Research Progress on Modern Biological Mechanism of Chinese Medicine in Prevention and Treatment of Gouty Nephropathy

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Abstract Chinese medicine prevention and treatment of gouty nephropathy often uses single drugs and compound formulae to regulate uric acid, which has the effect of lowering uric acid, protecting the kidneys and improving clinical symptoms. In conclusion, the mechanism of action of Chinese medicine against gouty nephropathy mainly involves oxidative stress, inflammatory response, *etc.*, with a view to providing new ideas and methods for the prevention and treatment of gouty nephropathy by Chinese medicine.

Key words Chinese medicine, Gouty nephropathy, Mechanism of action, Research progress

1 Introduction

Gouty nephropathy is a common clinical disease, referred to as gouty kidneys, which is caused by the formation of hyperuricaemia due to high blood uric acid or reduced excretion of uric acid, resulting in kidney injury, the main clinical manifestations of uric acid stones, oedema, small molecule proteinuria, tubular function damage, *etc.*[1] The disease is a common clinical metabolic disease, the body purine metabolism disorder or uric acid excretion is reduced, resulting in hyperuricaemia, manifested by acute characteristic arthritis and chronic gouty stone, the lesion may involve the kidneys[2]. Data show that the incidence of the disease has been on the rise in recent years, and about 40% of gout patients may suffer kidney damage, second only to joint clinical manifestations[3]. If the condition of gouty nephropathy cannot be controlled, it may progress to chronic renal insufficiency, which is more harmful. At present, clinical treatment of gouty nephropathy mostly adopts the method of controlling blood uric acid, which has achieved certain therapeutic effect, but the long-term use of medication is more damaging to the liver and kidney function, and easy to relapse, so it is especially important to explore new treatment options for this disease[4]. At present, the use of Chinese medicine to prevent and control gouty nephropathy has received more and more attention from medical doctors, and the effect is remarkable.

2 Pathogenesis of gouty nephropathy

There is no record of the name of gouty nephropathy in Chinese medicine theory, but according to the clinical characteristics of gouty arthritis such as joint pain and swelling in the early stage of the disease, it can be classified as "gout" and "paralysis". When proteinuria, haematuria, lumbago, and other kidney damages occur, it can be classified as "oedema", "haematuria", "Guan Ge", *etc.*[5] Ancient medical practitioners believe that early manifestation of gouty kidney disease is gouty arthritis, which leads to innate endowment deficiency or fatigue, and blocks qi and blood meridians with the wind, cold, dampness and other external evils, so that dampness, heat, turbidity, blood stasis invade the limbs and joints. Later damage to the kidneys is considered to be a symptom of deficiency, with kidney deficiency being the main cause of the disease. With the deepening of the understanding of this disease by contemporary medical doctors, each medical doctor has a new understanding of the etiology and pathogenesis of gouty nephropathy. Gouty nephropathy etiology and pathogenesis is due to the patient's innate endowment deficiency, or fatigue, dietary indiscretion, spleen and kidney deficiency, sense of external evil wind, cold, dampness, heat, resulting in phlegm, blood stasis stagnation of meridians, joints, internal organs and the onset of the disease. For example, Dong Zhigang[6] believed that the causes of gouty nephropathy are internal and external, the external causes are related to the feeling of wind, cold and dampness, and the internal causes are due to the innate endowment, or the deficiency of the liver, kidney and spleen, or the diet injures to the spleen, or the emotional and emotional injuries to the liver and the loss of detoxification, and it is believed that the pathogenesis is the deficiency of the liver, spleen and kidney, and the phlegm, dampness, blood and blood stasis internal obstruction. Sun[7] believed that gouty nephropathy is caused by innate deficiency and acquired loss of nourishment, then the spleen and kidney are deficient, and over a long period of time, dampness and turbidity, toxicity and stasis are embedded in the disease. Song [11] believed that the disease is caused by the deficiency of the spleen and kidney, dampness and turbidity obstruction, and the pathogenesis is characterized by weakened body resistance and prevailing pathogenic factors.

