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Research Progress of Astragalus in the Treatment of Membranous Nephropathy

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Abstract: ***The basic pathogenesis of membranous nephropathy (MN) is the primary deficiency accompanied by solid deficiency. The deficiency of spleen and kidney is the primary and the symptom of rheumatism and stasis. Astragalus is the essential medicine for tonifying spleen and kidney. In the treatment of membranous nephropathy, Astragalus can play the role of tonifying spleen and kidney, detumifying water, dispelling pathogenic wind and promoting blood flow. Its classic formula has also been widely used in the treatment of membranous nephropathy. This article reviews the research status of astragalus in MN treatment.***

Keywords: Membranous nephropathy, Astragalus, Research progress**.**

1. Introduction

MN, one of the types of adult nephrotic syndrome, is a pathological diagnostic term characterized by the deposition of immune complexes under the epithelial cells of the glomerular basement membrane [1]. The clinical manifestations are diverse, mainly proteinuria and edema, and the disease is not cured for a long time, about 40% of MN patients will eventually develop end-stage renal disease [2]. MN can be divided into idiopathic membranous nephropathy (IMN) and secondary membranous nephropathy (SMN) according to the etiology, and SMN can be associated with autoimmune diseases (such as systemic lupus erythematosus), infections (such as hepatitis B, infectious disease patients), malignant tumors, or drugs [3]. The diagnosis of the disease is based on percutaneous renal biopsy and serological PLAR21 antibody. In terms of treatment, Western medicine mainly uses immunosuppressants or glucocorticoids for treatment, but when such drugs are used in clinical application, patients are often prone to relapse, easy to infection and may even have complications such as renal function injury [4]. On the basis of reducing urinary protein and improving renal function, the treatment of MN by traditional Chinese medicine has fewer side effects and is widely used in clinic.

2. The Pathogenesis of MN

The pathogenesis of IMN is complex, mainly related to air pollution, genetic factors, autoimmune mechanism, complement activation, cell-specific adaptation and interaction between reaction processes [5]. At present, it is generally recognized that the pathogenesis of this disease is that circulating antibodies bind to glomerular podocyte target antigen to form immune complex and deposit in the skin [6], In turn, the complement is activated to form a membrane attack complex, which leads to morphological changes in the podocyte and ultimately causes the symptoms of nephrotic syndrome. However, from the target antigen to the body's production of autoantibodies to the clinical manifestations of nephrotic syndrome (the formation of massive proteinuria), there are still a lot of unknown mechanisms that need to be explored [7].

3. Etiology and Pathogenesis of MN in Chinese Medicine

There is no corresponding name of membranous nephropathy in Chinese medicine, which can be classified as "edema", "urine turbidity", "vacuous fatigue" and other categories according to different clinical manifestations [8]. The etiology and pathogenesis of the disease have different understanding, but it is recognized that the basic pathogenesis is the deficiency of the spleen and kidney as the basis, and the rheumatism and stasis as the standard.

Professor Chen Yiping believes that spleen and kidney qi deficiency is the basic pathogenesis, spleen deficiency causes water moisture accumulation, kidney deficiency causes water and liquid misbehavior, then edema. Vein stasis, dampness and heat are the pathological basis of repeated attacks and lingering difficulties. The formation of stasis by dampness-heat glue is the key to the development of membranous nephropathy. The pathological manifestations such as the deposition of immune complex in the epithelium and the thickening of basement membrane should be attributed to the syndrome of blood stasis, and the activation of complement and the formation of membrane attack complex are the syndrome of dampness-heat or heat-toxicity [9].

