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Advances in Traditional Chinese and Western Medicine Research on Diabetic Peripheral Neuropathy

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Abstract: Diabetic Peripheral Neuropathy (DPN) is a common chronic complication of diabetes, and its incidence and disability rates rising annually. Its symptoms are variable, and its course is lingering, and it is difficult to cure, ultimately leading to disability in diabetes mellitus (DM) patients, which has a huge impact on their physical and psychological well-being, increasing their economic burden. Traditional Chinese Medicine (TCM) attributes DPN to deficiencies in visceral yin-yang and qi-blood, along with blood stasis and blockage. Western medicine identifies dyslipidemia, oxidative stress (OS), autoimmunity, gut microbiota imbalance, and impaired insulin-mediated PI3K/protein kinase B (AKT) signaling pathways as causes of DPN. Western medicine does not have clear specific drugs, and mostly focuses on the etiology, symptomatic treatment, and surgical treatments. TCM employs various methods, including herbal treatments and acupuncture, to improve clinical symptoms from multiple perspectives. This article synthesizes DPN pathogenesis and treatment approaches from both TCM and modern medical perspectives, aiming to provide new insights for DPN treatment.

1. Introduction

The structure of neurons is shown in Figure 1. Nerve tissue in all parts of the body may be damaged by hyperglycemia. According to its location and function, diabetes neuropathy can be divided into central and peripheral neuropathy. Diabetic Peripheral Neuropathy (DPN) is a common yet difficult-to-treat complication in DM patients. Approximately 20% of type 1 diabetes (T1D) and 20% of type 2 diabetes (T2D) patients develop DPN within 20 years of initial diagnosis[1]. The prevalence of DPN is around 29% to 49%[2], with the rate rising to 60% to 75% when diagnosed using nerve conduction studies[3]. DPN complications include pain and sensory abnormalities, and the painful diabetic peripheral neuropathy is more severe, occurring in 10% to 26% of cases[4]. The chronic and recurrent nature of DPN can lead to hard-to-heal ulcers, infections, and in severe cases, disability or death. The pathogenesis of DPN is closely related to abnormal metabolism caused by hyperglycemia, although the detailed mechanisms remain unclear. In T1D, glucose control slows the progression of DPN[5]. However, in T2D, due to the presence of metabolic syndrome (MetS),

glucose control has only a minor effect on DPN progression. Therefore, managing DPN in T2D patients mainly involves weight loss and exercise to alleviate MetS[6]. The drug used to treat DPN has poor efficacy, partly due to insufficient understanding of DPN's pathogenesis and unconventional risk factors, and partly due to the lack of effectiveness and side effects of existing drugs. This article aims to analyze the relationship and development patterns of DPN pathogenesis from both TCM and Western medical perspectives, providing an important theoretical basis for clinical prevention and treatment.

