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Detoxification and Dispersion Method Intervenes Neurofibrillary Tangles in the Treatment of Diabetic AD

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Abstract: ***Neurofibrillary tangles (NFTs) is one of the pathological manifestations of diabetic encephalopathy that can irreversibly develop into AD. Detoxification and Dispersion Method may play an important role in preventing NFTs, preventing or reversing its formation, and delaying neuronal damage. Based on the theory of "internal knot of toxin and blood stasis" and the basic treatment of "Detoxification and Dispersion Method", this paper tries to explore the Detoxification and Dispersion Method for targeted intervention of neurofibrillary tangle, weaken the neurotoxic damage caused by inflammatory reaction, and protect the normal physiological function of neurons and nerve cells from the identity of "junction of toxin and blood stasis - neurofibrillary tangle" and "clearance of blood brain barrier". This study provides new ideas and methods for the prevention and treatment of diabetic encephalopathy, and provides methodological reference and scientific basis for enriching and developing the theory of "detoxing Sanjie" and "detoxing and stasis internal knot" in traditional Chinese medicine.***

Keywords: Detoxification and Dispersion Method, Alzheimer's disease, Diabetes mellitus, Toxic damage to the brain collaterals**.**

1. Introduction

With the aggravation of the aging population and the improvement of living conditions, the incidence and prevalence of Alzheimer's disease (AD) and Type 2 diabetes mellitus (T2DM) have increased significantly and shown an upward trend [1]. Furthermore, due to the correlation between AD and diabetes in epidemiology, histopathology, molecular physiology and biochemistry, such as both having abnormal insulin protease function, abnormal insulin signal transduction, oxidative stress, mitochondrial dysfunction, metabolic disorders, and the fact that diabetes-induced neuroinflammation can significantly increase the probability of AD, making it one of the main pathological factors of AD [2]. Therefore, AD has recently been referred to as "Type 3 diabetes" [3]. AD with diabetes has a prolonged course of illness, a long treatment cycle, high medical and nursing costs, and is a heavy burden for patients and their families, therefore it is of great research significance to find targeted Chinese herbal medicines and traditional Chinese medicine prescriptions that target the classic pathological features of diabetes-induced AD from the perspective of traditional Chinese medicine theory.

AD is a central nervous system degenerative disease, with a complex etiology and several hypotheses standing side by side. Tau protein hyperphosphorylation, neurofibrillary tangles, Aβ deposition, amyloid plaque formation, chronic inflammation, and neuron death are the main discussed causes [4]. Among them, the neuroprotective mechanism that has attracted extensive scientific research is the "tau protein hyperphosphorylation and neurofibrillary tangles theory" [5][6]. Previous studies have shown that tau protein in neurons becomes hyperphosphorylated under the induction of neuroinflammation, and the tau protein microtubule structure changes to form neurofibrillary tangles (NFTs) [7]. Furthermore, studies have shown that the number of NFTs is positively correlated with the degree of cognitive impairment in AD patients [8], so tau protein hyperphosphorylation and NFT have become the targeted treatment points for AD in recent years. Traditional Chinese medicine is an important cultural treasure of our country, although there are no ancient documents that directly record this disease, it belongs to the scope of traditional Chinese medicine such as "xiaoke dai" disease [9]. Based on the understanding of T2DM and AD from both Western and Chinese medicine, this paper starts from the perspective of "toxin and blood stasis accumulation," integrating the East and the West, aiming to reduce the level of phosphorylated tau protein in the brain and neurofibrillary tangles, and comprehensively and systematically explore the scientific basis of disrupting neurofibrillary tangles with de-toxifying and dispersing formula intervention. In order to provide new ideas and scientific research for further study of this disease.

2. "Poison and Blood Stasis"

2.1 The Internal Knot of Toxic Stasis is Co-morbid with Diabetic AD

Modern studies believe that "poison" plays an important role in its pathogenesis, and "poison and blood stasis internal knot" has also become a research hotspot in recent years. The concept of "blood stasis and poison" and its characteristics of slow accumulation and sudden occurrence were first put forward in Zhang Zhan's Compendium of Nourishing-sheng Yaji (Essential Collection of Health) of the Eastern Jin Dynasty [10]. Li Cheng et al. believed that the formation of toxins and pathogens in the body included dysfunction and dysfunction of viscera, qi and blood, and the formation of fire and heat toxicity, sugar toxicity, lipid toxicity, phlegm turbidity toxicity, and blood stasis toxicity, etc., which were accumulated over time. It also includes the combination of pathogenic factors such as phlegm, dampness, turbidity, cold and so on. Poison accumulation chokes up the channel for a long time, qi and blood run poorly, and accumulates as stasis; The accumulation of poison consumes body fluid, and the heat is decocted and steamed into blood stasis. Veins are