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3 Research progress on the mechanism of Chinese medicine against gouty nephropathy

3.1 NALP3 inflammasome/IL-1β inflammatory pathway NALP3 is in the nucleotide-binding oligomerisation domain (Nod)-like receptor family, which consists of three structural domains: leucine-rich repeat sequence (LRR) at the C-terminal end of the molecule, nucleotide-conjugated oligomerisation structural domain (NACHT), and pyroprotein structural domain (PYD) at the N-terminal end of the NALP molecule. The NALP3 inflammasome consists of three parts: the NALP3 protein, apoptosis-associated speckled protein (ASC), and cysteine-aspartate protease-1 (Caspase-1). ASC and cysteine aspartate protease-1 (Caspase-1)[8] mainly expressed in the cytoplasm of macrophages and monocytes, mediating the activation of caspase-1 and the release of inflammatory factors such as IL-1β and IL-18 from immune cells[9] initiates the inflammatory response through LRR recognition and binding to MUS crystals, *i. e.* first activates caspase-1, generates active caspase-1, and then processes the precursor IL-1, maturing it and releasing it extracellularly[10].

Mature IL-1 includes two types of IL-1α and IL-1β. As an immune and inflammatory response mediator, IL-1β can induce cellular inflammation and necrosis, and participate in the development of gouty nephropathy. The specific effects are as follows: (i) Regulating the function of immune cells such as dendritic cells, macrophages, helper T cells 2 (Th2), and converging them to gather in renal tissues, promoting the differentiation of Th17 cells and the production of their related factors; promoting the degranulation of eosinophils, enhancing their cytotoxicity, and damaging the renal tissues[11]. (ii) After binding to receptors on target cells, it activates IL-1 signalling pathway and myeloid differentiation factor-dependent NF-κB pathway, and positively promotes the transcription of IL-1 and other pro-inflammatory cytokines, inducing inflammatory reactions in renal tissues, causing renal injury and promoting the development of gouty nephropathy[12]. (iii) Increased synthesis, expression and release of a variety of cytokines and adhesion factors, including IL-18, intercellular adhesion molecules, vascular cell adhesion molecules, and E-selectin work together to promote the development of nephropathy[13].

3.2 NETs It is well established that neutrophils, as an important line of defence of the human immune system, are activated to release NETs that can be involved in the capture and killing of pathogenic bacteria, and recent studies have shown that NETs can lead to cell death, tissue damage, and are involved in the progression of a variety of diseases[14]. NETs are highly concentrated reticulocyte DNA complexes released extracellularly by activated neutrophils in various ways, which can induce cell necrosis. Their action is related to the cytotoxicity of their main component histones, which may damage endothelial cells, hydrolyse proteins and thus be involved in tissue damage and a variety of pathologies (including gouty nephropathy, pancreatitis, *etc.*)[15].

3.3 ICAM-1 ICAM-1 is in the immunoglobulin superfamily and is one of the important adhesion molecules in the immune response, and can be classified into tissue membrane-bound ICAM-1 (mICAM-1) and serum soluble ICAM-1[16]. mICAM-1 interacts with its corresponding ligands and is involved in the firm adhesion of various leukocytes (*e. g.* neutrophils, eosinophils, basophils, monocytes, lymphocytes) to tissue membranes and their chemotaxis from blood vessels to inflammatory tissues[17]. Thus, it plays an important role in the process of monocyte-macrophage infiltration, causing inflammatory cells to infiltrate into renal tissues, resulting in increased cytokine secretion, exacerbating inflammatory reactions, and causing renal endothelial cell injury. It has also been shown that the deposition of MUS crystals in the kidney may induce the expression of ICAM-1, enhance the interaction between HRMCs and macrophages, and promote the progression of gouty nephropathy[18].

4 Mechanisms associated with the prevention and treatment of gouty nephropathy by traditional Chinese medicine

4.1 Chinese medicine in a single flavour

4.1.1 Giant knotweed rhizome. Giant knotweed rhizome has the effect of inducing dampness, clearing heat and removing toxins, dispersing blood stasis and relieving pain, relieving cough and phlegm[19]. Modern pharmacological studies have shown that the extracts of giant knotweed rhizome can metabolise potential biomarkers related to the pathological process of hyperuricaemia, including purines, and found that the levels of blood uric acid and serum creatinine were significantly reduced, and renal function was improved compared with the previous levels, while renal fibres were reduced compared with the previous levels in rats with hyperuricaemia[20]. Experimental studies have shown that giant knotweed rhizome has anti-inflammatory and antioxidant effects, which are also protective of the kidneys[21]. All of the above studies prove that giant knotweed rhizome can have a certain protective effect on the kidneys of hyperuricemic rats by lowering the uric acid level, reducing the deposition of urate crystals in the kidney, and at the same time, reducing the inflammatory stimulation of urate crystals on the kidneys.

