal damage by Aβ_{25-35} while reducing neuronal death and lipid peroxidation in primary cultured rat cortical neurons. Panax notoginseng saponins (PNS) contains a variety of monomeric components that are widely used in the treatment of cardiovascular and cerebrovascular diseases; furthermore, it is neuroprotective by inhibiting β-amyloid peptide (Aβ)$_{25-35}$ mediated apoptosis. In addition, PNS has been reported to accelerate nerve cell growth, increase axon length, and promote synaptic plasticity. Liu *et al.* [98] found that because Aβ_{42} could reduce the number of CA1 neurons in the hippocampal corpus by inducing spatial learning and memory impairment in rats; the level of hyperphosphorylated β-secretase processing of APP at the Thr668 locus was increased, while BACE1 and PS1 were downregulated. Rg1, a monomeric component of PNS, was effective in ameliorating cognitive impairment and neuronal loss by reducing APP-Thr668 phosphorylation and BACE1/PS1 expression to inhibit β-secretase

shearing of APP, resulting in decreased Aβ production and increased degradation, thereby ameliorating cognitive impairment and neuronal loss [98].

9.2 Based on the Tau Hypothesis

Initially, tau-based therapies focused on kinase inhibition, tau aggregation, or microtubule stabilization, but most of these approaches have been discontinued due to safety concerns. Currently, the majority of tau-targeted therapies in clinical trials are immunotherapies. Recently, therapies targeting tau proteins or tau-related pathways have been proposed, such as small interfering RNA (si RNA) or antisense oligonucleotides (ASOs) to reduce tau expression [99]. In addition, reduction of Tau with chemical molecules may offer a novel strategy for treating AD [100]. Bushenhuatan-yizhi formula, a common clinical prescription in traditional Chinese medicine, can effectively reverse the decline of learning and memory ability in AD-like rats, and its effective mechanism is to delay NFTs by reducing the high phosphorylation level of tau protein, thus improving cognitive impairment [101]. In addition, research shows that berberine improves tau hyperphosphorylation and reduces axonal damage via restoring the PI3K/Akt/GSK3 signaling pathway, acting as a preventative agent against cognitive impairments [27].

9.3 Based on the Inflammatory Hypothesis

Neuroinflammation is a factor in the pathogenesis of AD, so anti-inflammation is considered an effective treatment. Aβ promotes neuronal death by damaging mitochondria, exacerbating neuroinflammation and oxidative stress, and long-term neuroinflammatory reactions can cause serious damage to the brain. A multitude of Chinese medicines is considered to have good therapeutic effects, Forsythoside A (FA) is the main constituent of Forsythia suspensa (Thunb.). Its effects are anti-inflammatory, antibacterial, antioxidant, and neuroprotective [102]. At the same time, the formation of pro-inflammatory factors IL-6, IL-1β, and NO in lipopolysaccharide (LPS)-stimulated BV2 cells could be reduced by FA treatment. In exploring the effects of FA on double transgenic (APP/PS1) mice, Chunyue Wang *et al*. [103] found that FA-treated mice had a significantly shorter avoidance latency than the other groups and spent more time crossing the effective area after removal of the platform than the other groups. FA-treated APP/PS1 mice showed significantly less Aβ deposition and lower levels of phosphorylated tau protein in the hippocampus than the other groups. The results of subsequent cellular experiments were similar to the previous reports, confirming that FA could protect cells from Aβ and LPS-induced damages. In addition, FA could reduce neuroinflammation in APP/PS1 mice [103]. Forsythoside B (FTB), one of the active ingredients of Forsythiae, has been shown to modulate neuroinflammation, reduce microglia and astrocyte activation, and decrease microglia-mediated neurotoxicity in APP/PS1 mice via the NF-κB signaling pathway [104]. Raisins have several active ingredients, including polyphenols, phenolic acids, and tannins, which are antioxidant and anti-inflammatory, and these properties have been shown to improve spatial memory in animal models of AD [105]. Matrine is an active ingredient extracted from the TCM Sophora flavescens Alt., and it has good anti-inflammatory effects. Matrine has been found to improve neuroinflammation and memory impairment in AD mice [106]. Leigong-gen is a useful anti-inflammatory agent whose active ingredient, triptolide, can inhibit microglial activation and the release of pro-inflammatory factors. In addition, it exerts biological activity in different types of brain cells [107].

