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Research Progress on the Pharmacological Mechanism of Chinese Herbal Medicine Mulberry Branch in the Treatment of Diabetic Peripheral Neuropathy

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Abstract: ***Diabetic peripheral neuropathy (DPN) is a common and potentially serious chronic complication of diabetes, significantly impacting patients' quality of life. Current clinical treatments for DPN have limitations, while traditional Chinese medicine (TCM) using mulberry branches has demonstrated unique advantages and potential in treating DPN. This paper systematically reviews the current research progress on the pharmacological mechanisms of mulberry twig in treating DPN, including its main chemical components, and the mechanisms through which it exerts therapeutic effects via multiple pathways such as antioxidant stress, anti-inflammatory effects, improvement of microcirculation, regulation of glucose metabolism, and promotion of nerve regeneration. It also analyzes the existing issues in current research and outlines future research directions, aiming to further provide theoretical basis for the use of mulberry twig in treating DPN.***

Keywords: Mulberry branches, Diabetic peripheral neuropathy, Pharmacolog**.**

1. Introduction

Diabetes is a global public health issue with an increasing incidence rate, and the prevention and treatment of diabetes complications are receiving increasing attention. DPN is one of the most common chronic complications of diabetes, with a high incidence rate. It can affect sensory nerves, motor nerves, and autonomic nerves, and clinically manifests as numbness, pain, sensory abnormalities, and muscle weakness in the limbs. In severe cases, it can lead to foot ulcers, infections, and even amputation, causing immense suffering and a significant economic burden for patients [1]. Currently, the exact mechanisms underlying DPN remain unclear, but it is generally believed to result from the combined effects of multiple factors, including metabolic disorders caused by hyperglycemia, oxidative stress, inflammatory responses, deficiency of nerve growth factors, and microcirculatory disorders [2]. Clinical treatments primarily include glycemic control, improvement of microcirculation, neurotrophic therapy, and antioxidant therapy, but these approaches have limited efficacy and may carry certain side effects.

Mulberry branches are a traditional Chinese medicine with effects such as dispelling wind-dampness, promoting joint mobility, and promoting water metabolism. They are commonly used to treat rheumatic pain and limb stiffness [3]. In recent years, research has found that mulberry branches have certain therapeutic effects in the treatment of DPN. Their mechanism of action involves multiple aspects and has the characteristics of multiple components, multiple targets, and multiple pathways, providing new ideas and methods for the treatment of DPN.

2. Main Chemical Components of Mulberry Branches

Mulberry branches have complex chemical compositions, mainly including the following categories:

2.1 Flavonoids

Flavonoids are one of the key active components of mulberry branches [4]. These flavonoid compounds exhibit various biological activities, including antioxidant, anti-inflammatory, lipid-lowering, and blood sugar-lowering effects. Research indicates that total flavonoids in mulberry branches, including rutin, quercetin, morin, and oxidized resveratrol, can inhibit the expression of pro-inflammatory cytokines while enhancing antioxidant enzyme activity.

2.2 Alkaloids

Mulberry branches contain various alkaloids, among which 1-deoxynojirimycin (DNJ) has attracted considerable attention [5]. DNJ can inhibit the activity of α-glucosidase, delaying the digestion and absorption of carbohydrates and thereby lowering postprandial blood glucose levels [6]. In addition, total alkaloids in mulberry branches also have effects such as regulating sugar metabolism and improving insulin resistance [7].

2.3 Polysaccharides

Mulberry branch polysaccharides are macromolecular compounds composed of multiple monosaccharides linked by glycosidic bonds. They have immune-regulating, antioxidant, hypoglycemic, and microcirculation-improving properties [8].

2.4 Other Ingredients

Mulberry branches also contain steroids, terpenoids, coumarins, essential oils, and various trace elements [9]. These components may exert synergistic effects in the

pharmacological action of mulberry branches and jointly participate in the treatment of DPN.

3. Pharmacological Mechanism of Mulberry Branch Treatment for DPN

3.1 Antioxidant Stress Response

Oxidative stress plays a key role in the pathogenesis of diabetic peripheral neuropathy (DPN). Under hyperglycemic conditions, the body produces a large amount of reactive oxygen species (ROS), which exceeds the scavenging capacity of the body's antioxidant defense system, leading to oxidative stress damage and causing pathological changes such as neuronal apoptosis and demyelination of nerve fibers [10]. The flavonoids, polysaccharides, and other components in mulberry branches exhibit strong antioxidant activity, capable of scavenging excess ROS in the body and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and reduce the levels of lipid peroxidation products such as malondialdehyde (MDA), thereby alleviating oxidative stress-induced damage to neural tissue [11]. Studies have shown that total flavonoids from mulberry branches can significantly increase the activity of SOD and GSH-Px in the sciatic nerves of diabetic rats, reduce MDA levels, improve the oxidative stress state of neural tissue, and have a protective effect against diabetic neuropathy.

