

Research Progress on Astragalus-Based Traditional Chinese Medicine Formulas for the Treatment of Diabetic Peripheral Neuropathy Based on the Qi-Luo and Blood-Luo Theories of Collateral Disease Theory

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Abstract: *Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus, clinically manifested mainly by abnormal limb sensations such as lower limb numbness, formication and pain. The pathogenesis of DPN has not been fully elucidated. Existing studies suggest that it may be associated with the interaction of multiple factors including disordered glycolipid metabolism, oxidative stress injury, deficiency of neurotrophic factors and autoimmune abnormalities. In traditional Chinese medicine (TCM), DPN is categorized as “collateral disease” and “blood bi syndrome”, with the core pathogenesis of “chronic disease invading collaterals and chronic pain invading collaterals”. Its pathological basis involves dysfunction and structural damage of qi collaterals and blood collaterals, manifested as disordered qi collaterals and stasis-obstructed blood collaterals, leading to abnormal qi and blood circulation; prolonged disease further results in collateral damage by toxins. The internal TCM treatment follows the principle of “simultaneous tonification and unblocking”, focusing on tonifying qi to unblock collaterals and activating stagnation to relieve bi pain. Astragalus, an essential herb for tonifying qi, can “tonify qi to activate blood circulation and unblock collaterals to eliminate stasis”. In recent years, in-depth research on prescriptions dominated by Astragalus for DPN treatment has been carried out, covering single herbs, herb pairs, three-herb combinations, compound formulas and combined external therapies, which have demonstrated favorable clinical efficacy and research prospects. Based on the theories of qi collaterals and blood collaterals in collateral disease theory, this paper systematically reviews the research progress of Astragalus-dominated Chinese medicines for DPN treatment.*

Keywords: Qi-Luo, Blood-Luo, DPN, Astragalus.

1. Introduction

Diabetic peripheral neuropathy (DPN) is one of the most prevalent complications of diabetes mellitus. Excluding other causative factors, it presents as peripheral neuropathy characterized by distal symmetric lesions accompanied by limb numbness, formication, cold stabbing pain, electric shock-like sensation, or even weakness and flaccidity of lower limbs that impairs normal limb movement. Without intervention, DPN may progress to diabetic foot ulcers, and amputation may be required in severe cases. Disability and mortality rates rise sharply in end-stage DPN. Among newly diagnosed patients with type 2 diabetes mellitus, the initial incidence of DPN ranges from 10% to 15%, while the incidence of this complication exceeds 50% in patients with a disease duration of ten years or more [1]. At present, the pathological mechanism of DPN has not been fully clarified. Most scholars hold that its pathogenesis involves the activation of the polyol pathway, oxidative stress, microcirculation disturbance, deficiency of neurotrophic factors and interactions among multiple factors. Clinical interventions mainly focus on blood glucose control, neuroprotection and regulation of oxidative stress. However, existing therapeutic regimens can only alleviate partial symptoms, with limited efficacy and obvious side effects. In addition, they generally carry strong drug dependence and aggravated metabolic burden, making it difficult to reverse nerve damage fundamentally. Multiple studies have verified

that Astragalus exerts definite clinical effects in scavenging free radicals, inhibiting inflammatory responses and regulating blood glucose. Combined with recent clinical studies, this paper reviews the treatment of DPN with Astragalus-dominated herbal prescriptions.

2. Significance of the Collateral Disease Theory

Collateral disease theory is an important branch of the theoretical system of traditional Chinese medicine, which originates from Huangdi Neijing (The Yellow Emperor's Internal Classic). This classic first records terms such as meridians and collaterals, and systematically constructs a diagnosis and treatment system, laying an academic foundation for collateral disease theory. Lingshu·Maidu (Spiritual Pivot·Vessel Measurement) first puts forward that “Meridians run deep inside the body; their horizontal branches are collaterals, and the smallest branches of collaterals are sun collaterals”, which clarifies that collaterals are branch networks of meridians. Collaterals not only undertake the functions of moistening and nourishing tissues, connecting qi between the exterior and interior, coordinating nutrient qi and defense qi, as well as the mutual transformation of body fluid and blood, but also serve as the channels for the circulation of qi and blood all over the body. Zhang Jingyue stated in Leijing (Classified Canon): “Blood vessels run inward, and qi collaterals distribute outward”, which expounds the circulation rules and distribution