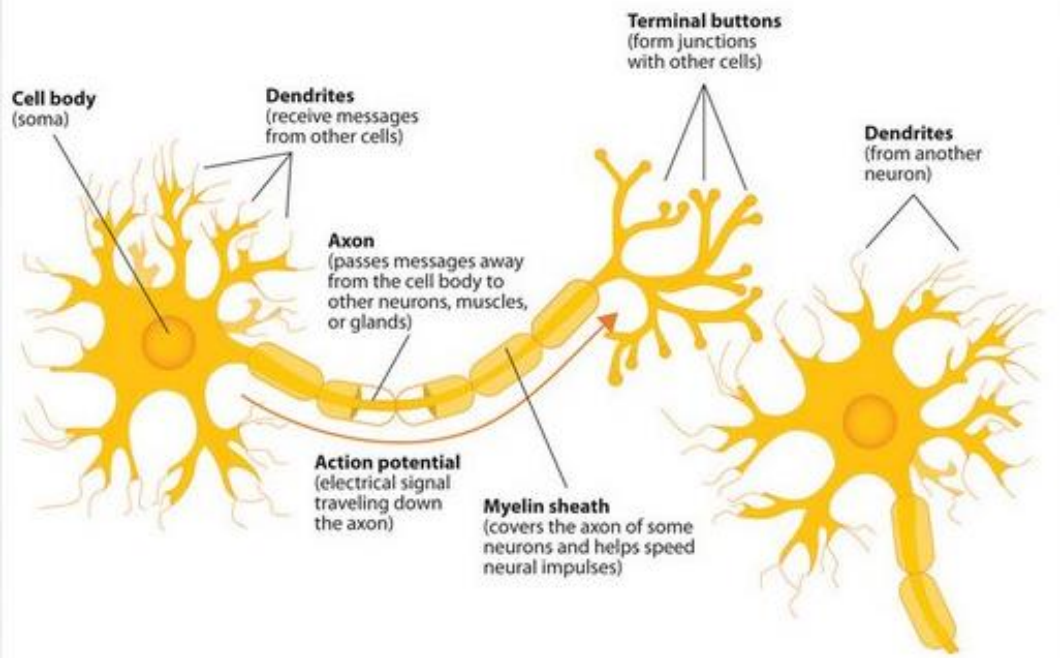

Figure 1: The structure of neurons.

2. Pathogenesis

2.1 Dyslipidemia

In a high-glucose metabolic environment, diabetic patients' peripheral nerves are highly susceptible to damage. Hyperglycemia increases the activity of aldose reductase, a key enzyme in the polyol pathway, leading to the accumulation of sorbitol and fructose in neurons. These substances cannot be fully utilized and metabolized, resulting in increased intracellular osmotic pressure, followed by swelling, and in severe cases, cell degeneration and necrosis[7]. This process further leads to dyslipidemia, endothelial cell dysfunction, and abnormal nerve microcirculation, ultimately increasing blood coagulability, causing vascular narrowing or even occlusion, microcirculation disorders, nerve ischemia and hypoxia damage, and continuous myelin destruction[8], further damaging nerves.

2.2 Oxidative Stress

DPN is closely related to oxidative stress (OS), which results from an imbalance between oxidation and antioxidation due to aging or disease, leading to the overproduction of reactive oxygen species (ROS). ROS and diacylglycerol (DAG) can activate the protein kinase C (PKC) pathway. PKC, composed of serine/threonine kinase, protein kinase A (PKA), and protein kinase G (PKG), is a major mediator of neurotrophic factor signal transduction and is involved in the

proliferation, differentiation, apoptosis, and transformation of vascular endothelial cells[9]. The DAG-PKC pathway regulates nitric oxide (NO) production, causing peripheral vascular dysfunction, thereby promoting DPN progression.

2.3 Autoimmunity

Under the influence of hyperglycemia, the blood-nerve barrier is compromised, breaking the immune tolerance of the central nervous system. Concurrently, the antigenicity of myelin proteins changes due to glycation, leading to their recognition by monocytes, macrophages, and glial cells, prompting the body to produce antibodies[10]. Activated immune cells secrete TNF-α, causing demyelination of nerve fibers and stimulating monocytes and endothelial cells to secrete inflammatory cytokines, resulting in nerve damage. Zhang et al. [11]found that hyperglycemia can activate microglia, producing nitric oxide, peroxynitrite, prostaglandins, and other pro-inflammatory cytokines involved in DPN neuropathic pain. Tian et al.[12] demonstrated that injecting diabetic mice with CU-CPT22 (a drug inducing macrophage polarization to the M2 type) alleviated neuropathic pain symptoms and reduced IL-1β and TNF-α levels.

2.4 Gut Microbiota

Imbalance The role of gut microbiota imbalance in DPN pathogenesis has garnered some scholarly attention. Experimental studies have found that the increase of potential pathogenic bacteria in the gut is positively correlated with ROS production levels, while beneficial gut bacteria are negatively correlated with ROS production levels. The gut microbiota may contribute to oxidative stress-induced myelin and axonal damage by upregulating amyloid precursor protein (APP) and Iba1 expression and downregulating contactin-associated protein (Caspr) expression in the sciatic nerve[13].

2.5 Impaired Insulin-Mediated PI3K/AKT Signaling Pathway

Insulin not only lowers blood glucose levels but also promotes growth and cellular proliferation. The chemical structure of insulin is similar to insulin-like growth factor 1 (IGF-1), which activates the PI3K/AKT and MAPK signaling pathways, subsequently activating downstream molecules and mammalian target of rapamycin (mTOR) expression, and inhibiting the expression of pro-apoptotic protein Bad[14]. This promotes axonal growth and maintains normal sensation. In diabetic patients, the number and affinity of insulin receptors decrease, and PI3K/AKT activation is hindered, causing downstream pathway abnormalities. Calcutt et al.[15] suggested that adequate insulin nutritional support prevents hyperglycemia from inducing neuropathy.

