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Research Progress on Mulberry Twig in the Treatment of Diabetic Peripheral Neuropathy

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Abstract: ***Diabetic Peripheral Neuropathy (DPN) is one of the most common and serious chronic complications of diabetes, severely impacting patients' quality of life. Mulberry twig, as a traditional Chinese medicine, is frequently used in TCM clinical practices for treating limb meridian-related disorders. In recent years, numerous studies have demonstrated the potential value of mulberry twig and its active components in alleviating diabetic peripheral neuropathy. This paper reviews relevant domestic and international literature, covering the chemical composition of mulberry twig, its mechanisms in improving diabetic peripheral neuropathy, clinical applications, and future research directions. The aim is to provide a theoretical basis and reference for further research on mulberry twig as a treatment for DPN, promoting its development and application in the field of diabetic peripheral neuropathy management.***

Keywords: Mulberry twig, Diabetic Peripheral Neuropathy, Chemical composition, Mechanisms, Clinical applications**.**

1. Introduction

Diabetic Peripheral Neuropathy (DPN) is one of the most common chronic complications of diabetes, with a prevalence of 50%–70% among diabetic patients [1,2]. DPN is primarily characterized by sensory abnormalities in the extremities, such as numbness, tingling, and burning sensations, and may also involve motor dysfunction and autonomic neuropathy [3]. It significantly affects patients' quality of life and may lead to severe consequences such as foot ulcers and amputations. Currently, modern medicine primarily treats DPN through strict blood glucose control, neurotrophic drugs (e.g., mecobalamin), and microcirculation-improving agents (e.g., prostaglandin analogs). However, these treatments offer limited efficacy and are associated with certain side effects.

Traditional Chinese Medicine (TCM) has unique theories and extensive clinical experience in treating Diabetic Peripheral Neuropathy (DPN) [4]. Numerous herbs and formulas have demonstrated effectiveness in alleviating DPN symptoms and delaying disease progression. Mulberry twig, derived from the dried tender branches of Morus alba L., a plant in the Moraceae family, was first documented in the Illustrated Classic of Materia Medica [5]. Slightly cold in nature and bitter in taste, it is associated with the liver meridian, offering therapeutic benefits such as dispelling wind-dampness and relieving joint pain. It is commonly used to treat conditions like rheumatic arthralgia and limb convulsions. In recent years, studies on mulberry twig have advanced, uncovering its potential applications in the treatment of diabetic peripheral neuropathy. This article summarizes the research progress on this topic.

2. Chemical Composition of Mulberry Twig

The chemical composition of mulberry twig is complex, comprising flavonoids, alkaloids, coumarins, sterols, polysaccharides, and other active components. The synergistic effects of these compounds may form the basis of its efficacy in improving diabetic peripheral neuropathy [6].

2.1 Flavonoids

Flavonoids are abundant in mulberry twig and exhibit various biological activities. Research has identified flavonoid glycosides such as rutin, isoquercitrin, and astragalin, as well as flavonoid aglycones like kaempferol and quercetin. These flavonoids have antioxidant, anti-inflammatory, and blood sugar-regulating properties, playing an essential role in the treatment of diabetes and its complications. For example, rutin reduces oxidative stress damage to nerve cells by scavenging free radicals, while quercetin regulates inflammatory factors and inhibits inflammatory responses to alleviate nerve damage [7].

2.2 Alkaloids

The primary alkaloid in mulberry twig is 1-Deoxynojirimycin (DNJ), a potent α-glucosidase inhibitor that slows carbohydrate digestion and absorption in the intestine, reducing postprandial blood glucose levels. DNJ also exhibits neuroprotective effects by regulating the metabolism and functions of nerve cells, thereby improving diabetes-induced neural damage.

2.3 Coumarins

Mulberry twig contains coumarins such as umbelliferone and scoparone. These compounds possess antioxidant, anti-inflammatory, and anticoagulant activities. Studies have shown that umbelliferone mitigates oxidative stress and inflammatory responses, reducing nerve tissue damage and offering protective effects against DPN.