characteristics of collaterals. Zhang Zhongjing pioneered the creation of classical formulas such as Xuanfu Decoction and Biejia Jian Pill, and was the first to apply insect medicinal herbs for collateral-dredging therapy, establishing himself as a forerunner in the clinical treatment of collateral diseases. In later generations, Ye Tianshi systematically put forward the academic viewpoint of "chronic disease invading collaterals" in **Linzheng Zhinan Yi'an** (Case Records of Clinical Guidance), emphasizing that protracted chronic diseases are often accompanied by the pathological state of collateral stasis, which further enriched the theory of collateral disease. By the Qing Dynasty, Wang Qingren formulated formulas including Xuefu Zhuyu Decoction, focusing on elucidating the pathogenesis of collateral lesions induced by "qi stagnation and blood stasis", and expanded the diagnostic and therapeutic approach to collateral disease from the perspective of activating blood circulation and resolving stasis. Academician Wu Yiling divided collaterals into qi collaterals and blood collaterals based on the distribution and circulation rules of collaterals, and put forward the "three-dimensional network system". Qi circulates in qi collaterals to exert the functions of warming and nourishing, defense and barrier, and maintaining the dynamic balance of the body; blood runs in blood collaterals (also named venation), undertaking the functions of permeation and nourishment, circulation and energy supply, body fluid-blood transformation and metabolic regulation [2]. The two are interdependent and synergistic. Collateral diseases refer to a series of pathological states caused by multiple pathogenic factors that block the circulation of nutrient-defense qi, qi-blood and body fluid, disturb the transportation and transformation of substances and metabolic disorders, and ultimately lead to blocked collateral stasis and abnormal circulation of qi and blood [3]. Suwen·Maijie (Plain Questions · Explanation of Vessels) mentioned "destruction of collaterals", pointing out that collateral damage can cause abnormal operation of qi and blood, laying a theoretical foundation for the pathology of collateral diseases. Combining collateral disease theory with modern vascular lesions, Academician Wu Yiling linked "venation stasis and obstruction" in TCM with "microcirculation disturbance" in Western medicine, innovatively put forward the new concept of "venation-vascular system diseases", and provided an interdisciplinary new idea for the treatment of nerve repair [4].

3. Exploration on the Etiology and Pathogenesis of DPN from Collateral Disease Theory

Academician Tong Xiaolin holds that the basic pathogenesis of DPN is root deficiency and superficial excess, with healthy qi deficiency as the root and qi stagnation and blood stasis blocking collaterals as the superficial manifestation, and it is classified as "collateral damage due to consumptive thirst" in TCM [5]. The occurrence of DPN is mostly caused by long-term consumptive thirst, which easily leads to unsmooth operation of qi, especially the dysfunction of the middle energizer pivot. Failed ascending of clear yang and descending of turbid yin will cause qi stagnation, and unsmooth transportation and transformation of body fluid all over the body. Qi deficiency will further damage yang qi; insufficient yang qi fails to warm the body, resulting in fear of

cold and lassitude. With the progression of the disease, both qi and yin get damaged, and insufficient yin fluid cannot moisten muscles, leading to numbness of limbs. Yin deficiency cannot generate yang, and damaged yang cannot transform yin, forming the pathological changes of qi failing to promote blood circulation and yin deficiency generating heat. Heat scorches body fluid to form phlegm, and blood stagnates in collaterals to form stasis. Eventually, phlegm and stasis interlock to block meridians and collaterals, further resulting in obstructed blood collaterals. Obstruction leads to pain, manifested as stubborn numbness and stabbing pain of limbs, even flaccid dysfunction of limbs. Zhang Lanyi [6] believed that the physiological functions of qi collaterals are similar to the nervous system, and abnormal blood collaterals will trigger microcirculation dysfunction. Academician Zhang Lan pointed out that the pathogenesis of DPN coexists with phlegm-stasis blockage and collateral damage, and its onset process and symptomatic characteristics are consistent with the pathogenesis rule of "persistent pain invades collaterals" in collateral disease theory, advocating that DPN should be categorized into collateral lesions for syndrome differentiation and treatment [7]. Hu Xiaojuan held that the pathological mechanism of DPN takes qi deficiency as the root and stasis as the key, and the lesions are concentrated in limb collaterals, manifested as blocked collaterals [8]. Professor Ni Qing believed that the main pathological basis of this disease is blood stasis induced by qi deficiency, and blood stasis runs through the whole course of DPN [9]. DPN patients often present with numb limbs, stabbing pain and other symptoms of collateral damage. Modern physicians generally believe that this is highly consistent with the TCM viewpoint of "chronic disease invades collaterals", so DPN should be classified as collateral disease.

