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Progress on the Pathogenesis and Treatment of Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD), commonly known as senile dementia, is a neurodegenerative disease with clinical manifestations of memory impairment, personality and behavior changes. The pathogenesis of AD is complex and inconclusive in the point of view of western medicine, which is the fundamental reason for the lack of drugs that can reverse the course of the disease. People have gradually shifted from simple amyloid hypothesis to new pathogenesis theories, such as gamma oscillation, prion like transmission, and so on. As an effective means to treat AD, traditional Chinese medicine has made some research progress in recent years. This article mainly reviews the etiology, pathogenesis and treatment of AD, so as to provide reference for the prevention and treatment of AD. **Methods:** Through systematic literature research, comparison and analysis, the main pathogenesis, influencing factors, progress and development tendency of traditional Chinese medicine and Western medicine in the treatment of AD are presented. **Results:** Alzheimer's disease is a kind of multiple neurodegenerative diseases. The pathogenesis and related targets of AD still need to be further explored. The main pathological phenomenon of AD is senile plaques formed by intracellular neurofibrillary tangles and extracellular amyloid protein aggregation. Existing possible pathogenesis includes β-amyloid cascade hypothesis, tau protein hypothesis, cholinergic hypothesis and so on. As the pathogenesis of AD has not been clarified, so far no effective therapeutic drugs or means have been found. The traditional drugs used to treat AD mainly include acetylcholinesterase inhibitor kabbalatin, galantamine, donepezil, and N-methyl-D-aspartate receptor antagonist memantine. However, although these marketed drugs can slow down the course of the disease and alleviate symptoms, they cannot totally cure the disease. Traditional Chinese medicine has the characteristics of personalized differentiation and treatment. The Western medicine can accurately

determine the lesion location and target. **Conclusions:** Integrated traditional Chinese medicine and West medicine is the most promising direction in the treatment of Alzheimer's disease.

Keywords

Alzheimer's Disease, Pathogenesis, Treatment, West Medicine, Traditional Chinese Medicine

1. Introduction

AD is a common neurodegenerative disease, and also brings serious social and economic burdens. For this kind of disease, people have proposed a variety of pathogenesis, but from the effect of clinical practice, the understanding of its pathogenesis is still very lacking, so the effect of the corresponding treatment scheme is also very limited. For example, the main antidepressants currently targeted at the "monoamine neurotransmitter hypothesis", such as serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), have clear pharmacological mechanisms, but have slow onset and many adverse reactions. The proportion of patients with AD based on stagnation of liver Qi and deficiency of heart and spleen in traditional Chinese medicine is high, but it takes effect slowly, and it is not generally effective for patients. Therefore, how to clarify its pathogenesis and formulate a reasonable and effective treatment scheme is still the direction of in-depth research in the future.

In a word, the pathogenesis of Alzheimer's disease is complex and inconclusive. The lack of correct understanding of the pathological process of the disease is the root cause of the lack of drugs that can reverse the course of the disease. The pathogenesis and related targets of Alzheimer's disease still need to be further explored. With the aging of the population, the continuous increase of disease cases in the elderly has also become an urgent problem to be solved. As an effective means to treat AD, traditional Chinese medicine has carried out a series of studies in recent years from the extraction of effective active ingredients of traditional Chinese medicine, the targeted research of compound prescription, the action pathway of acupuncture and other aspects, and has made some research progress, but there is no scheme to completely cure the disease.

In view of the large amount of research and diagnosis and treatment data on AD disease at present, it is necessary to conduct a comprehensive analysis of AD, clarify the current research and clinical application progress on the pathogenesis and diagnosis and treatment scheme of the disease, and provide ideas for the future research direction, diagnostic technology and methods on depression, with a view to providing ideas for further research and clinical practice.

2. Pathogenesis of Alzheimer's Disease

AD is a common neurodegenerative disease. Clinically, it is characterized by

memory impairment, aphasia, agnosia and impairment of visuospatial skills, even dementia. 30% - 50% of patients with AD have some mental behavior abnormalities more or less. The most common ones are vision and hallucinations, as well as aggressive behavior, restlessness, depression, etc. Its incidence rate is increasing year by year worldwide. However, almost all drugs targeting the classical pathogenesis have not achieved satisfactory clinical effects. This makes scientists gradually shift from simple amyloid-hypothesis to new pathogenesis theory, including gamma oscillation, prion like transmission, cerebral vasoconstriction, the role of growth hormone secretagogue receptor 1 (GHSR1) α pathways, microbial infection, and inflammation dissipation disorders. The amyloid cascade hypothesis and tau hyperphosphorylation hypothesis are considered to be the classical pathogenesis of AD [1].