2.4 Sterols

Sterols such as β-sitosterol and stigmasterol are present in mulberry twig. These sterols have lipid-regulating, antioxidant, and anti-inflammatory properties, making them potentially valuable in the prevention and treatment of diabetes and its complications. For instance, β-sitosterol lowers blood cholesterol levels, improves lipid metabolism

disorders, and reduces oxidative stress damage to nerve cells.

2.5 Polysaccharides

Polysaccharides are key active components in mulberry twig, consisting of monosaccharides such as glucose, galactose, and arabinose. They exhibit various biological activities, including immune modulation, antioxidant effects, and blood sugar reduction. Studies indicate that mulberry twig polysaccharides enhance antioxidant enzyme activity, lower oxidative stress levels, regulate immune system function, and alleviate inflammation, thereby providing protection against DPN [8].

3. Mechanisms of Mulberry Twig in Improving Diabetic Peripheral Neuropathy (DPN)

3.1 Regulation of Blood Glucose Levels

Hyperglycemia is a major factor in the development and progression of DPN. Various active compounds in mulberry twig regulate blood glucose through different pathways. Alkaloids such as DNJ, an α-glucosidase inhibitor, slow down the digestion and absorption of carbohydrates in the intestine, reducing postprandial blood glucose peaks. Flavonoids like rutin and quercetin promote insulin secretion, enhance insulin sensitivity, and improve glucose uptake and utilization by tissues [9]. Mulberry twig polysaccharides regulate the activity of enzymes involved in glucose metabolism, promote glycogen synthesis in the liver, and lower blood glucose levels. By effectively controlling blood glucose, mulberry twig reduces the neurotoxicity of hyperglycemia, thereby alleviating DPN.

3.2 Antioxidant Stress

Oxidative stress plays a key role in the onset and progression of DPN. In a hyperglycemic state, excessive reactive oxygen species (ROS) are produced, overwhelming the body's antioxidant capacity and causing oxidative stress imbalance, which damages nerve cells. Active components in mulberry twig, such as flavonoids, coumarins, and polysaccharides, possess strong antioxidant properties. For instance, flavonoids eliminate ROS like superoxide anions and hydroxyl radicals, inhibit lipid peroxidation, and protect the integrity of neuronal cell membranes. Mulberry twig polysaccharides enhance the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reduce malondialdehyde (MDA) levels, and mitigate oxidative damage to nerve tissues.

3.3 Anti-Inflammatory Effects

Inflammation is a critical pathological process in DPN. Hyperglycemia activates multiple inflammatory signaling pathways, such as the nuclear factor kappa B (NF-κB) pathway, leading to the overexpression of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which cause inflammatory damage to neural tissues. Active compounds in mulberry twig inhibit the activation of inflammatory pathways, reducing the production and release of inflammatory factors. Studies show that quercetin suppresses the activation of the NF-κB pathway, decreases the expression of TNF-α and IL-1β, and alleviates neuroinflammation. Additionally, mulberry twig polysaccharides regulate the levels of inflammatory cytokines, exerting anti-inflammatory effects to protect neural tissues.

3.4 Improvement of Neural Microcirculation

Patients with DPN often experience neural microcirculation disorders, leading to ischemia and hypoxia in nerve tissues, impairing nutrient supply and waste removal in nerve cells. Flavonoids and coumarins in mulberry twig improve microcirculation. Flavonoids enhance blood flow to nerve tissues by dilating blood vessels, reducing blood viscosity, and inhibiting platelet aggregation. Coumarins like umbelliferone exhibit anticoagulant effects and improve endothelial function, aiding in better neural microcirculation to provide a supportive metabolic environment for nerve cells.

3.5 Neuroprotective Effects

Active compounds in mulberry twig directly act on nerve cells to exert neuroprotective effects. DNJ regulates metabolic processes within nerve cells, promoting their repair and regeneration. Flavonoids inhibit neuronal apoptosis and maintain the normal function of nerve cells. Additionally, active components in mulberry twig may regulate the expression of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), promoting neuronal growth, differentiation, and survival, thus offering therapeutic effects for DPN.