damaged, blood is lost, and overflow is the main pathogenesis of poisoning and stasis [11]. The pathogenic process of poison and blood stasis is a long course, which belongs to the process of quantitative change to qualitative change. It can accumulate for a long time due to blood stasis, or be triggered by external factors, and then accumulate poison abruptly. Poison and blood stasis can erode muscle and injure flesh, block veins and veins, consume qi and injure Yin. However, according to its pathogenic factors, clinical manifestations and different stages of development of the disease, it is considered to be the prolonged disease of wasting-and-thirst, which is called wasting-and-thirst stay. The etiology and pathogenesis of idiopathy are closely related to the occurrence of wasting-and-thirst [12], such as eating disorder, fatigue, and internal injury. Qi bing Lun (on Qinbing of Su Wen) states that "fat people make the internal heat, and sweet people make the heart full, so their qi overflows and turns into wasting-and-thirst" [13]. The essence of water and grain cannot be absorbed normally and spreads disorders, which eventually accumulates and accumulates into turbidified poison. The Jingui Yao Lue Xin dian (Synopsis of the Golden Prescriptions) says, "The poison is the mother of all diseases"[14], and Wang GUI Yun of the Yuan Dynasty said, "phlegm is the mother of all diseases". After a long time of accumulation of phlegm and evil qi, it becomes turbidified poison, which damages Yin blood and is easily accompanied by blood stasis. Because the poison of sugar turbidity enters the blood and runs with the qi, its nature is sticky and most of it is stagnant, so it is prone to various complications in the later stage of diabetes, such as the stupor caused by the lack of marrow sea [15]. Although the basic pathogenesis of diabetic AD is kidney deficiency with insufficient marrow sea, the accumulation of imbalance of detoxification and blood stasis over time is the key pathological pathogenic factor for its occurrence and development [16]. The phlegm of endogenous toxic pathogens stagnates into stasis for a long time, and the accumulation of poison and stasis inside destroys the brain medulla and causes the primary spirit to lose nourishment, which becomes the core link of the aggravation of the symptoms of wasting-and-thirst stay [17]. Neuron death, neuroinflammation, plaque deposition, tau protein hyperphosphorylation, and the formation of neurofibrillary tangles in the brain of AD are also the manifestations of turbulotoxin deposition and stasis [18].

2.2 Physiology and Pathology of "Poison Stasis and Internal Knot"

Traditional medicine's interpretation of the concept of toxicopathies includes pathological factors, disease products, and clinical features such as etiology and pathology [19]. The pathological changes in modern medicine, such as hypercoagulation, hyperviscosity, hyperlipidemia, microcirculation disorders, endothelial dysfunction, chronic inflammation and neurofibrillary tangles, are consistent with the microstate of the TCM syndrome of poisoning and blood stasis, and the core etiology and pathogenesis is "the intersection of poison and blood stasis" [20].

Brain inflammation is a common complication observed in neurodegenerative diseases and lesions as well as in T2DM [21][22]. It has been shown that the anti-inflammatory effects of hypoglycemic agents and their ability to reduce inflammatory mediators, including IL-6, IL-1β, and TNF-α, in hyperglycemic mice have pleiotropic effects on inflammation, vascular damage, neuronal populations, and AD pathological features [23]. Studies have found that hyperglycemia promotes the release of pro-inflammatory cytokines, which in turn aggravates insulin resistance and neuroinflammation in the body. It also crosses the blood-brain barrier and increases its permeability, damaging neurons and affecting neurophysiological functions [24]. However, insulin resistance may also affect the balance between tau kinase and phosphatase, increase tau phosphorylation, and then produce neurofibrillary tangles, causing neuronal damage [25][26]. In addition, it has been found that the binding of insulin to its brain receptors is reduced in AD patients, and persistent hyperglycemia over time may lead to accelerated brain atrophy [27]. At the same time, free insulin may also interfere with the metabolic clearance of β-amyloid, stimulate the hyperphosphorylation of tau protein and the formation of neurofibrillary tangles in neuronal cells, and aggravate the synaptic toxicity and neurodegeneration observed in AD [28].