Amyloid cascade hypothesis: Aβ protein is a transmembrane protein, which mainly hydrolyzes Aβ precursor protein (APP). The accumulation of β-amyloid protein (Aβ) and accumulation in amyloid plaques are considered to be the key pathogenesis of AD. The first pathological change of AD is often the Aβ protein deposition in hippocampus. The Aβ protein in the form of amyloid plaques in hippocampus and basal ganglia will recruit more Aβ proteins to form insoluble aggregates, induce mitochondrial damage, destroy homeostasis, and cause synaptic dysfunction. Microglia and astrocytes are activated and induce related inflammatory reactions and oxidative stress, which eventually lead to neuronal dysfunction and apoptosis, causing the occurrence of AD.

Hypothesis of tau protein hyperphosphorylation mechanism: Tau protein is a microtubule associated protein produced by alternative splicing of microtubule-associated protein tau (MAPT) gene. The functions of Tau protein include maintaining microtubule structure and assisting in cytoplasmic transport, maintaining synaptic structure and function, and regulating neuronal signal transduction. Hyperphosphorylated tau protein in the brain of AD patients leads to the configuration changes and the loss of tubulin polymerization ability, resulting in the impairment of microtubule function. Meanwhile, tau acetylation and truncation inhibited its ability to bind to microtubules. Due to its ity, the pathogenesis of pathological tau remains to be clarified in the point of view of western medicine.

Gamma oscillation: Gamma oscillation is a synchronous rhythmic activity produced by network neurons. It generally resonates at 20 - 50 hz. It is related to many advanced cognitive functions. When some physiological parameters of human body change, the synchronous rhythmic activity produced by network neurons will change accordingly. Without gamma oscillation, cognitive problems will occur. Studies show that normal gamma oscillations can reduce inflammation and thus play an important role in improving neurodegeneration. Gamma oscillations have been reduced before plaque formation or cognitive decline begins. Reduced gamma oscillations can lead to memory impairment. Some researchers think Gamma oscillation is the pathogenesis of AD.

Prion like transmission: Prionprotein (PrPSc) is a host encoded protein with special conformation. Its characteristics include self reproduction ability, strong infectivity, tenacious survival ability and the ability to hide itself to avoid recognition and clearance by the host immune system. Aβ protein can spread in the brain through a pathogenic conformation similar to PrPSc, leading to plaque formation and extensive deposition of Aβ. This suggests that virus like Aβ is first formed in one or more brain regions and then spread to other brain regions, that is, there is the possibility of cross synaptic transmission to cause lesions.

Hippocampus GHSR1 α Mediated signaling pathway: GHSR1 α is a member of the a-type G protein of coupled receptor family. In normal hippocampus, GHSR1 α involves the signal pathways mainly related to learning eating and producing pleasant feelings. It plays a role in maintaining hippocampal synaptic physiological function and memory by regulating dopamine receptor D1 to activate calmodulin dependent protein kinase II. Hippocampal lesions are one of the earliest lesions in AD, and affect cognitive function, which is likely to be related to GHSR1 α related to signal pathway. New evidence suggests that the loss of GHSR1 α can lead to AD like stress and memory impairment in hippocampal synapses.

Cerebrovascular dysfunction: In the early stage of AD, there will be impaired angiogenesis and decreased cerebral blood flow. Thus Aβ is promoted to produce. deposition of Aβ can also constrict cerebral blood vessels, which leads to a decrease in cerebral blood flow. Therefore, cerebrovascular dysfunction is considered to be one of the initial changes of AD.

Microbial infection: Researchers think that microorganisms are involved in the pathogenesis of AD. Herpesvirus is one of the potential pathogenic factors of AD, especially HHV-6A participates in the host regulation of many AD risk genes (such as BACE1 and APBB2), and promotes the sedimentation of Aβ and the loss of neuronal by inhibiting miR-155. Porphyromonas gingivalis has been identified as the important risk factors of Aβ plaque and AD. Patients with active periodontitis had significantly lower cognitive function within 6 months than AD patients without active periodontitis. Porphyromonas gingivalis lipopolysaccharide has been detected in the brain of AD patients, indicating that it may play a role in AD and that porphyromonas gingivalis DNA in cerebrospinal fluid can be used as a diagnostic marker.