3.2 Anti-inflammatory Effects

Inflammatory responses are also one of the key factors contributing to the development and progression of DPN. Hyperglycemia can activate inflammatory cells, leading to the release of a large amount of inflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), resulting in inflammatory infiltration and edema of neural tissue, thereby impairing neural conduction function [12]. The active components in mulberry branches can exert anti-inflammatory effects by inhibiting inflammatory signaling pathways and reducing the release of inflammatory factors. Studies have shown that total flavonoids from mulberry branches can inhibit the activation of the NF-κB signaling pathway, reduce the expression of inflammatory factors such as TNF-α and IL-6, alleviate inflammatory reactions in the neural tissue of diabetic rats, and thereby improve neural function [13].

3.3 Improving Microcirculation

Microcirculatory disorders can lead to ischemia and hypoxia in neural tissue, serving as an important pathological basis for the onset of diabetic peripheral neuropathy (DPN). Mulberry twig extract has vasodilatory effects, reduces blood viscosity, and inhibits platelet aggregation, thereby improving peripheral microcirculation in the extremities, increasing blood perfusion to neural tissue, providing adequate oxygen and nutrients to neural cells, and promoting the recovery of neural function [14]. Research has reported that mulberry branch extract can increase mesenteric microcirculatory blood flow velocity and the number of open capillaries in diabetic rats, thereby improving microcirculatory disorders and exerting a certain preventive and therapeutic effect on diabetic neuropathy.

3.4 Regulation of Sugar Metabolism

Persistent hyperglycemia is the fundamental cause of the development and progression of diabetic peripheral neuropathy (DPN), so effective glycemic control is crucial for the treatment of DPN. The alkaloid components in mulberry branches (such as DNJ) can inhibit α-glucosidase activity, delay the digestion and absorption of carbohydrates in the intestines, and reduce postprandial blood glucose peaks [15]; mulberry branch polysaccharides can improve glucose metabolism disorders and stabilize blood glucose levels by enhancing insulin sensitivity and regulating the activity of enzymes related to glucose metabolism [16]. Clinical studies have also shown that mulberry branch granules (a traditional Chinese medicine formulation primarily made from mulberry branches) exhibit good hypoglycemic effects in patients with type 2 diabetes, effectively reducing fasting blood glucose, postprandial blood glucose, and hemoglobin A1c levels [9].

3.5 Promotes Nerve Regeneration

A deficiency in nerve growth factor (NGF) is one of the key reasons why nerve damage in diabetic peripheral neuropathy (DPN) is difficult to repair. Mulberry branches may promote nerve regeneration by upregulating the expression of neurotrophic factors such as NGF and brain-derived neurotrophic factor (BDNF), activating nerve regeneration-related signaling pathways, and facilitating the regeneration and repair of damaged nerve fibers, thereby improving nerve conduction velocity [17]. Studies have shown that mulberry branch extract can promote the proliferation and differentiation of cultured neurons, increase the length and number of neurites; in a diabetic rat model, mulberry branch extract can increase the expression levels of NGF and BDNF in the sciatic nerve, improve nerve conduction velocity, and promote the recovery of nerve function.

4. Current State of Research and Existing Issues

Currently, research on the use of mulberry branches for the treatment of diabetic peripheral neuropathy (DPN) has made significant progress. In basic research, through cell experiments and animal studies, the chemical composition, pharmacological effects, and mechanisms of action of mulberry branches have been thoroughly investigated. These studies have confirmed the role of mulberry branches in antioxidant stress, anti-inflammatory effects, improving microcirculation, regulating glucose metabolism, and promoting nerve regeneration, providing a theoretical basis for their clinical application. In clinical research, some small-scale clinical observations have shown that mulberry branch preparations, either alone or in combination with other traditional Chinese medicines, can improve clinical symptoms in DPN patients, such as numbness, pain, and sensory abnormalities in the limbs, and enhance nerve conduction velocity, with good safety profiles. Additionally, mulberry branch total alkaloid tablets, a natural medicine extracted from mulberry branches, have been approved for marketing to treat type 2 diabetes and show potential in improving diabetes

symptoms and complications. Although research on mulberry branch treatment for DPN has achieved some results, there are still some shortcomings. Firstly, research on the mechanism of action is not yet sufficiently in-depth or comprehensive and requires further investigation. For example, clinical studies have small sample sizes and lack large-scale, multi-center, randomized controlled trials. Additionally, the extraction, separation, and purification techniques for the active components of mulberry branches need further optimization to enhance the content and purity of these active components.

5. Conclusion

In summary, Chinese herbal medicine mulberry branches have unique advantages and potential in the treatment of diabetic peripheral neuropathy. They exert therapeutic effects through multiple pharmacological mechanisms, including antioxidant stress, anti-inflammation, improvement of microcirculation, regulation of glucose metabolism, and promotion of nerve regeneration. Although current research has achieved certain results, there are still many issues that need to be further addressed. With the continuous advancement of research and technology, mulberry branches are expected to become an effective drug for the treatment of DPN, bringing good news to a large number of diabetic patients.

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