4. Treatment of DPN with Astragalus Based on Qi-Luo and Blood-Luo Theories

The basic pathological characteristics of DPN are stagnant deficient qi collaterals and obstructed blood collaterals. Ye Tianshi wrote in *Linzheng Zhinan Yi'an*: "For deficient collaterals, simultaneous tonification and unblocking is the optimal therapy." It indicates that treatment for empty collaterals should take tonification as the foundation and unblocking as the application. Astragalus is sweet and slightly warm in nature, with the effects of tonifying qi to dredge collaterals and activating stagnation to relieve bi syndrome. The ancient monograph *Bielu* (Records of the Materia Medica) records that Astragalus can "smooth and unblock blood vessels", which has a good therapeutic effect on DPN of qi deficiency and blood stasis type. *Benshu Shuzheng* (Annotations on the Materia Medica Classics) emphasizes that Astragalus can regulate and smooth nutrient-defense qi. It can not only resolve stagnation between nutrient qi and defense qi to promote their circulation and unblock qi collaterals, but also disperse stasis to smooth blood collaterals, which perfectly matches the pathogenesis of DPN. When DPN patients mainly present with numbness and loss of sensation of limb skin, it can be categorized as "blood bi syndrome" recorded in *Jinkui Yaolue* (Synopsis of Prescriptions of the Golden Chamber). This syndrome is mainly caused by insufficient qi and blood and blocked collaterals leading to malnutrition of skin and muscles, clinically manifested as distal symmetric abnormal sensation

aggravated at night, accompanied by pain, muscle weakness and autonomic nervous dysfunction in severe cases. Huangqi Guizhi Wuwu Decoction created by Zhongjing has a significant curative effect on such syndromes. Its formula characteristics are highly consistent with modern medical mechanisms, reflecting both simultaneous regulation of qi and blood and the therapeutic principle of “treating the root of disease”. Huangqi Guizhi Wuwu Decoction is also a representative formula for tonifying qi and dredging collaterals created by Zhang Zhongjing for DPN patients with deficient qi collaterals and obstructed blood collaterals. A large dose of Astragalus tonifies qi to eliminate stagnation; sufficient qi promotes smooth blood circulation, dissipates stasis, and unblocks meridians and collaterals. Relevant studies have shown that Buyang Huanwu Decoction exerts nerve-protective effects through the AMPK/CREB pathway [10]. Other studies have found that Astragalus therapy can significantly optimize patients’ nerve function indicators, obviously relieve symptoms of abnormal sensation and motor disorders, and effectively improve the regulatory function of autonomic nerves [11].

5. Internal TCM Therapies with Astragalus - Dominated Prescriptions for DPN with Deficient Qi Collaterals and Obstructed Blood Collaterals