Cerebro intestinal axis: The disorder of brain gut microbiome axis may play an important role in the pathogenesis of AD. With the increase of age, the diversity and stability of intestinal microbial components decrease, resulting in the continuous inflammation of intestinal mucosa. As the source of a large number of amyloid proteins, lipopolysaccharides and other toxins, the intestinal microflora may lead to systemic inflammation and damage to the blood-brain barrier. Bacteria or their products can move from the gastrointestinal tract and the oronasal cavity to the central nervous system, and may also damage the blood-brain barrier, promote nervous inflammation, nerve damage, and eventually lead to neurodegeneration and occurrence of AD. The patients with abnormal intestinal

microecological structure will have serious cognitive impairment [2].

Inflammation dissipation disorder: Many evidences support that chronic inflammation is involved in the pathogenesis of AD. Inflammation dissipation disorder is one of the causes of chronic inflammation. The termination of inflammatory response is a biological process strictly regulated by pro-resolving mediators (SPMS), which is called inflammatory dissipation. So far, four types of SPMS have been found: LxA4, NPD1, RVs and MaR1. It is found that the levels of four types of SPMS in the brain tissue of AD patients are significantly reduced, suggesting that SPMS may play an important role in maintaining the cognitive level of patients. In other words, inflammation dissipation disorder may be the cause of AD.

Genetic difference: According to the age of onset before or after 65 years old, AD can be divided into early onset (Eoad) and late onset (load). Eoad accounts for 1% - 5% of all cases, and is mainly related to autosomal dominant APP, PSEN1 and PSEN2 gene mutations.

Study shows that the risk factors of AD can be divided into controllable factors and uncontrollable factors. Uncontrollable factors mainly include heredity, age, gender, etc. Controllable factors include diabetes, history of hypertension in middle age, hyperlipidemia, history of obesity in middle age, lack of exercise, depression, smoking, low education level, sleep, etc. In addition, metal elements in the environment, brain trauma, hypothyroidism [3] [4] [5]. The factors present references for diagnosis and treatment of AD.

We can see that the West medicine have presented many kinds of explains. There is no name of Alzheimer's disease in ancient books of traditional Chinese medicine. Traditional Chinese medicine mostly attributes this disease to the categories of "stupidity", "forgetfulness", "fatigue" and "dementia". In the perspective of traditional Chinese medicine, there is a consensus, *i.e.*, abnormal metabolism of Qi, blood and body fluid is the pathogenic factor of AD. Deficiency of Qi and blood is the pathological basis of the body's original deficiency though the location of the disease is in the brain. The characteristics are deficiency in origin and excess in superficislity. Deficiency in origin means deficiency of kidney essence, Qi and blood, which causes the lack of nutrition for brain. Excess in superficislity means the existence of phlegm and stasis, which causes that the food cannot be effectively absorbed and transformed into nutrients. The ideological system on disease of West medicine and traditional Chinese medicine is different, so the names of disease and treatment ideals for the same disease are different also.

In the viewpoints of above summary and analysis, it is shown that the pathogenesis of AD is still not clarified and so many hypotheses are presented, which directly affects the effect of treatment.

3. Diagnosis

Although PET is an early method to diagnose AD, its high cost seriously hinders its popularity. In addition, the scale test cannot timely distinguish and predict

the possible risk of disease, meantime the strong invasion of cerebrospinal fluid extraction also makes people seldom take the initiative to choose. As a basic means of diagnosing various diseases, blood testing is the first choice to solve the above problems. More and more studies have begun to diagnose and predict AD through blood. As the core content of blood testing, its biomarkers also need to be further explored [6]. According to the analysis of the above section, there are many kinds of theories of pathogenesis and corresponding biomarkers, which brings the difficulty that which one is the most best and practical.

MRI can quantify iron deposition in gray matter nuclei and whole cerebral cortex of AD patients. In AD patients, iron deposition increases in some gray matter nuclei and many brain regions including parahippocampal gyrus, olfactory cortex and cerebellum, which can be used as an important imaging marker of AD. The magnetic sensitivity of the left putamen has the best diagnostic efficacy in the diagnosis of AD [7].

In addition to the above imaging and blood testing methods, scales can also be used to determine whether the score meets the standard. Some internationally used scales, such as MMSE (mini mental state examination), MoCha scale and special cognitive impairment scale, are commonly used to determine whether the score is up to the standard. For example, patients with college level can be confirmed to have cognitive impairment if the score is less than or equal to 23 after measurement。

In fact, because the pathogenesis of AD is not clear, the diagnostic criteria are difficult to choose, which can affect the diagnostic results and treatment program. In other words, pathogenesis and targets of AD are required to be further studied to help finding more effective method of treatment.

4. Treatment

4.1. Drugs for Single-Target Treatment of AD

At present, the commonly used West drugs in clinic are mainly single target drugs for symptomatic treatment, such as tacrine, donepezil hydrochloride, lisdimene, galantamine, etc., which can only alleviate the symptoms of patients to a certain extent. Almost all of them which have been identified as single target Aβ or tau protein in the phase III clinical study of new drugs are declared failed.