4. Research on the Clinical Application of Mulberry Branch in Diabetic Peripheral Neuropathy

4.1 Clinical Application of Monomeric Mulberry Branch

In clinical practice, some physicians have attempted to use monomeric mulberry branch to treat diabetic peripheral neuropathy. It has been reported that decoction of monomeric mulberry branch taken orally once daily for 12 consecutive weeks can significantly improve symptoms such as limb numbness and pain in patients with diabetic peripheral neuropathy, and also increase nerve conduction velocity. However, clinical studies on the use of monomeric mulberry branch for diabetic peripheral neuropathy are relatively few at present, with small sample sizes. Its exact efficacy and safety still need to be further verified by large-scale, multi-center, randomized controlled clinical trials.

4.2 Clinical Application of Mulberry Branch Compound

Mulberry branch is often combined with other traditional Chinese medicines to form compound prescriptions for the treatment of diabetic peripheral neuropathy. For example, the Mulberry Branch Circulation-Activating Formula, composed of mulberry branch, astragalus, cinnamon twig, angelica, ligusticum, and other traditional Chinese medicines, has achieved good therapeutic effects in clinical applications. A clinical study showed that compared with the use of mecobalamin alone, the combination of Mulberry Branch Circulation-Activating Formula and mecobalamin for the

treatment of diabetic peripheral neuropathy resulted in more significant improvement in clinical symptoms and greater increase in nerve conduction velocity, with no obvious adverse reactions during the treatment process. In addition, mulberry branch can also be combined with pueraria root, salvia, achyranthes, and other traditional Chinese medicines. Through synergistic effects, it can play a comprehensive therapeutic role in regulating blood glucose, improving microcirculation, and nourishing nerves, effectively alleviating the symptoms of patients with diabetic peripheral neuropathy [10].

5. Existing Problems and Future Research Directions

5.1 Existing Problems

Despite the potential of mulberry branch in improving diabetic peripheral neuropathy, there are still some problems in the current research. Firstly, the chemical composition of mulberry branch is complex, and its material basis and mechanism of action have not been fully elucidated, especially the synergistic mechanism of multiple components needs further in-depth research. Secondly, clinical studies on the treatment of diabetic peripheral neuropathy with mulberry branch are relatively few, and most studies have small sample sizes and less standardized research methods, lacking high-quality clinical evidence to support its efficacy and safety. In addition, the quality standards and processing specifications of mulberry branch need to be further improved. Mulberry branches from different origins, harvesting seasons, and processing methods may have differences in chemical composition and pharmacological effects, which affect the stability and effectiveness of clinical applications.

5.2 Future Research Directions

Future research on the improvement of diabetic peripheral neuropathy by mulberry branch can be carried out in the following aspects: First, modern separation and analysis techniques and pharmacological methods should be used to further study the chemical composition and mechanism of action of mulberry branch, clarify its main active ingredients and targets of action, and reveal the molecular mechanisms of the synergistic effects of multiple components. Second, large-scale, multi-center, randomized controlled clinical trials should be carried out to scientifically evaluate the clinical efficacy and safety of mulberry branch and its compound prescriptions in the treatment of diabetic peripheral neuropathy, providing reliable basis for clinical application. Third, quality standards and standardized processing procedures for mulberry branch should be established to ensure the stability and consistency of the quality of mulberry branch. Fourth, the synergistic effects of mulberry branch in combination with other drugs for the treatment of diabetic peripheral neuropathy should be explored to optimize treatment plans and improve clinical therapeutic effects.

6. Conclusion

As a traditional Chinese medicinal material, mulberry branch provides a material basis and theoretical support for the improvement of diabetic peripheral neuropathy with its rich chemical composition and diverse biological activities. Current research indicates that mulberry branch has potential therapeutic effects on diabetic peripheral neuropathy through multiple mechanisms, including regulating blood glucose, antioxidant stress, anti-inflammation, improving nerve microcirculation, and exerting neuroprotective effects. In clinical applications, both monomeric mulberry branch and mulberry branch compound prescriptions have achieved certain effects in alleviating the symptoms of patients with diabetic peripheral neuropathy. However, further in-depth research is needed to clarify its material basis and mechanism of action, and high-quality clinical studies should be carried out to verify its efficacy and safety. With the continuous deepening of research, mulberry branch is expected to play a greater role in the treatment of diabetic peripheral neuropathy and bring new treatment options and hope for patients with this condition.

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