3. "Poison and Blood Stasis Internal Knot" is the Theoretical Basis of Jiedu Sanjie Method in the Treatment of Diabetic AD Comorbidity

The core etiology and pathogenesis of diabetic AD is "the junction of toxin and blood stasis (Hujie)". Therefore, the treatment of AD is based on the method of detoxing and dispersing knots. The prescription of "Qing", "Xing" and "SAN" is used to achieve the purpose of detoxing and dispersing knots, so as to remove the poison and blood stasis, which is called by modern medicine to reduce or block the occurrence of cognitive impairment and disease progression by mediating the improvement of inflammatory response [29]. The method of Jiedu Sanjie combines "disease differentiation" and "syndrome differentiation", takes "blood stasis" and "poison" as the cause, "block" as the pathogenesis, and "tong", "xing" and "powder" as the treatment method. The method of detoxifying Sanjie embodies the principle of treating according to the syndrome and guiding the situation to benefit. It was first proposed in Neijing (Internal Canon of Medicine). It is recorded in the Great Treatise on the Ultimate Truth of Plain Questions that "those who are strong cut them" and "those who are strong scatter them" [30]. It is recorded in the "Lei Jing" that "where fire lives, it is not suitable to conceal and repress, so it should be resolved, dispersed, elevated, and advanced because of its potential" [32]. For the application of Jiedu Sanjie method, ancient doctors mostly used this method to remove poison and blood stasis, and it was applied to cardiovascular and cerebrovascular diseases, surgery, tumor and other diseases. Yin Ju et al. proposed that phlegm and blood stasis would turn into heat and poison over a long period of time, obstructing blood vessels, stagnation of qi machinery, and the combination of poison and blood stasis. Therefore, the method of removing poison and blood stasis was selected to remove poison and blood stasis [32].

4. Application of Jiedu Sanjie Method in Diabetic AD Comorbidity

4.1 Theoretical Basis of Neurofibrillary Tangle Removal

Tau protein is mainly composed of tubulin in nerve cells, and its main physiological function is that tubulin binds to form microtubule and double helix structure and maintains its stability [33]. Normal phosphorylated tau protein is involved in important biological processes such as cell morphology maintenance, intracellular information transmission, cell proliferation and division, and is a key factor for maintaining synaptic plasticity and normal physiological function of neuronal cells [34]. On average, there are only 2-3 phosphorylation sites per mole of tau protein in normal adult nerve cells, and tau protein binds to microtubules and is structurally stable and difficult to be phosphorylated [35]. However, studies have shown that the structure of tau protein in the neurons of AD patients is unstable, and abnormal hyperphosphorylation often occurs, and on average every mole of tau protein is connected to 9-10 moles of phosphorylation sites [36]. In addition, abnormal aggregation of tau protein can form the precursor structure of neurofibrillary tangles [37]. Current studies have shown that pathological changes such as hyperphosphorylation of tau protein, Aβ and neural plaques, formation of neurofibrillary tangles, brain hypometabolism, neuroinflammation, and mitochondrial dysfunction are the main characteristics of cognitive impairment. Among them, the excessive accumulation of Aβ and its neurotoxic effects are the first prominent events of neuronal injury. Hyperphosphorylation of Tau protein and the formation and accumulation of NFTs are usually the second events of neuronal apoptosis and necrosis, which are manifested as brain atrophy in AD patients, as well as changes in the structural characteristics of brain regions such as hippocampus, cerebral cortex and basal forebrain [38].

With the deepening of research, the role of tau protein phosphorylation and neurofibrillary tangles in the pathogenesis of neuropathies under high glucose-induced neuroinflammation has attracted more and more attention. Under normal physiological conditions, tau protein is soluble and will be transferred outside the cell to exert its function. However, in the pathological mechanism of neurofibrillary tangles, tau protein acts as the aggregation core to promote further aggregation and misfolding, and the aggregated inclusions can be transmitted between nerve cells [39]. In addition, the pre-filaments formed by tau protein can be transferred to other nerve cells both in vitro and in vivo, and their conventional secretion pathway is the ER-Golgi pathway. tau protein carrying signal peptide leads them to the endoplasmic reticulum membrane, forms from the plasma membrane pore, and is secreted outside the cell through the Golgi alternative pathway [40]. In addition to extracellular clearance, tau protein can also be removed by intracellular autophagy. Autophagy is a conserved catabolic process of tau, in which lysosomal exocytosis of tau mediates tau clearance. Once the autophagy process is blocked, tau clearance is impaired, the phosphorylation level of tau protein in neurons is increased, insoluble tau aggregates accumulate significantly, and tau diffusion is enhanced to form neurofibrillary tangles. The blood brain barrier (BBB) is a highly selective semipermeable membrane that keeps neurotoxic blood-derived components, xenobietics, cells and pathogens out of the brain. At the same time, it provides nutrients and oxygen to the brain, and helps to remove waste and neurotoxins from the brain [41]. Reduced clearance of tau protein and neurofibrillary tangles across the BBB is a key event in the pathogenesis of diabetic AD comorbidity. One study has shown that efficient clearance of misfolded tau and inhibition of tau aggregation are essential for the normal and coordinated function of the nervous system. However, failure of this process may also lead to neurofibrillary tangles, causing neurotoxicity and neurodegeneration, accelerating the decline of learning and memory ability, and resulting in cognitive impairment [42]. The presence of multiple tau clearance mechanisms in the brain reduces the deleterious effects of tau, with metastatic clearance mechanisms across the BBB playing an important role. BBB microglia can phagocytose and remove misfolded tau protein and NFTs, and they can also significantly promote the removal of tau protein by transferring abnormally phosphorylated tau protein from the intercellular matrix to the blood [43].