The cascade hypothesis of Aβ holds that AD originates from the dysregulation of Aβ production and clearance. By activating protein kinase, abnormal secretion and accumulation of Aβ can promote protein kinase and tau protein phosphorylation, trigger chronic inflammation, activate cell apoptosis, produce free radicals and oxidative stress, and finally cause nerve cell death. These pathological processes further promote Aβ deposition, thus forming a cascade amplification effect. However, there are no effective drugs developed based on this hypothesis at present. Whether those to inhibit β, γ-secretory enzyme activity, or to decrease Aβ generation, or to generate anti-Aβ antibody, or to use Aβ vaccines, no effectiveness is observed in clinic treatment [8].

In AD and related tau protein diseases, tau protein is hyperphosphorylated, and aggregates in cells in the form of double helix filaments, straight filaments, and tangled skeletons to form intracellular nerve fiber tangles, which eventually leads to degeneration and death of neurons. This symbolic damage is directly related to the degree of dementia. At present, the drug for tau protein in the treatment of AD mainly focuses on reducing tau protein hyperphosphorylation, inhibiting tau protein aggregation, stabilizing microtubules and immunotherapy. But there is still a lack of effective drugs.

The abnormal mechanism of cholinergic system suggests that the functions of the enzymes in the cholinergic nervous system (choline acetyl transferase (ChAT), acetylcholinesterase (AChE)), receptors (muscarinic receptors, nicotinic receptors); and transporters (high affinity choline uptake system) are gradually weakened in the process of aging decrease of ChAT and insufficiency of the catalytic activity will result in a decrease in the synthesis of acetylcholine (ACh), a kind of cholinergic neurochemical transmitter. When the nerve impulse reaches the nerve endings, the ACh in the synaptic vesicles is not sufficient, resulting in the dysfunction of the whole central and peripheral cholinergic system (parasympathetic and sympathetic preganglionic fibers, parasympathetic and some sympathetic preganglionic fibers, skeletal muscle nerves, cholinergic nerves in the central nervous system). Accordingly the dysfunction of the second signal system of the brain, visceral and limb nerves happen. The cholinergic abnormalities in AD are significant. Based on this hypothesis, the first choice of drugs is reversible AChEI (AChE inhibitor). The mechanism of action of AChEI is to inhibit the activity of AChE at the synapse, and to prolong the space-time effect of neurotransmitter ACh, and to improve the symptoms of patients. Such drugs can alleviate symptoms to a certain extent for mild or moderate AD patients, but cannot prevent the progress of AD disease. With the development of the disease, the efficacy becomes worse and worse, and it is difficult for late patients to be effective.

At present, there is no specific treatment for AD. Acetylcholinesterase inhibitors are commonly used in clinic. There are five drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD patients, namely tacrine, donepezil, kabalatin, galantamine and memantine. The first four drugs are all acetylcholinesterase inhibitors [9].

In the perspective of traditional Chinese medicine, deficiency of Qi and blood is the pathological basis of the body's original deficiency. Therefore, regulating Qi and invigorating blood are often used throughout the treatment of AD. Doctors in different times emphasize the relationship between phlegm and dementia, so the clinical syndrome is based on the gas-liquid theory, and the treatment is based on the method of Xuanfu and ventilating fluid, such as Xingnao powder and Ditan decoction. Qi deficiency can cause phlegm and blood stasis. Phlegm and blood stasis often cause diseases together. Therefore, we should pay attention to the drugs treating both phlegm and blood stasis for AD patients, such as Didang decoction and Danggui Shaoyao powder. Modern medical treatment

methods, such as cholinesterase inhibitors and excitatory amino acid receptor antagonists, often have adverse reactions such as nausea and vomiting [10].

Huperzine A is a monomer compound first analyzed, extracted and isolated from huperzine Serpentis in China. The unique chemical structure makes it easy to penetrate the blood-brain barrier and have a good oral bioavailability. It is also has a high selectivity for acetylcholinesterase in the brain and lasts long. It can improve learning and memory in animal models with a variety of cognitive deficits. The clinical trial time of huperzine A is relatively short, so further clinical trial is required to understand the efficacy. Aspirin is a non steroidal anti-inflammatory drug and is proved to be able to reduce the inflammatory response of degenerative dementia.

