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LETTER TO THE EDITOR

Roles of traditional Chinese medicine extracts in hyperuricemia and gout treatment: Mechanisms and clinical applications

Yan-Bo Wang, Chang-Zhong Jin

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Abstract

In this manuscript, we comment on the article by Liu *et al* published in the recent issue of the journal. Hyperuricemia (HUA) has become the second most common metabolic disease after type 2 diabetes mellitus and is the most important risk factor for gout. This discussion focuses on the targets and clinical application value of traditional Chinese medicine (TCM) extracts in the treatment of HUA and gout, emphasizing the role of gut microbiota. Liu *et al*'s study demonstrated that *Poecilobdella manillensis* protein extract alleviated HUA through multiple mechanisms, including inhibition of uric acid (UA) reabsorption, promotion of UA excretion, repair of intestinal barrier function, and regulation of gut microbiota and metabolome. Unlike the commonly used urate-lowering drugs such as allopurinol and febuxostat, which have clear and single targets, many TCMs have multi-target effects. However, the active components and mechanisms of TCMs are not fully understood, limiting their clinical application in the treatment of HUA and gout. Additionally, the role of gut microbiota in UA metabolic homeostasis needs to be further explored.

Key Words: Hyperuricemia; Gout; Traditional Chinese medicine; Gut microbiota; Multi-target; Uric acid metabolic homeostasis

Core Tip: Traditional Chinese medicines (TCMs) have significant potential in treating hyperuricemia (HUA), gout and other metabolic diseases. However, the "multi-target effects" do not fully explain the mechanisms of TCMs, hindering their clinical application. The active components and mechanisms of TCMs should be elucidated in detail. Additionally, the side effects of TCMs need attention. The role of gut microbiota in treating HUA also warrants further investigation to improve HUA and gout treatment strategies.

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TO THE EDITOR

Hyperuricemia (HUA), characterized by chronically elevated serum uric acid (UA) concentration, results from an imbalance between UA production and excretion[1]. The incidence of HUA and gout has been rising globally, making HUA the second most common metabolic disease after type 2 diabetes mellitus. In Western countries, approximately 15%-20% of the population has HUA, and 3.9% exhibit clinical features of gout[2,3]. Besides gout, HUA is also closely related to the development of inflammatory arthritis, renal disease, and cardiovascular diseases, posing a significant public health challenge[4,5]. UA is a catabolic product of purine nucleotides, with around 80% derived from cellular metabolism and 20% from dietary sources. In the liver, small intestine and kidney, purine nucleotides are converted to xanthine by various enzymes, which is then converted to UA by xanthine oxidase (XOD). In most mammals, UA is converted to freely soluble allantoin *via* urate oxidase (uricase), which is then excreted *via* the kidney. However, early in human evolution, progressive mutations occurred in the uricase gene, resulting in complete loss of uricase function[6]. Approximately 70% of the UA is excreted in the urine through the kidneys, while the remaining 30% of UA is excreted into the intestinal cavity, and then broken down by intestinal bacteria and excreted with feces. The imbalance of UA synthesis and excretion can lead to the occurrence of HUA. In order to prevent and control HUA, the first step is to reduce the intake of purines and nucleosides through diet control, thereby reducing the synthetic substrates of UA[7]. However, long-term dietary restrictions can significantly reduce the quality of life. Clinically, XOD inhibitors such as allopurinol and febuxostat, are used to inhibit the activity of XOD to reduce UA generation. In addition, uricosuric agents like probenecid and benzbromarone are used to inhibit human urate transporter 1 to reduce renal reabsorption of UA. These drugs have specific targets but may cause side effects on the liver, kidneys, and gastrointestinal tract, which have been clearly studied.

TRADITIONAL CHINESE MEDICINE AND ACTIVE EXTRACTS IN THE TREATMENT OF HUA AND GOUT

Gout, an ancient disease, is understood in traditional Chinese medicine (TCM) theory as resulting from congenital weakness, kidney qi deficiency, exogenous pathogenic factors, emotional distress, and dietary imbalances[8]. There are many TCM prescriptions for the treatment of HUA and gout with good therapeutic effects[8,9]. Unlike the drugs such as allopurinol and febuxostat, TCMs exhibit multi-target effects (Figure 1). In the study by Liu *et al*[10], *Poecilobdella manillensis* protein extract alleviated HUA by multiple effects, including inhibition of UA reabsorption, promotion of UA excretion, repair of intestinal barrier function, and regulation of gut microbiota and metabolome. Modern pharmacological studies have identified many TCMs that inhibit the synthesis of UA or promote the excretion of UA. For example, plantamajoside, the main active ingredient of *Plantaginis*, can reduce the UA level in HUA mice by regulating the expression of renal UA transporters and inhibiting inflammatory signaling pathways. Polydatin, the active *Polygonum cuspidatum* Sieb. et Zucc., can promote UA excretion and alleviate inflammation-induced kidney injury[11]. In addition, other TCMs such as *Poria cocos*[12], *Cichorium intybus*[13,14] and *Dioscorea spongiosa*[15], can also regulate the excretion and reabsorption of UA, and reduce the inflammatory injury of the kidney.

In the realm of TCM, doctors tailor treatment plans to the unique conditions of individual patients, eschewing a one-size-fits-all approach. Therefore, we should avoid overgeneralizing the functions of TCM, as this may be contrary to TCM theory. Moreover, the misuse or overuse of certain medicinal substances can precipitate harmful side effects. For instance, an excessive intake of *Radix* et *Rhizoma Asari* can manifest in symptoms such as vomiting, irritability, convulsions, respiratory paralysis, and damage to the kidneys and liver. Similarly, overconsumption of *Aconiti Lateralis Radix Praeparata* may lead to arrhythmias, conduction block, *etc*. Without clear component identification, it is difficult to quantify TCMs' efficacy and side effects, limiting their clinical application. In order to further elucidate the mechanism of TCM in the treatment of HUA and gout, the synergistic effect of various bioactive components in Chinese medicines should be considered, and multi-omics strategies such as genomics, transcriptomics, proteomics and metabolomics should be combined with network pharmacology.