5.1 Single Herb Astragalus

Astragalus tonifies spleen qi to reinforce qi collaterals; sufficient healthy qi promotes the circulation of blood collaterals, harmonizes nutrient and defense qi to unblock collaterals, regulates qi movement, and promotes the generation of qi and blood. The main active ingredients of Astragalus include astragalus polysaccharides, flavonoids and astragaloside IV. Zhao Lu’s research found that flavonoids can exert therapeutic effects through multiple molecular targets and signal pathways, proving that flavonoids have anti-inflammatory and anti-oxidative damage effects [12]. Wang Chenxiu also found that Astragalus flavonoids can increase insulin levels, delay the apoptosis of pancreatic β cells, reduce blood glucose and body weight [13]. Dong Li et al. confirmed through experiments that Astragalus can improve nerve function, relieve symptoms of abnormal sensation and motor disorders, and regulate autonomic nerve function [11]. High glucose can induce oxidative stress and reduce the activity and quantity of endothelial progenitor cells (EPCs) [14]. Studies have shown that astragaloside IV in Astragalus mediates the NFE2L2 (Nrf2)/ARE signaling pathway to resist oxidative stress and reduce cell damage [15]. Du Jialin found that the active ingredients in Astragalus have favorable analgesic, anti-inflammatory and blood glucose-regulating effects [16]. Eighty patients with qi deficiency type diabetes were divided into experimental group and control group. The experimental group received insulin combined with Astragalus granules, while the control group received insulin combined with placebo. The results showed that compared with the control group, the experimental group had significantly decreased scores of shortness of breath, lassitude, fatigue, spontaneous sweating and disinclination to speak, and elevated GLP-1 levels [17]. Clinically, ginseng and radix scrophulariae can be added for severe qi deficiency.

5.2 Herb Pairs

Based on network pharmacology, Du Jialin found that the combined use of Astragalus and Earthworm may act on DPN through active ingredients such as quercetin and kaempferol to regulate targets related to the AGE-RAGE and PI3K-Akt pathways [16]. Li Wenting et al. conducted an integrated analysis based on network pharmacology, and found that the mechanism of Astragalus-Chuanxiong herb pair in treating DPN involves active components including quercetin and kaempferol [18]. These substances carry out systematic regulation of nerve repair through multi-target regulation and complex network interaction to simultaneously activate blood circulation to dissipate stasis. Studies have found that quercetin can eliminate reactive oxygen species, reduce inflammatory factors through regulating related pathways, improve cell activity under high glucose environment and reduce cell apoptosis [19]. Li Yu’s clinical research showed that the effective rate of the group added with *Euonymus alatus* was much higher than that of the metformin group, pointing out that *Euonymus alatus* can improve diabetes by regulating lipid metabolism and changing hemodynamics [20]. Li Bowu et al. applied the herb pair of Astragalus and *Euonymus alatus* to DPN patients of qi deficiency and blood stasis type, which may improve the disease through anti-oxidative stress, regulating glycolipid metabolism and improving hemodynamics, though the exact mechanism remains unclear [21].

5.3 Three-Herb Combinations (Jiao Yao)

Three-herb combinations follow the principles of four natures and five flavors, ascending and descending, meridian tropism and seven herb compatibilities. Three herbs are used together to achieve synergistic curative effects, which is a common compatibility form in TCM. The earliest record of three-herb combinations can be traced back to Shanghan Lun (Treatise on Febrile Diseases). Yang Qingqing et al. adopted the three-herb combination of Astragalus-Cyathula officinalis-Spatholobus suberectus to treat DPN with qi deficiency and blocked collaterals. Astragalus is the key herb for tonifying qi; qi is the commander of blood, and blood is the foundation of qi. Smooth qi circulation naturally dissipates stasis. Spatholobus suberectus activates collaterals to eliminate stasis and nourishes blood; Cyathula officinalis removes blood stasis and unblocks meridians, guiding medicinal effects to the lesion site in lower limbs [22]. Some studies also show that the three herbs have significant effects on nerve repair. Professor Kang Xuedong created Bushen Tongluo No.1 Prescription based on clinical experience, consisting of Cyathula officinalis, Astragalus, Spatholobus suberectus, etc. It can significantly relieve clinical symptoms of patients, delay disease progression and stabilize blood glucose levels [23]. Academician Tong Xiaolin often selects the three-herb small formula of Astragalus-Cinnamon Twig-Spatholobus suberectus for long-term illness invading collaterals. Astragalus tonifies meridian qi to relieve bi syndrome, cinnamon twig warms and unblocks meridians, and Spatholobus suberectus activates blood circulation to eliminate stasis in blood collaterals, which has a good curative effect on DPN with qi deficiency, blood stasis and cold coagulation [24]. Ni Yingqun carried out animal experiments

with the three-herb combination of Ginseng-Astragalus-Pueraria lobata, showing that the three herbs can improve insulin resistance, repair damaged pancreatic islets and reduce inflammatory factors by regulating the AGE-RAGE/PI3K-Akt/NF- κ B signaling pathway [25].