In summary, Figure 2 shows part of the pathogenesis of diabetes neuropathy. DPN is primarily caused by abnormal glucose and lipid metabolism, inducing oxidative stress and inflammatory responses in the nervous system, leading to nerve cell damage. Gut microbiota imbalance and reduced insulin-mediated nutritional support also contribute to the development and progression of DPN. Previous animal models and clinical trials targeting individual pathogenesis mechanisms have not achieved the desired therapeutic outcomes. Therefore, a multi-faceted, multi-layered study of DPN pathogenesis will provide new insights for early screening and treatment.

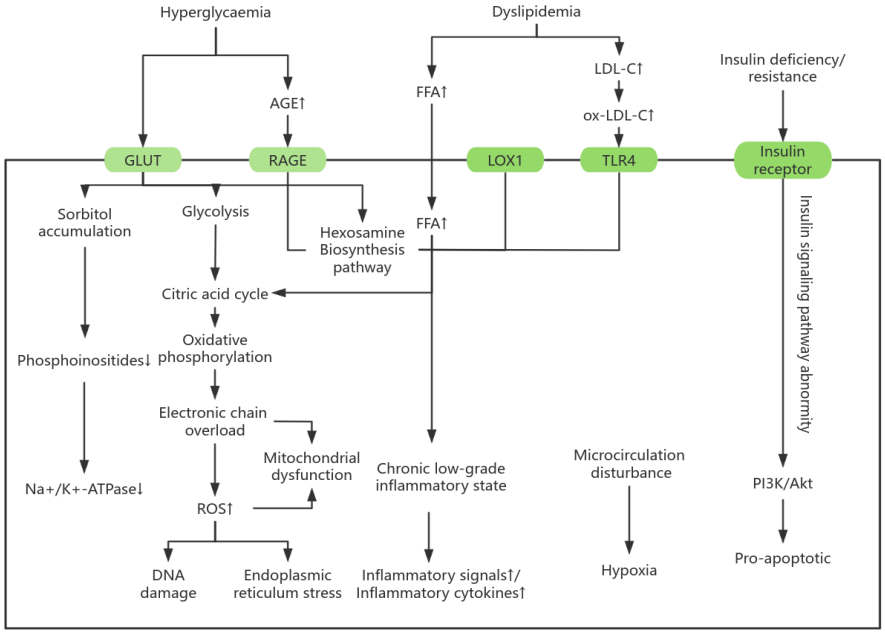

Figure 2: Pathogenesis of diabetes neuropathy

3. Western medicine treatment

Due to the lack of established disease-modifying therapies, the clinical management of DPN patients focused on enhanced education, proper foot care, appropriate footwear selection, and annual foot examinations. Clinically, etiological treatment, symptomatic treatment, and surgical treatment are commonly used.

Etiological treatment: 1). Blood glucose control: This is the primary goal and key aspect of treatment. Hyperglycemia is the pathogenic basis of various chronic complications of diabetes, and timely correction of hyperglycemia is fundamental and prerequisite for treating various complications. Depending on the patient's blood glucose levels and actual condition, oral hypoglycemic drugs or subcutaneous insulin injections are used to achieve blood glucose targets, thereby reducing the occurrence of various complications or critical acute conditions.

2). Nerve repair therapy: Mesenchymal stem cells (MSCs) improve peripheral nerve repair and upregulate the mRNA expression levels of neurotrophic factors (NTF) in streptozotocin-induced DPN patients to improve symptoms. Clinically, mecobalamin and epalrestat are commonly used as nerve repair therapy drugs. Mecobalamin supplements the body's production of vitamin B12, and has a special affinity for nerve tissue, and helps repair nerve tissue, regenerate peripheral nerves, and improve neuronal conductivity[16].Epalrestat reduces oxidative stress by decreasing the activation of antioxidant enzymes and aldose reductase, and alleviates peripheral neuropathy by inhibiting the overexpression of the polyol pathway[17]. Additionally, nerve growth factors, neurotrophins, neuropeptides, and 4-methylcatechol are also used to treat DPN[18].