Professor Liu Yuning believes that the three viscera deficiency of lung, spleen and kidney is the foundation, wind evil is the inducement, blood stasis runs through the disease, the phlegm and dampness, the heat for a long time make the course of the disease long, lingering and difficult to cure. Resulting in spleen-kidney Yang deficiency. Wind evil is the long of all diseases, invading the human body, and the conflict between good and evil play a major role in the acute attack of IMN. Evil gas into the damage of the jiao, phlegm endogenous, anti-trapped spleen soil, spleen loss of control, heat, subtle depression can be seen a large amount of proteinuria. After a long time spleen kidney Yang deficiency, water stopped gathering, hair edema. The spleen Yang is weak, the kidney is lost, the fine matter is released, proteinuria and hypoproteinemia can be seen. Blood stasis throughout the disease, and similar to Western medicine immune complex

deposition in the kidney [10].

Professor Wang Baokui believes that renal qi deficiency and internal disturbance of renal wind are common causes of membranous nephropathy. Kidney qi deficiency, qi solid function is low, kidney loss seal, fine matter leakage and proteinuria. The wind evil attacks the outside, disturbles the lungs, circulates the channel into the inside, invents the kidney, the kidney loses the seal, the fine matter leaks out to form proteinuria. Moreover, the characteristics of membranous nephropathy edema are mixed with the diffuse and ubiquitous characteristics of wind evil [11].

4. Main Mechanism of Astragalus Treatment of MN

4.1 Traditional Chinese Medicine

Astragalus has many applications in the treatment of MN at present. Astragalus sweet taste, mild nature, return to the lung spleen meridian, with tonifying qi, water detumification, solid sweat stop surface, blood, stagnation Tongbi and other effects [12]. The pathogenesis of MN is based on the deficiency of spleen and kidney, which should be used throughout the disease. Astragalus first appeared in Shennong's Herbal Classic and has the reputation of "long tonic medicine". "Decoction Materia Medica" said astragalus "not only to treat typhoid, but also to supplement kidney Qi", can be big tonifying kidney qi. Edema is the most common and typical symptom of IMN. Professor Genping Lei believes that a large amount of astragalus alone can treat edema of deficiency syndrome, which has a better effect on edema of Qi-deficiency and can play the effect of strengthening spleen and promoting water [13].

Professor Wang Baokui believes that raw astragalus can not only tonify kidney Qi, strengthen the body, make the kidney closed, reduce the leakage of fine matter, reduce proteinuria; It can also dispel wind and disperse evil, reduce proteinuria. It also has the effect of obviously reducing water and swelling, which is suitable for edema caused by membranous nephropathy [11]. Astragalus in supplementing Qi and producing essence at the same time has the function of pushing blood through the veins, "Materia Medica Fengyuan" records Astragalus "is sweet and warm, can regulate the blood, circulation channels, so that it is not obstructed in the obstruction", Astragalus is good for supplementing Qi and blood, and can Tongli the blood, so that the whole body Qi and blood flow freely, therefore, Astragalus can treat membranous nephropathy in the middle and late stage of blood stasis blocking kidney collateral syndrome [14].

4.2 Modern Pharmacology

The chemical active components of Astragalus mainly include polysaccharides, saponins, flavonoids and amino acids [15]. It has the functions of improving immune function, anti-inflammatory, antibacterial, anti-stress, antioxidant, regulating blood pressure, protecting cardiovascular system, protecting organs and so on [16]. In the kidney, in addition to the obvious diuretic effect, it can also increase the renal blood flow, facilitate the elimination of harmful substances such as lipid peroxide, reduce the deposition of lipid in the glomeruli and renal interstitial and the formation of microthrombi, thereby protecting the kidney [17].

4.2.1 Astragalus polysaccharide

Astragalus polysaccharide can regulate the balance of cytokines, endothelin and nitric oxide, resist peroxidation, improve platelet function, water and sodium metabolism, resist protein non-enzymatic glycosylation, stabilize the molecular barrier and charge barrier of hiatus membrane, and improve the glomerular filtration barrier, thus alleviating the damage of glomerular podocytes [18]. Studies have shown that Astragalus polysaccharide can regulate intestinal homeostasis, improve microinflammation, repair intestinal mucosal damage, restore the protective effect of intestinal barrier function, reduce the burden on the kidney, and improve kidney injury [19].