4.2. Drugs for Multi-Target Treatment of AD

As the pathogenesis of AD is unknown in the perspective of West Medicine and there is no confirmed drug target, the further exploration of the pathological mechanism and biomarkers of AD is the basis for the development of effective drugs. Some scholars think that AD is a complex disease with multiple factors. It is difficult to use drugs with a single mechanism, and the drugs must have multiple actions and multiple targets to achieve the desired results clinically.

The main strategy of treating AD in traditional Chinese medicine is "tonifying the kidney" and "regulating Qi". It has been found that "tonifying the kidney" in traditional Chinese medicine theory has the function of nourishing nerves [11]. The study of anti AD drugs in the future should mainly focus on the following aspects. First of all, because the pathogenesis of AD is complex and various pathological factors affect each other, it is difficult to find a good starting point for treatment. For a long time, the therapeutic effect of single target drugs is not very obvious. Therefore, multi target therapy and combined medication may bring new hope to the treatment of AD. Secondly, researchers mainly focus on Aβ, the toxic effects of tau protein, inflammatory factors and other pathological factors on the body before, but little attention has been paid to their physiological significance in the pathological state and their production pathway. So researchers should think more about what factors lead to the complex pathological phenomena of AD. Thirdly, with the development of "microorganism brain gut axis" hypothesis and peripheral inflammation hypothesis, peripheral treatment will become a new hope for the treatment of AD. For a long time, AD has been considered as a simple central nervous system disease. However, studies have confirmed that systemic inflammation and intestinal flora imbalance have also become important factors in inducing AD, suggesting that AD may be the result of the joint action of peripheral and central systems, Peripheral therapy can effectively solve the problem that drugs are difficult to penetrate the blood-brain barrier. In addition, because the central nervous system has a wide range of complex receptors, it is very easy to cause serious adverse reactions caused by drug off target. Peripheral therapy fundamentally solves this difficulty [12]. For

example, it is shown that Huanglian Jiedu decoction combined with compound Cistanche Yizhi and donepezil tablets is effective and safe in the treatment of patients with AD [13]. Several components of alpiniae oxyphyllae fructus (AOF) can synergistically regulate the metabolic disorder of AD, mainly involving amino acid metabolism, lipid metabolism, energy metabolism, etc. [14]. Expriments show that the number of neuronal inflammatory cells is significantly higher in mice with AD, and the release of glial cells and pro-inflammatory factors can cause damage to mouse brain neurons [15]. This result can provide us new ideas for AD treatment.

The most commonly used traditional Chinese medicines have the tonic functions and can activate blood circulation and remove blood stasis such as acorus tatarinowii and radix rehmanniae preparata. The property of these drugs is mainly mild, gentle and lukewarm. The flavor is mainly sweet, pungent and bitter. The groups of high-frequency traditional Chinese drugs are " Cistanche deserticola + Acorus tatarinowii", "leech + Acorus tatarinowii", "Yizhiren + Lycium barbarum + Acorus tatarinowii" and "Yizhiren + Chuanxiong + Acorus tatarinowii + Curcuma" [16].

Curcumin, resveratrol and dihydrocaffeic acid can be well combined with the key anti AD targets and have good pharmacokinetic and toxicological properties. In other words, curcumin, resveratrol and dihydrocaffeic acid have great potential to enhance synaptic plasticity, and can achieve the effect of anti AD through multi-target and multi-channel synergistic mechanism [17].

The active components of Buyang Huanwu Decoctio can affect biological processes such as proteolysis, protein phosphorylation, estrogen response and inhibit Aβ, accordingly to reduce neuronal inflammatory reaction and neuronal apoptosis, and weaken cholinesterase activity, so as to achieve the purpose of treating AD [18]. "Ginseng pilose antler" can act on the signal pathways such as neuroactive ligand receptor interaction, serotonergic synapse, cAMP signal pathway, PI3K AKT signal pathway and cancer pathway, So as to play a role in the treatment of AD [19].

AD belongs to the category of "dementia" and "forgetfulness" in the view points of traditional Chinese medicine. The main reason is the deficiency of kidney essence, which leads to the stagnation of five internal organs' Qi, the insufficient transformation of essence and Qi, and the emptiness of brain and marrow, leading to dementia. Therefore, the treatment should strengthen Yang and tonify the kidney. In Mahuang Fuzi Asarum decoction, aconite warms and invigorates the kidney Yang, wolfberry invigorates the eyes, nourishes the liver and kidney, ephedra perspires and dissipates cold, dodder invigorates Yin and Yang, asarum promotes resuscitation, Morinda officinalis and epimedium are prepared to invigorate the kidney and Yang, dried ginger invigorates the spleen Yang, cinnamon invigorates the fire and helps Yang, Gastrodia elata dredges meridians and activate collaterals, white peony nourishes blood and Yin, and roasted licorice is used to harmonize the effects. The combined use of these drugs has the effect of