3). Antioxidant stress drugs: Inhibiting the generation of ROS or mitigating its harmful effects may be a promising strategy for treating DPN. Alpha-lipoic acid is widely used as a potent antioxidant. It synthesizes reduced dihydrolipoic acid in body tissues, activates the metabolic cycle of various antioxidants, forms a regenerative cycle, exerts antioxidant effects, and improves local blood circulation. By scavenging free radicals and increasing glutathione content, it reduces lipid peroxidation, enhances neurotrophic activity and ATPase activity, protects vascular endothelial function, and regulates cellular dysfunction, thus positively affecting nerve conduction

velocity[19].MSCs can also improve cell survival by regulating intracellular calcium ion homeostasis and reducing excessive ROS[20].

4). Circulatory improvement therapy: Drugs that improve microcirculation mainly include angiotensin-converting enzyme inhibitors, calcium channel blockers, prostaglandin analogs, and others. Common drugs include alprostadil, cilostazol, pancreatin, and calcium channel blockers. Reduced peripheral nerve blood flow is a major factor in DPN, and clinical treatments can include dilating blood vessels and improving the blood-oxygen supply to nerve cells, thereby effectively improving patient symptoms. Prostaglandins have strong vasodilatory effects, inhibit platelet aggregation in DPN patients, and improve microcirculatory disorder[s][21]. However, some studies suggest that prostaglandin drugs can cause hypotension and bradycardia[22].

Symptomatic treatment: The main goal is to relieve pain symptoms. DPN patients are prone to pain in both lower limbs, and external application of anisodamine cream can improve local metabolism and alleviate DM limb pain symptoms. Anticonvulsants and antidepressants such as carbamazepine can also be used appropriately according to the patient's condition to reduce numbness and pain in the lower limbs. Hyperbaric oxygen therapy has also emerged in recent years as a treatment for DPN. In a hyperbaric oxygen environment, body tissues work in high-concentration oxygen, promoting increased ATP production in mitochondria, facilitating normal functioning of various body cells and tissues, significantly improving the hypoxic state of already blocked or completely obstructed distal blood vessels, aiding in capillary blood flow and maintaining normal function, reducing local edema, and alleviating neurogenic pain caused by hypoxia.

Surgical treatment: In recent years, with the continuous development of surgical techniques, new methods have provided new approaches for improving peripheral nerve blood supply and relieving pain such as limb revascularization, peripheral nerve decompression, and neural regulation surgery . Peripheral nerve decompression can relax nerves and relieve the anatomical structures compressing the nerves, including tendons, ligaments, and bone tissue. Neuroelectrical stimulation is a minimally invasive and reversible neuromodulation technique, which involves implanting electrodes into the human body within a reasonable parameter range and generating electricity to intervene in nerve conduction to treat diseases[23].

4. Traditional Chinese Medicine's Understanding of DPN

4.1 Disease name

In TCM theory, there is no explicit record of DPN. However, there are descriptions of similar clinical manifestations. For instance, the "Key to Diagnosis and Treatment" states: "After a long period of the three diabetes, essence and blood are depleted; one may lose sight or have impaired limbs like wind syndrome, but it is not wind." Based on symptoms such as limb numbness, pain, and weakness, these conditions are often classified under the ancient medical records of "numbness," "blood impediment," "wind impediment," and "wilt syndrome." Modern physicians categorize it as "paralysis syndrome of diabetes."

4.2 Etiology and pathogenesis

Paralysis syndrome of diabetes, as a complication of diabetes, has etiology consistent with diabetes. The "Inner Canon of Huangdi" first recorded the name of diabetes and attributed its causes to visceral weakness, excessive consumption of rich and greasy food, extreme emotional stress, and excessive sexual activity. The main pathogenesis of diabetes is the deficiency of both Qi and Yin, and DPN gradually develops during the course of diabetes. Modern people’s preference for gresay

and sweet foods easily damages the spleen, leading to impaired spleen function and subsequent pathological products like phlegm and dampness. Modern physicians point out that paralysis syndrome of diabetes is caused by prolonged illness, improper treatment or mistreatment, which depletes Qi and injures Yin. Yin deficiency leads to internal heat, which scorches bodily fluids and Qi and blood. Thus, the root cause is the deficiency of Qi, blood, Yin, and Yang, while the blockage of channels by pathological products like phlegm and blood stasis is the manifestation. The interplay of deficiency and excess often affects the limbs and involves the liver, kidneys, and spleen. As the disease progresses, symptoms such as numbness, pain, and muscle atrophy may appear. Blood stasis obstructing the channels is a key factor in its occurrence and development.