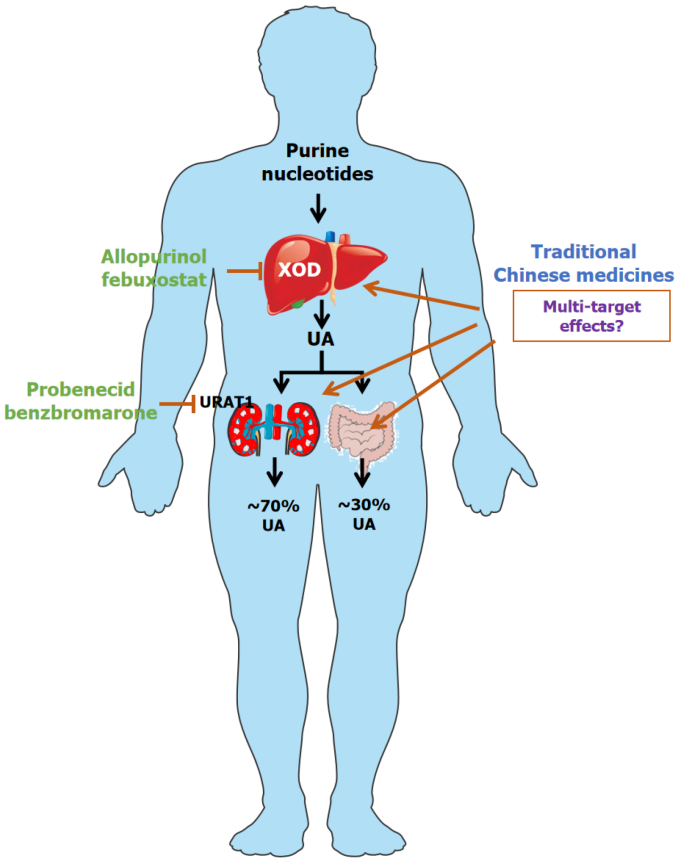

Figure 1 Traditional Chinese medicines exhibit multi-target effects. Mechanisms for the treatment of hyperuricemia (HUA) and gout. Purine nucleotides are catalyzed by a variety of enzymes to synthesize uric acid (UA). About 70% of the UA produced by the body is excreted through the kidneys, and the remaining 30% of UA is excreted into the intestinal cavity and excreted with feces. Clinically, allopurinol and febuxostat are used to inhibit the activity of oxidase to reduce UA generation. In addition, probenecid and benzbromarone are used to inhibit human urate transporter 1 to reduce renal reabsorption of UA. Traditional Chinese medicines (TCMs) alleviate HUA by multi-target effects, including inhibition of UA reabsorption, promotion of UA excretion, repair of intestinal barrier function, and regulation of gut microbiota and metabolome. But the mechanisms and side effects of TCMs in the treatment of HUA and gout must be further elucidated to promote the clinical applications of TCMs. XOD: Xanthine oxidase; UA: Uric acid; URAT1: Urate transporter 1.

THE ROLE OF GUT MICROBIOTA IN HUA TREATMENT

Gut microbiota is one of the important targets for the treatment of HUA. Gut microbiota participates in the synthesis of purine metabolic enzymes and the release of immune factors, which is closely related to the occurrence and development of metabolic immune diseases such as HUA and gout. In their article, Liu *et al*[10] highlighted that *Poecilobdella manillensis* protein extract affected the serum concentrations of UA and various other metabolites. This modulation was intricately linked to alterations in the relative abundance of intestinal commensal bacteria, including *Prevotella*, *Delftia*, *Akkermansia*, *Lactococcus*, *Escherichia_Shigella*, *Enterococcus*, and *Bacteroides*. Furthermore, Amatjan *et al*[16] demonstrated that the aqueous extract of *Cichorium intybus* L. formula increased the abundance of *Lactobacillaceae*, *Erysipelotrichaceae*, *Lachnospiraceae*, *Ruminococcaceae*, and *Bifidobacterium* and alleviated hyperuricemic nephropathy. Similarly, Bian *et al*[17] reported that the Guizhi Shaoyao Zhimu Decoction, known for its efficacy in alleviating gouty arthritis, was associated with an increase in the abundance of *Lactobacillus*, *Ruminococcaceae*, and *Turicibacter*, alongside a decrease in *Blautia*. These findings underscore the potential of TCM in modulating the gut microbiome to modulate UA metabolism[18]. Intestinal symbiotic bacteria such as *Lactiplantibacillus plantarum*, *Enterocloster bolteae*, and *Escherichia coli* can degrade the nucleosides and purines, which are substrates for UA synthesis, thereby reducing serum UA levels[19,20]. Moreover, anaerobic bacteria of the gut microbiome are able to metabolize UA, compensating for the uricase deficiency of their host. For example, *Alistipes indistinctus*-derived hippuric acid promotes intestinal urate excretion to alleviate HUA[21]. Therefore, the role of gut microbiota should be emphasized when analyzing HUA treatment mechanisms, and its clinical application warrants consideration.

CONCLUSION

TCMs hold significant potential for treating HUA and other metabolic diseases, potentially guiding the development of new treatments for HUA and gout. However, the complex composition of TCMs and their "multi-target effects" require more detailed investigation to fully understand their mechanisms. Additionally, the role of gut microbiota in HUA

treatment is crucial and warrants further study to improve therapeutic strategies.

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FOOTNOTES

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