nourishing the kidney and filling the marrow. Pharmacological studies show that Gastrodia elata can promote brain blood circulation, antagonize central nervous system apoptosis, delay brain cell aging and improve memory ability; Aconitine contained in Asarum can improve body metabolism, anti-aging effect, inhibit free radical production and reduce body damage; Radix paeoniae alba can inhibit platelet aggregation, promote the recovery of hemorheology, prevent cerebrovascular diseases and reduce the incidence of AD. Therefore, Mahuang Fuzi Asarum decoction can eliminate oxygen free radicals, inhibit p38 MAPK activation, improve cognitive function, improve clinical symptoms, and promote the improvement of self-care ability [20]. It is shown that the measure technology of West medicine is used in the components of effects of traditional Chinese medicine, which is the practice of combination of West and traditional Chinese medicine.

Quetiapine is an antagonist that can block a variety of receptors and can resist AD and depression by blocking serotonin 2A and dopamine D_1 and D_2 receptors. Meantime, it also has a calming effect. Taking a small dose of quetiapine can improve patients' insomnia symptoms and improve their sleep quality. However, clinical studies shows that the single quetiapine treatment for patients with AD and sleep disorders is not ideal, mainly because it is difficult to break the long-term vicious circle when taking small doses of quetiapine alone, while large doses of quetiapine will produce adverse reactions. Midazolam is a typical benzodiazepine drug with anti anxiety and muscle relaxation effects. Compared with traditional benzodiazepine drugs, midazolam has the characteristics of prolonging half-life and better water solubility. The use of midazolam combined with quetiapine in the treatment of AD patients with sleep disorders can effectively improve their sleep quality and cognitive function. The clinical effect is significant [21].

Dietary nutrition intervention is of great significance in the prevention and treatment of AD. Reasonable intake of multi vitamins, unsaturated fatty acids and bioactive substances, and diet structure close to the Mediterranean diet model can reduce the incidence of AD or delay the onset time to a certain extent [22].

The methods of acupuncture and moxibustion to treat AD include traditional ways (body acupuncture and cluster needling at head points) and special ways (electroacupuncture, moxibustion, acupoint catgut embedding and acupoint injection).

The main mechanisms of Huanglian Jiedu Decoction in the treatment of AD include the following: anti-inflammatory and immune response inhibition; inhibition of lipid peroxidation; inhibition of acetylcholinesterase activity; intervene β amyloid and tau protein toxicity; and regulation of gene expression. Acupuncture combined with Huanglian Jiedu Decoction can achieve significant effects in the clinical treatment of AD, effectively improve the clinical symptoms of patients, and promote the improvement of learning and memory function and cognitive function [23].

The advantage of traditional Chinese medicine in the treatment of AD is to improve people's mental and emotional state, so as to alleviate or control the occurrence and development of AD patients by adjusting the Yin/Yang, Qi/blood and the deficiency/excess of viscera of human. Clinical traditional Chinese doctors have unique views on the pathogenesis and corresponding treatments of AD. At the same time, single treatment has been instituted by comprehensive treatment. The combination of drug treatment, physical therapy and psychotherapy has achieved the obvious clinical efficacy.

Polysaccharide is a kind of natural high molecular polymer which is connected by aldose or ketose through glycosidic bond. It has anti-tumor, anti-aging, anti-inflammatory, anticoagulant and other pharmacological activities. Schisandra chinensis polysaccharide, atractylodes macrocephala polysaccharide and rhizoma corydalis polysaccharide have good effects on AD. Natural medicines containing polysaccharides also include ganoderma lucidum, cornus officinalis, poria cocos, astragalus membranaceus, codonopsis pilosula, angelica sinensis, etc. Most of these natural drugs have the ability of anti-oxidation and anti-apoptosis. Natural drugs with anti-oxidation components have broad prospects for the treatment of AD [24].

Flavone is a compound composed of two benzene rings with phenolic hydroxyl groups connected by the central three carbon atoms. The total flavone extracted from persimmon leaves can protect PC12 cells and reduce Aβ25-35-inducded neurotoxicity, and its anti AD mechanism may be related to scavenging free radicals.