5. TCM Treatment

5.1 Staged treatment

Staged treatment is divided according to the severity and duration of the patient's condition, including early, middle, and late stages.

In the early stage, the main symptoms are numbness and significant pain in the limbs, but with relatively minor side effects during physical activity. At this stage, TCM attributes the pathological mechanism to Qi and Yin deficiency, accompanied by mild blood deficiency. The treatment should be targeted, with the primary treatment plan involving drugs that invigorate blood circulation, nourish Yin, and tonify Qi to promote blood flow.

In the middle stage of DPN, the severity of symptoms significantly worsens, with nerve problems extending beyond the initial stage. There is a marked increase in the numbness of limb sensations, particularly with reduced nerve transmission efficiency, and the extent of neuronal damage increases. TCM attributes the pathological mechanism at this stage to insufficient liver and kidney Qi and blood deficiency. The treatment plan should focus on strengthening liver and kidney Qi regulation and promoting blood flow.

In the late stage, the neuropathy in the limbs becomes very pronounced, with significant pain and numbness, and a marked decline in nerve conduction function. Some patients may even be unable to move normally due to muscle atrophy. TCM attributes the pathological mechanism during this period to a significant deficiency of spleen and kidney Yang Qi, and obstruction of the meridians and blood flow. Therefore, the treatment should primarily focus on tonifying the spleen and kidneys and promoting blood circulation and meridian flow.

5.2 Classical Prescription

Buyang Huanwu Decoction, originating from "Corrections on the Errors of Medical Works", is often used for patients with Qi deficiency and blood stasis type sequelae of stroke. Many clinicians have found it effective in treating Qi deficiency and blood stasis type DPN as well[24]. Liu Wanyi et al.[25] conducted chromatographic analysis of the components of Buyang Huanwu Decoction and discovered that its lyophilized extract contains active ingredients such as hydroxysafflor yellow A and paeoniflorin, which can reduce neuronal damage, lower the activity of coagulation factors, reduce thrombosis, and promote improvement in DPN. Zhang Tianya et al.[26] demonstrated through animal experiments that Buyang Huanwu Decoction might regulate oxidative stress responses via the AMPK/Nrf2 pathway to treat DPN, with higher doses of Astragalus showing more significant effects within a certain range. Gao Xinming[27] observed the clinical efficacy of Buyang Huanwu Decoction combined with mecobalamin injection in treating DPN, noting that the two treatments have a synergistic effect that can improve nerve conduction velocity and enhance therapeutic outcomes.

Danggui Sini Decoction, from the "Treatise on Febrile Diseases", is effective in warming the meridians and dispelling cold. It is widely used to treat DPN. Clinical studies have shown its efficacy in treating various types of DPN such as cold coagulation and blood stasis type[28], blood deficiency and cold coagulation type[29], Qi deficiency and blood stasis type[30], and cold-dampness obstructing the spleen type[31]. Xiang Qingwei et al.[32] built a rat model to demonstrate that Danggui Sini Decoction reduces the expression of RhoA/ROCK pathway proteins, lowers ROS induced by high glucose levels, decreases the production of inflammatory factors, reduces the inflammatory response, mitigates mitochondrial fragmentation, and alleviates dorsal root neuron damage in the rat model. Chen Yan et al.[33] conducted clinical research indicating that Danggui Sini Decoction can effectively improve clinical symptoms of DPN, reduce body inflammation and OS, stabilize blood glucose levels, enhance nerve conduction velocity, and has significant efficacy with high safety.

Huangqi Guizhi Wuwu Decoction, from the "Synopsis of the Golden Chamber", has the effects of benefiting Qi, warming the meridians, harmonizing the blood, and relieving obstruction. Dai Fang et al.[34] studied the improvement in symptoms of Qi deficiency and blood stasis type DPN using Huangqi Guizhi Wuwu Decoction, confirming its effectiveness in improving blood glucose and lipid-related indicators, enhancing nerve sensory and motor functions in DPN patients, alleviating related clinical symptoms, and improving patient quality of life. Zhang et al.[35] found through meta-analysis that Huangqi Guizhi Wuwu Decoction has significant efficacy in treating DPN, with notable effects on improving nerve function, regulating blood glucose levels, improving hemorheology, and ensuring safety. Gao Cen et al.[36] and Liu Xiaomeng et al.[37] showed that Huangqi Guizhi Wuwu Decoction can effectively improve nerve conduction function, particularly enhancing the conduction velocity of the median and common peroneal nerves, proving more advantageous than simple Western medicine treatment. Bai Qing[38] found that Huangqi Guizhi Wuwu Decoction might improve nerve conduction function by ameliorating pathological phenomena such as myelin nerve fiber and endoneurial glycoprotein deposition in DPN patients, and reducing blood viscosity.