4.2.2 Astragaloside

Astragaloside can inhibit the proliferation of mesangial cells, and inhibit the activation of PI3K/AKT/AS160 in vivo and in vitro to improve autophagy activation, reduce inflammatory response, and improve kidney function [20]. The expression of iNOS in endothelial cells can also be up-regulated to inhibit inflammatory damage and improve the function of endothelial cells [21]. It has been pointed out that astragaloside can obviously restore the normal form of podocytes, reduce the degree of damage to the cytoskeleton, and reduce the phosphorylation of JNK and ERKI. Therefore, some scholars believe that it can play a pharmacological role in the treatment of membranous nephropathy by regulating the role of cytoskeletal protein and MAPK pathway [22]. Studies have shown that astragaloside may reduce urinary protein, increase serum albumin, and alleviate pathological injury by inhibiting the protein kinase R-like endoplasmic reticulum kinase pathway during ER stress, thus alleviating kidney injury in passive Heymann nephritis rats [23]. It can also up-regulate the expression of ATP-binding box transporter A1 in aortic tissue by inhibiting the production of miR-33a. It can induce cholesterol effection in macrophages and improve lipid metabolism disorder [24].

4.2.3 Astragalus flavones

Flavonoids are one of the important members of the natural antioxidant family. They have strong free radical scavenging and lipid peroxidation inhibition properties, and have obvious protective effects on cell membrane, protein and DNA damage caused by free radicals. Total flavonoids of Astragalus membranacea can significantly reduce plasma cholesterol concentration and cholesterol deposition in aortic wall [25]. It also exerts immunomodulatory and anti-inflammatory effects by regulating MAPK and NF-κB signaling pathways in RAW264. 7 macrophages [26].

5. Study on Classic Formula of Astragalus

5.1 Buyang Huan Wu Decoction

Buyang Huanwu Decoction from the Qing Dynasty Wang Qingren "medical forest correction", the composition of astragalus, angelica tail, dragon, Chuanxiong, red peony,

peach kernel, safflower. Astragalus for the king, Gan Wen big tonics, Qi Wang blood line, so that the stasis to go and collaterals, with angelica as minister Huoxue Tongluo, with red peony, Chuanxiong, peach kernel, safflower huoxue to remove blood stasis, to the dragon to make direct access to collaterals. Treat both symptoms and root causes to benefit Qi and promote blood circulation. So that tonifying qi without obstructing, activating blood without injuring the right.

The combination of Astragalus and Angelica tail can increase the liver synthesis protein, increase the plasma albumin concentration, increase the renal blood flow, and reduce the lipid level [27]. Modern pharmacological studies have shown that the active components of Angelica sinensis can antagonize the effect of endothelin on the kidney, improve the hemodynamic state, and alleviate the state of "high pressure, high filtration and high perfusion" in the glomeruli. Inhibit platelet aggregation, reduce blood hypercoagulability and improve microcirculation; Inhibit oxidative stress, anti-inflammatory, etc., to reduce kidney damage. Peach kernel, safflower two drugs combined, xin open bitter drop, can fight against renal interstitial fibrosis [28]. Studies have shown that Buyang Huanwu decoction can reduce protein leakage of membranous nephropathy, reduce podocyte and epithelial mesenchymal transformation, thereby reducing proteinuria and delaying the development of kidney disease [29].

5.2 Fangji Huangqi Decoction

Out the astragalus root soup from the synopsis of spasm, wet drink was pulse license and cure ", "rheumatism, pulse floating body weight, the sweat out of the evil wind, stephania huangqi decoction of god", the formula for the own, astragalus root, White art, licorice, ginger, jujube, good for qi and wind, spleen and water. Fang in the prevention of wind and water, Astragalus health Qi, tonifying kidney, and can benefit water, a total of Jun medicine, Achieve the effect of Qi movement to water, Qi movement to blood. white art spleen qi, help Astragalus soil to make water, as minister medicine, with the benefit of ginger, jujube and ying Wei.