The total flavonoids, quercetin, apigenin and other natural active flavonoids of ampelopsis grossedentata have also been proved to have the ability of anti AD. Alkaloid is a kind of nitrogen-containing compound, which accounts for a large proportion in the study of natural organic compounds. Galanthamine is a reversible inhibitor of AChE. It is one of the common drugs used to alleviate the symptoms of AD. However, at the initial stage of galantamine treatment, patients will have abdominal pain, diarrhea, nausea, vomiting and other intestinal adverse reactions. Huperzine A, a sesquiterpene alkaloid extracted from huperzine, is a strong reversible inhibitor of AChE. It can enhance memory and protect nerves. Berberine can promote Aβ to alleviate the cognitive decline of AD model mice by eliminating tau protein and alleviating tau protein hyperphosphorylation. Gladiolus, kaempferine, evodia rutaecarpa and other plant extracts also contain alkaloids.

Saponins exist in a variety of plants and have many pharmacological activities, such as nerve protection, anti-cancer, sedation and so on. Ginsenosides mainly plays a neuroprotective role by inhibiting Aβ. Salidroside also has corresponding curative effect on AD.

Oridonin is a kind of tetracyclic diterpenoids, which can improve the synaptic loss and alleviate the inflammatory reaction in the hippocampus of AD model mice. So oridonin can be used as a potential drug for the treatment of AD. According to experimental results, ginkgolide B can shorten the escape latency of

AD model rats and improve their dementia symptoms. At present, there are few studies on the treatment of AD by terpenoids, which need to be further explored. Resveratrol is a polyphenol compound and has great potential for anti AD. Maple leaf polysaccharide has antioxidant activity and can delay the onset of AD. It also has the role of reversing and improving Aβ neurotoxicity, inhibiting Aβ aggregation. Curcumin can significantly reduce the spatial memory deficit of APP/PS1 mice, and promote the function of cholinergic neurons in vivo and in vitro. It means that curcumin can treat AD by inhibiting inflammatory response. Epigallocatechin gallate (EGCG) is the main component of green tea, which has potential neuroprotective effect on AD animal model. Naringin, rosmarinic acid, lycopene and other polyphenols also show good therapeutic effects in AD.

The elimination of metabolites such as Aβ needs the combined action of the enzyme degradation, blood-brain barrier, the overall flow of brain tissue fluid ISF and the absorption of cerebrospinal fluid (CSF) into the circulatory system and lymphatic system. The damage of any link may lead to the deposition of metabolites and then lead to the occurrence or development of disease. The study on the elimination of metabolites such as Aβ by glial-lymphatic pathway and meningeal lymphatic vessels provides a new target for the treatment of neurodegenerative diseases such as AD [25]. More study is needed in the future to further explore Aβ cleaning path and to find methods of improving cleaning efficiency.

Modern physicians constantly refresh their understanding of AD from different angles. Acupuncture combined with medicine has also achieved certain results in the treatment of AD. Traditional Chinese medicine has a good research prospect in the prevention and treatment of AD [26]. The quality of life of AD patients is affected by the course of disease, treatment scheme, hearing status, music hobbies and other factors. Clinical trials show that the combination of music therapy in a single treatment scheme can improve the quality of life of AD patients [27].

4.3. Combined Treatment of Traditional Chinese Medicine and West Medicine

The commonly used West medicine drugs with either single target or multiple targets are clinically not very effective. Compared with West medicine drugs, natural products and traditional Chinese medicine have obtained more prominent curative effects in the prevention and treatment of complex diseases with multiple causes because of their unique advantages of multiple components, multiple targets and multiple pathways. For example, ellagic acid (EA), a natural product, is a natural phenolic antioxidant widely found in plant tissues such as potentilla discolor, gallnut, raspberry, soft fruits and nuts (such as strawberry, cranberry, pecan) [28]. EA may be a potential therapeutic agent for AD. EA can effectively inhibit the generation of Aβ in APP/PS1 mice and reduce Aβ deposition to protect neurons. In addition, it can activate GSK3β/AKT signaling pathway and inhibit tau hyperphosphorylation. The natural product Wuling powder

can improve the learning and memory impairment of APPswe/PS1dE9 double transgenic mice and inhibit the formation of Aβ aggregates, thereby reducing the generation of age spots.

Aged garlic is a non-toxic solvent extracted from garlic powder. Aged garlic extract (AGE) has a very strong antioxidant activity and a variety of biological activities. Ethyl acetate in AGE can reduce cell oxidative stress, enhance cell activity, and reduce the death of cell PC12 due to Aβ induced cytotoxic.

The Danshensu can be better used in AD by inhibiting Aβ generation and activating PI3K/AKT pathway in N2a/APP695 cells to reduce amyloid precursor protein β lyase 1 (BACE1). Tianwang Buxin pill combined with rosemary essential oil can resist the adverse reactions caused by medication. Radix asparagus, ophiopogon japonicus, radix scrophulariae and rehmanniae in the prescription can reduce fire and phlegm, but the drug property is cold and can damage the spleen, stomach, heart and liver. But if it is combined with rosemary essential oil, the central nervous system can be excited and the adverse reactions can be eliminated.