4.1.2 *Rhizoma Dioscoreae septemlobae*. The Rhizoma Dioscoreae Septemlobae has the effect of inducing dampness and removing turbidity, dispelling wind and removing paralysis[22]. *Rhizoma Dioscoreae Septemlobae* can inhibit xanthine oxidase activity and reduce uric acid synthesis in the serum of hyperuricemic rats, and by reducing the expression of tumour necrosis factor, intercellular adhesion factor and monocyte chemotactic proteins in the renal tissues of rats , it can delay renal functional damage and protect the kidneys[23].

4.1.3 Rhubarb root and rhizome. The main effects of rhubarb root and rhizome are curing diarrhoea, clearing heat and fire, cooling the blood and removing toxins, removing blood stasis and clearing menstruation, inducing diuresis and eliminating yellowish discolouration[24]. NI[25] *et al.* found that rhubarb root and rhizome can lower the blood uric acid level in rats with gouty nephropa-

thy, reduce the deposition of urate in renal tubules, and at the same time inhibit the expression of bFGF and COX-2 in the kidneys, which will in turn reduce the damage to the kidneys caused by hyperuricemia, thus reducing renal fibrosis, and protecting the kidneys.

4.1.4 Chinese fevervine. The main effects of Chinese fevervine are: digestion, stomachic, resolving phlegm and cough, clearing away heat and removing toxins, relieving pain and so on[26]. Jin[27] found that Chinese fevervine has obvious inhibitory effect on XOD, which can reduce the clinical symptoms of gouty nephropathy in rats, and at the same time, reduce the level of blood uric acid and urinary uric acid, and improve the renal function.

4.1.5 Chinese clematis root. The main effects of Chinese clematis root are dispelling wind-dampness, clearing the channels and relieving pain[28]. Lin Fengping[29] demonstrated through experimental studies that Chinese clematis root could reduce urate deposition in renal tubules of rats with gouty nephropathy, inhibit the activated portion of NF-KB, and down-regulate the expression of MCP-1 protein, thus protecting renal tissues.

4.1.6 *Poria*. *Poria* not only has little adverse effects, but also improves internal circulation and inhibits T-cells, plays a role in lowering uric acid and relieving pain and inflammation, and protects the liver and kidneys, and Compound *Poria cocos* granules can also reduce the expression of inflammatory factors and alleviate the renal injury due to the elevation of uric acid[30].

4.2 Compound prescription of Chinese medicine

4.2.1 Tongfengke Soup. Tongfengke Decoction is a classic formula for the treatment of gouty nephropathy in Chinese medicine. Studies have shown that Scr, UA, BUN, 24 h urine protein, Cys-C, β2-MG, NAG, XOD levels were significantly reduced and GFR levels were significantly increased after treatment with Tongfengke Decoction[31].

4.2.2 Yishen Tongluo Compound. Yishen Tongluo Compound is used to promote dampness and remove turbidity, dispel wind and remove paralysis; *Psyllium* is used to promote diuresis and relieve diarrhoea; all the herbs work together to tonify the spleen and kidney, remove dampness and turbidity, expel blood stasis and remove toxins. Clinical studies show that after receiving treatment with Yishen Tongluo Compound, patients' SCr, SUA, β2-MG, α1-MG, 24-h urinary protein quantification were reduced, and eGFR was increased, having the function of treating gouty nephropathy[32].

4.2.3 Ten flavours of frankincense powder. Tibetan medicine ten flavour frankincense powder has the efficacy of dispelling wind and drying dampness, drying yellow water, clinically used for rheumatoid arthritis, gout caused by joint redness, swelling and pain as well as eczema of the skin caused by excessive yellow water. Modern research has shown that the drug has sedative and anti-inflammatory, uric acid lowering effect[33-34]. Zhu[35] found that ten flavours of frankincense powder can reduce the serum levels of UA, BUN, SCr, as well as renal tissue urate crystal deposition and renal tissue cell apoptosis, and can alleviate the gouty renal injury by inhibiting the release of inflammatory factors, such as L-1β and TNF-α, and activating mitochondrial autophagy pathway.

5 Conclusions

In recent years, Chinese medicine has shown unique advantages and positive effects in the prevention and treatment of gouty nephropathy. Due to the complexity of the pathological process of gouty nephropathy, the comprehensive treatment of Chinese medicine has a positive effect on the overall improvement of the patient's physical condition. In the clinical treatment of gouty nephropathy, the application of compound prescription and proprietary Chinese medicines can be expanded to comprehensively improve the overall condition of the patient's body and improve the overall health level.

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