A large number of studies have shown that the effective ingredients have diuretic, anti-inflammatory, anti-arrhythmia, analgesia, antipyretic, antibacterial, antiviral, anti-tumor, anti-fibrosis and so on. It can also reduce the concentration of IL-18, TGF-B1 and CTGF in kidney tissue, reduce the content of AQP2 to reduce the accumulation of water in the body, improve the urine protein of rats, and have a protective effect on the kidney of rats with adriamycin induced nephropathy [30]. Studies have shown that Fangji Huangqi Decoction can improve the local microenvironment of the kidney, reduce urine protein and promote the recovery of kidney function by regulating the immunity of the body [31]. Some studies have also shown that Fangji Huangqi Decoction can treat refractory edema and improve coagulation function in patients with membranous nephropathy, indicating that Fangji Huangqi Decoction can improve renal function and microcirculation [32].

5.3 Shenqi Dihuang Decoction

Shenqi Dihuang Decoction was originally written by Shen Jinao in Qing Dynasty. It was derived from Liuwei Rehmannia Decoction, Remove alisma with ginseng, astragalus, It was composed of ginseng, Astragalus, cooked Rehmannia, peony bark, yam, poria and Cornus officinalis meat. Cooked Rehmannia nourishing Yin and tonifying kidney, filling essence and marrow; Fructus officinalis astringent essence, tonifying liver and kidney; Yam invigorating spleen tonifying deficiency, reinforcing kidney and astringent essence; Astragalus tonifying qi and strengthening surface, rehydrating and detumifying; Ginseng big tonifying vitality, tonifying spleen and promoting fluid; Tuckaia and peony bark can strengthen spleen and calm heart, and promote water infiltration and dampness. Together play the role of invigorating qi and spleen, nourishing Yin and nourishing kidney.

Modern pharmacological studies have found that ginsenosides can alleviate inflammation and prevent renal fibrosis by inhibiting the release and activation of pro-inflammatory factors and inflammatory bodies. Ginsenosides can also reduce podocyte injury, reduce proteinuria and reverse podocyte epithelial mesenchymal transformation by enhancing autophagy. Cooked Rehmannia has a variety of pharmacological effects, such as anti-inflammatory, immunomodulatory, improving hemorheology, antioxidant, regulating calcium pathway and anti-tumor [33]. Studies have shown that Shenqi Dihuang decoction can reduce urinary protein and increase serum albumin in patients with idiopathic membranous nephropathy. And the improvement of edema, fatigue, dry mouth and other symptoms is better than western medicine treatment [34]. Shenqi Dihuang Decoction can also reduce foot process fusion and IgA deposition, and improve mesangial hyperplasia of renal tissue, which may be related to regulating the expression of podocyte related factors. Therefore, Shenqi Dihuang Decoction is effective in treating IMN, which can effectively reduce urinary protein, increase serum albumin and improve clinical symptoms [35].

6. Summary and Prospect

In summary, the pathogenesis of membranous nephropathy is complex, and astragalus is an important drug for the treatment of membranous nephropathy. The function of tonifying spleen and tonifying kidney fits the pathogenesis of membranous nephropathy with spleen and kidney deficiency. Its active ingredients play an important role in the treatment of membranous nephropathy, which can improve immune function, reduce inflammatory response, relieve podocyte damage, protect filtration barrier, improve microcirculation, and improve lipid metabolism disorders, thus alleviating clinical symptoms and kidney injury of patients. The classic formula composed of Astragalus has a good effect in the treatment of membranous nephropathy, Effectively reduce proteinuria, increase serum albumin, improve high fat, high coagulation and other states, relieve patients with edema, fatigue and other clinical manifestations, but also effectively reduce the adverse reactions brought by western medicine treatment to patients. In the future, we can further study the effective components and molecular mechanism of Astragalus. Explore more and better Chinese medicine formulations to further improve the treatment effect of membranous nephropathy.

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