9.4 Based on the Synaptic Deficiency

Carthamus tinctorius L. is a common TCM widely used for bruises and injuries. Safflower yellow (SY) is the active ingredient of Carthamus tinctorius L., and Hydroxysafflor yellow A (HSYA) is the highest single active ingredient in SY. Jiawei Hou *et al*. [108] used rats injected with Aβ_{42} bilaterally in the hippocampus as an AD model, and after treatment with SY and HSYA for a period, they found improved learning and memory abilities and the structural damage of dendritic spines and synaptic loss of the model rats, and reduced deposition of Aβ in these AD rats. Additionally, the loss of synapse-associated proteins was alleviated, and glutamatergic cycling impairment was improved. SY and HSYA have been proved to have the effect of regulate excitatory neurotransmitter transmission; furthermore, they could enhance the synaptic structural plasticity of brain tissue and reduce the structural damage of Aβ1 dendritic spines in the gluteal region [108]. In addition, Bushen-Huatan-Yizhi formula (BSHTYZ) is also widely used in the treatment of dementia, which not only has a good effect of regulate excitatory neurotransmitter transmission but also enhances synaptogenesis within the neurons. Yang *et al*. [101] found that BSHTYZ is a potential compound preparations for the treatment of AD by inhibiting the GSK-3β/CREB signaling. The involved mechanism of BSHTYZ was found to improve the learning/memory ability of the rat AD model under the influence of Aβ_{42} through the inhibition of the GSK-3β/CREB signaling pathway. They also identified the “thin/mushroom” type of dendritic spines by Golgi staining and observed a decrease in the population of “thin/mushroom” type dendritic spines when rats were injected with Aβ_{42}, but these dendritic spines could be rescued by treatment with BSHTYZ. These data suggest that Aβ_{42} induces a neuronal and dendritic loss in the CA1/DG regions of the hippocampus and that BSHTYZ reverses the loss in these regions [101].

9.5 Based on the Oxidative Stress

Oxidative stress plays a very important role in neurodegenerative diseases, so reducing oxidative stress is a potential therapeutic strategy. Curcumin is a phenolic com-

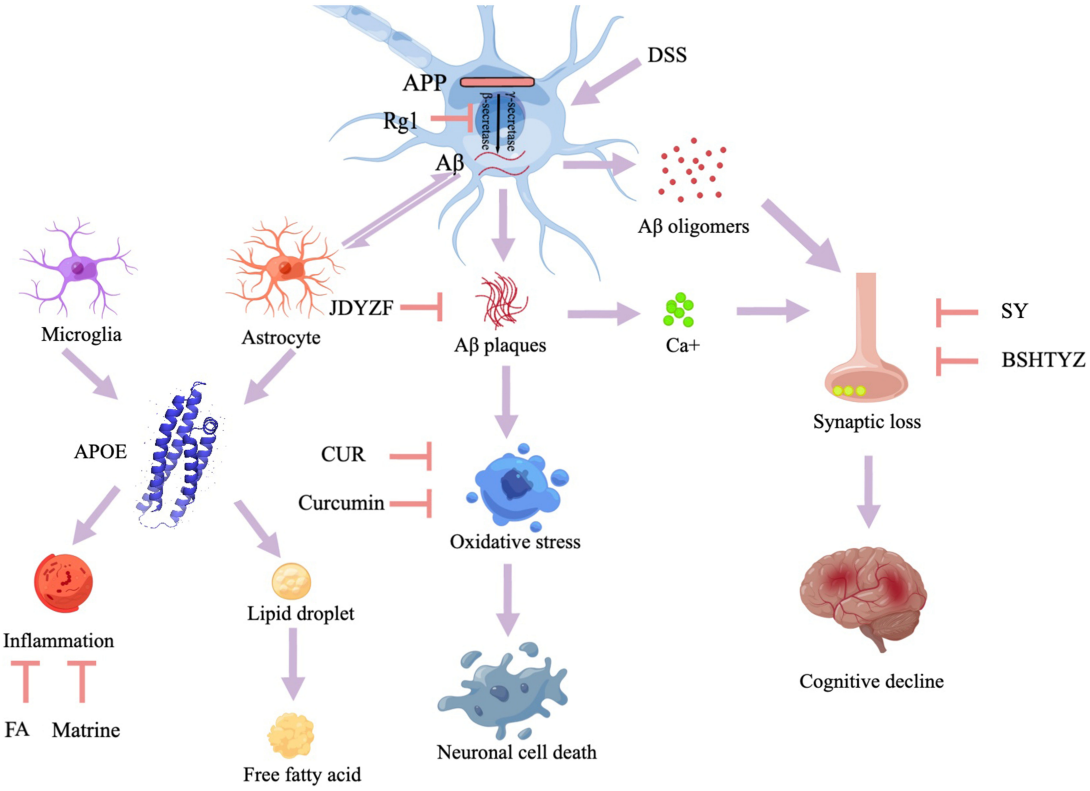

Fig. 4. Schematic diagram of Aβ generation and possible mechanism of traditional Chinese medicine (TCM) intervention. When Aβ is in excess, senile plaques and Aβ oligomers are formed, and microglia are also activated. Rg1 reduces Aβ production by inhibiting β-secretase, JDYZF can decrease Aβ aggregation, safflower yellow (SY) and the Bushen-Huatan-Yizhi formula (BSHTYZ) can reduce synaptic loss and enhance the plasticity of synaptic structures, curculigoside (CUR) and curcumin can reduce oxidative damage by enhancing antioxidant properties, and forsythoside A (FA), matrine FA and matrine can regulate neuroinflammation.