In conclusion, reducing the level of neurotoxic tau in the brain, whether by inhibiting the abnormal phosphorylation of tau or clearing NFTs, is currently the main therapeutic strategy to reduce NFTS and prevent the progression of DE. The removal of abnormally phosphorylated and misfolded tau protein can block the formation of neurofibrillary tanges, which has become an important target for the prevention and treatment of cognitive impairment.

4.2 Treatment by Stages, Each has Its Own Emphasis

Diabetes induces neuroinflammation and promotes the occurrence of cognitive impairment, which often goes through several processes and does not directly develop into AD. In the early stage of cognitive impairment, the manifestations are hidden, but the pathological characteristics are generally present. It is necessary to nourishing the kidney, promoting the spleen and nourishing Yin first, supplemented by detoxification and dispersing accumulation. At this stage, we should pay attention to nourishing the sea of marrow for wisdom, and combine with Jiedu Sanjie method for early intervention of AD pathology. The early stage of the disease is characterized by metabolic disorders, microcirculation disorders, and the appearance of neuroinflammation. In the etiology and pathogenesis of traditional Chinese medicine, it gradually becomes a wasting-and-thirst disease due to insufficient marrow, spleen and kidney deficiency. The sea of marrow is gradually empty, the spleen is not dispersed and refined, and the brain is not allowed to be nourished, resulting in intelligent defects. Therefore, in the early treatment of diabetic AD, we should give priority to tonifying the kidney, promoting the spleen and nourishing Yin, making the vitality of qi and blood biochemistry, filling the sea of marrow and nourishing the brain. Symptoms such as cognitive impairment often appear in the stage of the disease developing into AD, and TCM syndrome differentiation is mostly in the fluctuation stage or even the decline stage. In the pathogenesis, deficiency and excess are often mixed with poison and blood stasis, and phlegm, blood stasis, turbidity and poison, and fire and heat are retained in the brain and damage the brain collaterals, resulting in disconnection between brain qi and zang qi, and blurred consciousness, which is manifested as severe intellectual defect. Accompanied by emotional abnormalities, mental fatigue such as sleep, life can not take care of themselves. In addition, neuroinflammation, tau protein hyperphosphorylation and neurofibrillary tangles

formation can also be observed under high glucose conditions, which is the pathological manifestation of the interaction of "phlegm", "blood stasis" and "turbidity and toxin" [44]. During this period, we should focus on resolving phlegm, detoxifying and dispersing accumulation, emphasizing the improvement of clinical symptoms and delaying the progress of the disease. However, due to its long course of disease and long treatment cycle, we should emphasize the care of stomach qi during treatment and pay attention to the strength of stomach qi [45].