In recent years, acupuncture has made some progress in the treatment of AD. Its prevention and treatment of AD lies in regulating and restoring the body's self-steady state and self-repair ability. Among them, a large number of animal experimental studies on electroacupuncture in the treatment of AD have been carried out, and its action pathway has been expounded, which provides experimental basis and theoretical guidance for clinical treatment of AD. For example, electroacupuncture can reduce Aβ. Stimulating Guanyuan and Sanyinjiao points can regulate the secretion level of HPO axis and related hormones and, meantime inhibit APP and expression of Aβ1-42 content in cerebral cortex. Electroacupuncture stimulation of Baihui and Shengting points can improve the impairment of learning and memory of APP/PS1 mice. The relevant mechanism may be that it can regulate the polarization of microglia in the hippocampus, thereby reduce Aβ sedimentation. Stimulation of Baihui, Yintang and Renzhong points by using electroacupuncture of Du meridian can significantly improve the cognitive impairment of AD mice. The mechanism may be the reduction of electroacupuncture β secretase (BACE1) expression, and reduction of the β abnormal cleavage of amyloid precursor protein (APP), which reduces the generation of Aβ. Acupuncture at Baihui point can promote the polarization of microglia towards M2 type, and reduce the generation of M1 type microglia, and accordingly effectively correct M1 type microglia inflammatory factor (IL-1 β, TNF-α) and achieve the effect of treating AD. Electroacupuncture stimulation can also regulate synaptic plasticity by inhibiting the expression of PSD-95, so as to improve the learning and memory impairment.

Neural stem cell transplantation can fundamentally solve the problem of neural cell loss in AD. This is also confirmed by the experiment that MG53 protein combined with human umbilical cord mesenchymal stem cells (hUC-MSCs) transplantation can regulate oxidative stress in the brain through Nrf2 pathway.

The treatment of substances in a nanoscale way can promote the more effective passage of drugs through BBB. Loading α inverted twist nano preparation (NP-αM) can effectively clear Aβ. Solid lipid nanoparticles of compound huperzine combined with terahertz wave can inhibit AD by affecting cholinergic nervous system and monoamine neurotransmitters [28] [29].

Calcium pyroglutamine can protect the neurons in the hippocampus by improving the antioxidant capacity and anti-inflammatory capacity, and improve the cognitive impairment due to scopolamine by protecting the neurons in the hippocampus [30].

If only a single West medicine is used for patients, it will lead to an increase in the incidence of adverse reactions and the dosage, which will affect the medication compliance of patients and cause poor treatment effect. The traditional Chinese medicine replication prescription often has a good effect on improving the condition of patients. The reason is mainly because traditional Chinese medicine often contains a variety of ingredients, which has a very significant effect on improving the condition of patients. Meanwhile, traditional Chinese medicine theory has a unique understanding of AD and a relatively complete treatment system. Combined with modern medical diagnosis and treatment methods, it can play a certain advantage in the field of AD treatment. Therefore, treatment combined traditional Chinese medicine and West medicine will be an important direction of AD treatment.

5. Conclusions

The traditional West drugs used to treat AD mainly include acetylcholinesterase inhibitor kabbalatin, galantamine, donepezil, and N-methyl-D-aspartate receptor antagonist memantine. However, although these marketed drugs can slow down the course of the disease and alleviate symptoms, they cannot totally cure the disease. The pathogenesis of AD is complex and inconclusive in the point of view of western medicine. The lack of correct understanding of the pathological process of the disease is the fundamental reason for the lack of drugs that can reverse the course of the disease. The pathogenesis and related targets of AD still need to be further explored.

Interdisciplinary integration is the general trend of disease research in the future. The application of new technology makes it easier for drugs to pass through the blood-brain barrier (BBB), and greatly improves the bioavailability of drugs in vivo, such as exosomes from neurons and glial cells, painless and minimally invasive microneedle transdermal drug delivery.

Studies have confirmed that systemic inflammation and intestinal flora imbalance have also become important factors in inducing AD, suggesting that AD may be the result of the joint action of the peripheral and central system. Peripheral treatment can effectively solve the problem that drugs are difficult to penetrate the blood-brain barrier. In addition, because the central nervous system has extensive and complex receptors, it is very easy to cause drug miss and cause

serious adverse reactions. Peripheral therapy fundamentally solves this difficulty.

Though many advances in understanding the pathology and treatment of AD have been got by decades of research and clinical practice, further study is required to totally clarify the pathogenesis and find more effective drugs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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