pound extracted from the rhizome of turmeric and is a natural antioxidant, with bifunctional oxidative properties. It not only protects astrocytes from H_2O_2-induced oxidative stress but also reverses oxidation-induced mitochondrial damage and dysfunction. Curcumin inhibits oxidative stress-induced inflammation and apoptosis by regulating transaminases, inducing endogenous antioxidants and anti-inflammatory defense mechanisms. In addition, it also reduces astrocyte damage and apoptosis [109–111].

Curculigoorchioides belongs to the family Amaryllidaceae and is a common herbal medicine in TCM. Curculigoside (CUR) is the main active ingredient in curculigoorchioides, which has a wide range of pharmacological activities such as neuroprotection, anti-immune stimulation, antioxidant, and anti-osteoporosis. CUR can promote calcium deposition through antioxidant properties and increase the levels of alkaline phosphatase and the transcription factor Runx2 in osteoblasts under oxidative stress. It has been found that CUR can reduce oxidative damage and induce proliferation in oxidative stress and differentiation [112].

9.6 Effects on Fatty Acids

HFDs have been shown to cause systemic inflammation and obesity, which in turn may interfere with immune processes in the brain [113,114]. Obesity causes prolonged activation of inflammatory pathways, and HFDs lead to neuroinflammation and reactive gliosis in the hypothalamus of mice. Toll-like receptor 4 (TLR4) is a receptor for LPS and plays a vital role in innate immunity. Most TLR4 signaling is mediated through myeloid differentiation primary response 88 (MyD88). Studies have shown that free fatty acids induce TLR4 signaling associated with MyD88 and can use TLR4 signaling to induce inflammatory responses in macrophages [115]. TCM has vast clinical experience in treating obesity, and Rhubarb is one of the most widely used herbs in TCM. Chrysophanol, a yellow crystalline substance extracted from rhubarb, was shown to regulate lipid metabolism by activating AMPK signaling and reducing HFD-induced fat accumulation in metazoan hepatocytes [116].

10. Other Effective Treatment Methods for the Treatment of Alzheimer's Disease

Other than medication, some effective treatment methods are gaining increasing attention, including acupuncture, electro-acupuncture, aromatherapy, pulsed electromagnetic field, etc.

Acupuncture is widely accepted by patients because of its good treatment effect and fewer adverse effects. A randomized trial was conducted between November and May 2016 by YJ Jia *et al*. [117]. They recruited 152 residents aged 50–85 years, collected their personal information, and randomly assigned patients to the AG and DG groups. Treatment was thrice a week for 12 weeks, with patients in the DG group given 5 mg/d donepezil hydrochloride for the first 4 weeks. The AD Assessment Scale-Cognitive (ADAS-cog) and Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus) were used to assess the effect after treatment. The ADAS-Cog scores improved by 6.99 (standard deviation: 3.23) and 4.02 (standard deviation: 2.11) in the acupuncture and control groups, respectively. The CIBIC-Plus scores in the AG group decreased substantially compared to the DG group, with a statistically significant difference between the two groups ($p < 0.05$). Finally, acupuncture is effective in improving cognitive function and clinical status [117].

11. Conclusions

AD is a disease with complex pathogenesis and many factors, and the exact pathogenesis has not been determined, so it is difficult to develop targeted drugs. The difficulties that make drug development difficult so far include complex pathogenesis, inability to determine the exact pathogenesis, difficulty in finding suitable animal models, and the side effects of drugs already on the market that have affected the quality of life of patients. Therefore, with numerous active ingredients and a wide range of pathways of action, TCM has brought a ray of hope for the treatment of AD (See Fig. 4). Its multi-target and multi-pathway advantages make up for the shortcomings of existing drugs; in addition, its human-centered treatment concept improves the life quality of patients. Nowadays, with the rapid development of science and technology, together with the increasing depth of scientific research, more new technologies are providing a strong scientific basis for Chinese medicine, which can unveil the implications of TCM and improve the working efficiency of Chinese medicine researchers. New gene-editing technologies such as high-throughput screening technology and CRISPR/Cas have brought us convenience. Meantime, new brain imaging technologies make early diagnosis possible. All these new technologies are helpful in discovering the exact pathogenesis and providing effective treatment of AD.

Credit Author Statement

All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Author Contributions

JZ wrote the manuscript. JY and LD participated in the conception and writing the articles. FW revised the manuscript. LL designed and revised the manuscript and got the funding. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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