Danggui Buxue Decoction, from the "differentiation on endogenous and exogenous diseases", addresses the significant pathogenesis of blood stasis in DPN, which mainly arises from deficiency leading to stasis. Qi deficiency results in insufficient propulsion, causing poor blood circulation, so this formula heavily employs Astragalus to benefit Qi and nourish blood. Sun Lili et al.[39] administered Danggui Buxue Decoction to high glucose and high-fat model mice via gastric gavage and used relevant testing methods to confirm that Danggui Buxue Decoction adjusts levels of various amino acids, regulates bile acid metabolism, and modulates glycerophospholipid metabolic pathways to increase the body's insulin sensitivity, thereby balancing disorders in glucose and lipid metabolism.

5.3 Acupuncture

Acupuncture adjusts the Qi of various viscera and meridians in the patient's body, accelerating blood circulation in different parts of the limbs. Liu Kejia et al.[40] searched major databases for literature on acupuncture treatment of DPN and found that the best acupoint combinations for treating DPN are Zusanli (ST36) - Weiwangu (EX-B3) and Zusanli (ST36) - Sanyinjiao (SP6). Zusanli is the He-sea point of the Stomach Meridian, which can protect the postnatal constitution, and has the functions of replenishing the middle Qi and harmonizing Qi and blood. Wang Anna et al.[41] found that the overall efficacy of therapies such as acupuncture combined with acupoint injection, warm acupuncture, plum-blossom needle tapping, bloodletting with electroacupuncture, electroacupuncture combined with ear acupoint pressing, and acupoint injection combined with

herbal fumigation was superior to mecobalamin. Mo Yuting[42] found that Dong's Sanchong acupoint combined with acupuncture has a definite therapeutic effect on lower limb DPN. Cui Yan et al.[43] found that for Qi deficiency and blood stasis type DPN patients, using the Tonifying Root and Unblocking Collaterals electroacupuncture method combined with acupuncture at the Eight Confluent Points achieved better therapeutic effects.

The above studies show that acupuncture treatment accelerates nerve conduction velocity, promotes the development of nerve cells, and reduces the degree of nerve dysfunction and limb pain.

5.4 Foot bath fumigation and washing

Herbal application and fumigation are characteristic treatment methods in TCM. Guided by the basic diagnostic and therapeutic principles of TCM, they involve the application and fumigation of corresponding herbs to the affected areas, promoting blood circulation, improving local blood supply, and having the effects of warming the meridians, dispelling cold, unblocking the meridians, activating blood, and relieving pain. These methods are simple and free of toxic side effects. In the treatment of DPN, herbal fumigation combined with other TCM treatments has shown remarkable efficacy and has been widely applied clinically. Jiang Junling et al.[44] used herbal foot baths combined with Xiaoke An Tang formula to treat DPN. The study results showed that this therapy can increase the levels of serum insulin-like growth factor-1 and adiponectin, and elevate serum myelin basic protein levels, thereby improving glucose and lipid metabolism disorders, enhancing neurotrophic levels, and ultimately alleviating related clinical symptoms such as pain, numbness, and sensory disturbances in DPN patients.

6. Summary

This paper presents a review of the pathogenesis and treatment methods of DPN in both TCM and Western medicine. As a common complication of diabetes, DPN significantly impacts the physical and mental health and quality of life of patients, presenting a considerable challenge. TCM treatments, including internal medicine, external applications, acupuncture, and herbal medicine, have certain advantages in treating DPN, particularly the comprehensive and multi-target benefits of traditional herbal formulations, which are proven effective. In the future, we can further utilize the strengths of both TCM and Western medicine, continuously improve the quality of clinical research, and explore effective treatments with minimal adverse reactions. This will provide a basis for the development of new drugs and the formulation of integrated TCM and Western medical treatment plans.

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