5.4 Classical Prescriptions Dominated by Astragalus

Jinkui Yaolue (Synopsis of Prescriptions of the Golden Chamber) records: "Huangqi Guizhi Wuwu Decoction treats blood bi syndrome." Huangqi Guizhi Wuwu Decoction is composed of Astragalus, Cinnamon Twig and other herbs. Based on collateral disease theory, modified Huangqi Guizhi Wuwu Decoction is combined with four therapies of acrid fragrance, acrid warming, tonification and insect medicinals for dredging collaterals to maximize the efficacy of TCM herbs and delay disease progression [26]. In this study, 46 DPN patients were randomly divided into two groups. The control group received conventional western medicine treatment, while the observation group was treated with modified Huangqi Guizhi Wuwu Decoction on the basis of conventional therapy. The observation group showed significantly improved symptoms and vital signs, with a total effective rate of 95.65%, obviously superior to the control group's 82.61% [27]. Buyang Huanwu Decoction is composed of Astragalus, Angelica sinensis, Chuanxiong and other herbs. A clinical study included 120 DPN patients of qi deficiency and blood stasis type, randomly divided into control group (single epalrestat treatment) and combined intervention group (epalrestat combined with Buyang Huanwu Decoction plus acupoint application). The efficacy evaluation showed that the total effective rate of the combined intervention group reached 93.33%, 13.33 percentage points higher than that of single western medicine therapy [28]. Other studies showed that modified Buyang Huanwu Decoction composed of raw Astragalus, Cyathula officinalis, Pseudostellaria heterophylla, etc., can improve hemorheology, increase efficacy and reduce the release of inflammatory factors. The motor nerve conduction velocity of common peroneal nerve and median nerve in the observation group was higher than that before treatment and the control group [29]. Clinical practice verified the combined application of Huangqi Guizhi Wuwu Decoction and Taohong Siwu Decoction. The results showed that after treatment, the Michigan Diabetic Neuropathy Score (MDNS) of patients in the observation group was improved, and motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) were higher than those of the control group, effectively improving the nerve function of DPN patients [30]. External TCM therapies also play an indispensable role in treatment. Feng Wei selected acupoints according to midnight-noon ebb-flow theory, and adopted Huangqi Guizhi Wuwu Decoction combined with acupoint application for DPN treatment. The control group received conventional mecobalamin treatment, while the observation group took herbal decoction combined with acupoint application. The results showed that the effective rate of the observation group reached 94%. Acupuncture is a traditional therapy that can stimulate yang qi to resist pathogenic factors [31]. Wang Liqun applied Yiqi Huazhuo Lishui Decoction combined with Dong's acupuncture, selecting nine acupoints including Dihuang and Tianhuang acupoints, which can effectively relieve numbness and pain symptoms of DPN patients. The

improvement range of MNCV and SNCV of three types of nerves (median nerve, posterior tibial nerve, common peroneal nerve) in the treatment group was higher than that of the control group [32].