In the middle and late stages of the development of AD, the positive qi gradually becomes deficient, the evil qi becomes more and more abundant, and the phlegm and blood stasis become cloudy and toxic. The accumulation of poison and blood stasis over time gradually consumes Yin and essence, and Yin deficiency leads to Yang hyperactivity, so heat and toxin are endogenous. Therefore, the method of detoxifying and dispersing knot is urgently needed to clear heat, cool blood and detoxify, activate blood, dissipate knot and dredging collaterals, so as to delay the irreversible progress of the disease and improve the discomfort symptoms of patients. During this period, the combination of deficiency and excess, the combination of poison and blood stasis, the blockage of the cerebral collaterals by the obstruction of poison and blood stasis, the loss of nourishment in the brain medulla, and the disorder of the supernatural mechanism leading to dementia [46]. In Yi Lin Jiu Cuo, musk, acorus tatarinosus and Tujin were used to promote blood circulation, disperse knot and clear collaterals for the state of the junction of poison and blood stasis. Peach kernel, safflower, red peony and so on to promote blood circulation and dissipate blood stasis; Gastrodia, Scorpio, etc. are used to clear collaterals and disperse them; With jujube and ginger to Sanda rising [47]. If the heart and liver fire is strong or the phlegm and blood stasis turns the fire, the fire disturbed the poison, the upper disturbance of the clear orifices, and the god machine is not used, it is mainly to clear the heat and detoxify. Scutellaria baicalensis and Gardenia jasminoides were selected to clear the fire of three jiao; Raw, red peony, moutan peel to detoxify and dissipate blood stasis; Gypsum and buffalo horn are used to cool blood to detoxify and disperse [48]. In addition, for the clinical application of Jiedu-Sanjie method, it is emphasized that the treatment should be based on the changes in the pathogenesis and symptoms of the patient, syndrome differentiation and treatment, according to the location of the disease and the deficiency of Yin and Yang on the surface and excess of the syndrome. In addition, it is also necessary to pay attention to disease differentiation and treatment, considering the cause of the disease, specifically targeting the pathogenic factors of poison and blood stasis.

4.3 Based on the Jiedu Sanjie Method, Pay Attention to the Prevention of Disease

Diabetic AD is a common complication in diabetic patients, which is the result of long-term poor blood glucose control. Therefore, the basis of prevention and treatment is strict self-management. Wasting-and-thirst patients should give priority to diet control, keep daily light diet, avoid partiality, excessive eating fat, sweet, thick and greasy and other habits that greatly damage the spleen and stomach, and achieve temperance and calm mind. At the same time, high blood glucose or large blood glucose fluctuation should be avoided as far as possible to reduce the damage to neurons and nerve cells. In terms of traditional Chinese medicine, early intervention should be given to the pathological formation of AD to prevent its irreversible nerve damage. In this thesis, we propose that Jiedu-Sanjie (Jiedu-Sanjie), a traditional Chinese medicine (TCM) therapy, may play an important role in delaying the progression of AD by targeting tau protein to prevent its hyperphosphorylation and the accumulation of NFTs. In addition, we should also emphasize the importance of tonifying qi, nourishing Yin and protecting the stomach while based on the method of detoxifying Sanjie, so that the "turbidity and poison" can be avoided to improve the prognosis level, delay the process of dementia, and improve the quality of life of patients. In addition, emotional regulation plays an equally important role in the progression of AD. In Danxi Xinfa · Six Depression, it is recorded: "If Qi and blood are harmonious, all diseases will not occur; As long as there is depression, all diseases will be born. Stagnation of liver qi hinders qi production, phlegm accumulates in the chest, and spittooning and qi intermingle, making the mind unclear, and becoming stupid. Phlegm accumulates for a long time, qi and blood are not conducive to operation, stagnation is stasis, stasis festival for a long time turns heat and poison, and the manifestation of stupidity is more prominent. Therefore, diabetic patients with AD should pay more attention to the regulation of seven emotions and avoid excessive excitement or happiness and sadness. In conclusion, in clinically suitable patients, detoxification may prevent tau hyperphosphorylation, reverse neurofibrillary tangling, and delay the process of irreversible neurodegenerative diseases. Early application of Jiedusanjie method to intervene neurofibrillary tangles has a better effect on the prognosis of diabetic AD.

5. Conclusion

Both in modern western medicine and traditional Chinese medicine, AD and diabetes share common pathogenic factors and pathogenesis. Therefore, both of them have cross-reference significance in the clinical selection of traditional Chinese medicine and the application of traditional Chinese medicine. With the in-depth research on the pathogenesis of the two diseases and the application of traditional Chinese medicine theory, more common mechanisms and effective prescriptions can be discovered, which provides new directions and ideas for the multi-angle research and treatment of diabetic AD comorbidity, and the realization of simultaneous treatment of different diseases and early targeted intervention. However, in recent years, the method of Jiedusanjie has been studied for Parkinson's disease, coronary heart disease and other cardiovascular and cerebrovascular diseases. At the same time, studies have shown that Jiedusanjie traditional Chinese medicine or traditional Chinese medicine formulations can affect inflammatory response to improve symptoms and disease progression. However, there are few studies on the application of Jiedu Sanjie method in diabetic AD comorbidity, and more animal experiments and clinical studies are needed to confirm its practicability in the future.

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