5.5 Chinese Patent Medicines and Self-Made Prescriptions

Qizhi Jiangtang Capsule consists of four herbs: sweet and warm Astragalus tonifies qi, flat Polygonatum odoratum tonifies spleen qi and nourishes yin to promote fluid production, Rehmannia glutinosa generates fluid, and Hirudo medicinalis breaks blood stasis. The whole formula jointly tonifies qi and nourishes yin blood, eliminates blood stasis and unblocks collaterals. Pu Chunli applied this formula in clinical practice, and the DPN score of patients decreased after treatment, proving that Qizhi Jiangtang Capsule can improve clinical manifestations of DPN and provide new therapeutic strategies for subsequent treatment [33]. Mudan Granule takes Astragalus to tonify qi; Panax notoginseng, Corydalis yanhusuo and Chuanxiong activate blood circulation to dissipate stasis, promote qi movement and relieve pain; Sappan wood and Salvia miltiorrhiza relax tendons and unblock collaterals. Wang Gang's research showed that Mudan Granule can reduce FBG and 2hPBG, increase HDL-C level, decrease TC, TG and LDL-C levels, and elevate nerve conduction velocity, providing more treatment options for DPN patients with hyperlipidemia [34]. Ye Xiaoping detected TCSS and nerve conduction velocity, proving that self-made Yiqi Tongbi Decoction can reduce the severity of peripheral neuropathy and has favorable clinical efficacy [35]. Leng Shaoguang formulated Pibi Furen Decoction composed of Astragalus, Rehmannia glutinosa, etc. Statistical verification showed that the total effective rate of the experimental group reached 90.63%, significantly higher than the control group's 68.75% [36]. Xiaobi Tongluo Powder is composed of Astragalus, Salvia miltiorrhiza, Angelica sinensis tail and other herbs, modified from Buyang Huanwu Decoction. Xu Xiangyun evaluated the efficacy of this self-made formula by detecting levels of inflammatory factors and vasoactive substances. After treatment, the concentrations of hypersensitive C-reactive protein and tumor necrosis factor (TNF- α) decreased significantly, with a larger decline range in the treatment group than the control group. Meanwhile, the nitric oxide (NO) level of the treatment group was significantly higher, and hemorheological indicators (plasma viscosity, fibrinogen, erythrocyte specific volume) were also improved better [37]. Liu Yehui established DPN mouse models, and the experimental conclusion showed that Qige Tongluo Decoction can effectively regulate blood glucose levels, protect and prevent nerve damage, and improve nerve conduction velocity, indicating its protective and therapeutic effects on DPN [38]. Wang Qing's self-made Yangxue Tongluo Prescription consists of raw Astragalus, Angelica sinensis, Cinnamon Twig, Raw Paeonia lactiflora, etc., combined with eight extraordinary meridians intersecting acupoint acupuncture for treatment. The study showed that the intervention group achieved better improvements in VPT, MNCV and SNCV compared with the control group [39]. Zu Libin applied Jianpi Tongluo Decoction combined with mecobalamin treatment. The formula contains more than ten herbs including Clematis chinensis, Codonopsis pilosula,

Atractylodes macrocephala and Astragalus, jointly tonifying spleen qi, unblocking collaterals to relieve pain, activating blood circulation and dissipating stasis. Combined with mecobalamin, it can improve patients' nerve conduction velocity and abnormal limb sensation [40].

6. Conclusion

Diabetic peripheral neuropathy is a common complication of diabetes mellitus, categorized as "collateral disease" and "blood bi syndrome" in TCM. Its core pathogenesis is deficient qi collaterals and obstructed blood collaterals. Long-term consumptive thirst consumes healthy qi, leading to unsmooth qi movement, phlegm and stasis blocking collaterals, and eventually malnutrition of muscles, tendons and skin, manifested as numbness, stabbing pain and flaccidity of limbs. The core therapeutic principle is simultaneous tonification and unblocking, tonifying qi to dredge collaterals. Astragalus has the effects of tonifying spleen qi, activating stagnation to relieve bi syndrome, promoting fluid production and nourishing blood, astringing skin and promoting granulation. It tonifies nutrient-defense qi to fill qi collaterals; smooth qi collaterals regulate qi movement all over the body, and activate blood circulation to eliminate stasis in blood collaterals. It can resist oxidative stress, relieve inflammation, regulate glycolipid metabolism, protect pancreatic islet function, improve microcirculation and nerve conduction, perfectly matching the root pathogenesis of DPN with qi deficiency and blood stasis. Clinically, single Astragalus, herb pairs, three-herb combinations, Astragalus-dominated self-made formulas and integrated internal-external therapies all show unique advantages of TCM in improving patients' symptoms. In conclusion, based on the theories of qi collaterals and blood collaterals, Astragalus-dominated Chinese medicines intervene DPN from multiple dimensions of tonifying deficiency, dredging collaterals and dissipating stasis, and simultaneously improve blood glucose, microcirculation and nerve injury, with outstanding curative effects when combined with internal and external therapies. At present, relevant studies mostly focus on clinical efficacy observation, while mechanism research is mostly predicted by network pharmacology, with insufficient in-depth animal and cell experiments. Further research can explore the action targets of Astragalus compound prescriptions, and carry out large-sample and long-term follow-up clinical trials, so as to provide sufficient objective evidence for TCM prevention and treatment of DPN.

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