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Review Article

The potential of Chinese medicines in the treatment of hyperuricemia

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Abstract: The annual incidence of gout is increasing along with lifestyle and dietary changes. Accumulation of urate crystals in joints and tissues when the amount of uric acid exceeds its saturation concentration causes acute inflammation that leads to gout. Reducing the serum uric acid concentration is the key to treating gout. Allopurinol, febuxostat, benzbromarone, and other drugs are effective, but side effects of treatment such as toxicity and recurrence after drug withdrawal cannot be ignored. Recent studies have found that many Chinese medicines are effective and safe, provide durable efficacy, and are associated with low recurrence rates. This article reviews recent investigations of Chinese medicines for lowering uric acid, including components such as berberine, luteolin, and others; single medicines such as *Smilax glabra* Roxb., *Reynoutria japonica* Houtt., and *Plantago asiatica* L.; and compounds such as Wuling Powder and Compound Tufuling Granules. Mechanisms of lowering uric acid, including inhibiting uric acid production and promoting uric acid excretion are discussed. Clinical studies and basic research are reviewed.

Keywords: Hyperuricemia, uric acid lowering, xanthine oxidase, uric acid metabolism transporter, Chinese medicines

Introduction

Uric acid is the end product and normal metabolites of endogenous and exogenous purines [1]. Exogenous purines are supplied by diets high in foods such as animal viscera, seafood, and beer, among others. Endogenous purines are synthesized primarily in the liver, intestine, and other tissues, and purine metabolism is the main source of uric acid [1, 2]. Abnormal purine metabolism can maintain increased uric acid concentration for a time that is long enough to cause hyperuricemia, which is a serum uric acid concentration in both men and women of more than 420 μmol/L, measured on two different days [3]. If the urate exceeds its saturation concentration, urate crystals will be deposited in the joints, kidneys, cartilage, and other tissues, and the resulting acute inflammation can be diagnosed clinically as gout. Changes in dietary habits and lifestyles have spurred increases in the annual incidence of gout. The most recent estimates of the overall prevalence of hyperuricemia in China was 13.3%; the estimated prevalence of gout was 1.1% [3]. There is increasing evidence that chronic hyperuricemia causes not only urate deposition but also induces gout and is an independent risk factor for hypertension, metabolic syndrome, chronic kidney disease, and cardiovascular disease [4]. Currently available urate-lowering drugs indicated for treating hyperuricemia and gout include xanthine oxidase (XOD) inhibitors like allopurinol and febuxostat and uricosuric drugs like benzbromarone [5]. Allopurinol may cause skin allergic reactions and affect liver and kidney function, as well as fatal exfoliative dermatitis and other severe hypersensitivity syndromes [6]. Febuxostat treatment has been associated with elevated liver enzymes, and more gastrointestinal symptoms and cardiovascular events than allopurinol [5]. Benzbromarone use has been associated with diarrhea, stomach discomfort, nausea and

other digestive symptoms, skin allergies, and abnormal liver function. The urate-lowering drugs effectively reduce serum uric acid, but their side effects limit clinical use [7], and lead to poor patient compliance. Uric acid concentrations have been reported to increase rapidly after the drug is stopped.

Recently, studies of the use of Chinese medicine to lower uric acid have become more frequent, and the clinical application has become more extensive. Shuai *et al.* [8] treated 56 patients with asymptomatic hyperuricemia with 15 g of *Lysimachia christinae* Hance decoction (Lysimachiae Herba) once daily. After 3 months, serum uric acid was significantly reduced compared with that before treatment. Zhao *et al.* [9] evaluated the efficacy of integrated traditional Chinese and Western medicine in 60 gout patients with tophi who were randomly assigned to 6-months of treatment with febuxostat combined with Qingre Lishi or with febuxostat only. Serum uric acid significantly decreased in both groups ($P < 0.01$), but the reduction was greater with combined treatment compared with the febuxostat only control group ($P < 0.05$). Compliance was 96.43% in the treatment group and 77.78% in the control group. Other studies have shown that, compared with Western medicine, Chinese medicine has the advantages of decreasing the severity and frequency of gout attacks, lowering the concentration of uric acid, and having fewer side effects [10]. This review summarizes the urate-lowering effect of Chinese medicine that are derived from inhibiting uric acid production and promoting uric acid metabolism.

Uric acid metabolism

Physiology of uric acid

The causes of hyperuricemia include excessive uric acid production and reduction of excretion that result from excess intake of exogenous purines and abnormal purine metabolism *in vivo*. About two thirds of uric acid is eliminated by the kidneys, and one third by the intestine [1]. Decreased uric acid excretion is mainly the result of renal excretion dysfunction. Renal excretion of uric acid involves four processes, glomerular filtration, reabsorption by proximal tubules, active secretion and reabsorption [11], with 100% of it being filtered through the glomerulus and 90% is reabsorbed by the renal tubules. Reabsorption by the proximal tubules of the kidney is the main reason for the increase in serum uric acid and accounts for 90% of hyperuricemia [12]. Uric acid is a polar molecule that cannot freely penetrate the cell membrane and must rely on multiple transporters to complete its metabolism [11].

Proteases involved in uric acid synthesis

Adenosine deaminase (ADA) regulates endogenous adenine nucleoside levels, and catalyzes the conversion of adenine nucleoside to hypoxanthine nucleoside, an important intermediate in the formation of uric acid, and ADA. Purine metabolism ultimately involves XOD, which catalyzes the conversion of hypoxanthine to xanthine and the oxidation of xanthine uric acid [13] (**Figure 1**).

Uric acid transporters

Uric acid salt secretion depends on a number of transport proteins that regulate reabsorption and excretion to influence serum urate levels [14]. Uric acid reabsorption transporters include urate anion transporter 1 (URAT1), organic anion transporter 4 (OAT4), and glucose transporter 9 (GLUT9). Uric acid excretion transporters include organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and ATP Binding Cassette Subfamily G Member 2 (ABCG2) [15]. URAT1 is the primary reabsorption transporter, and maintains a physiological balance by exchanging urate with inorganic (chloride) and organic (lactate and salt) anions in proximal tubule epithelial cells. GLUT9 is a high-capacity uric acid transport protein that accelerates the reabsorption of uric acid by trans-shipping glucose, and urate from negative to positive in a voltage-dependent manner [16]. Organic anion transporters (OATs) are important for renal retention and removal of uric acid salts [2]. OAT1 and OAT3 are expressed in the basal lamina of renal tubular epithelia, which transports uric acid from capillaries into tubular epithelial cells, completing the first step of uric secretion. OAT4 is encoded by the *SLC22A11* gene and is mainly expressed in the renal tubular epithelium, where the reabsorption process is accomplished through the exchange of uric acid with alpha-ketoglutaric acid or hydroxyl ions [17, 18]. ABCG2 is located in brush border membranes, epithelial cells of bile ducts, proximal tubules, and is involved in

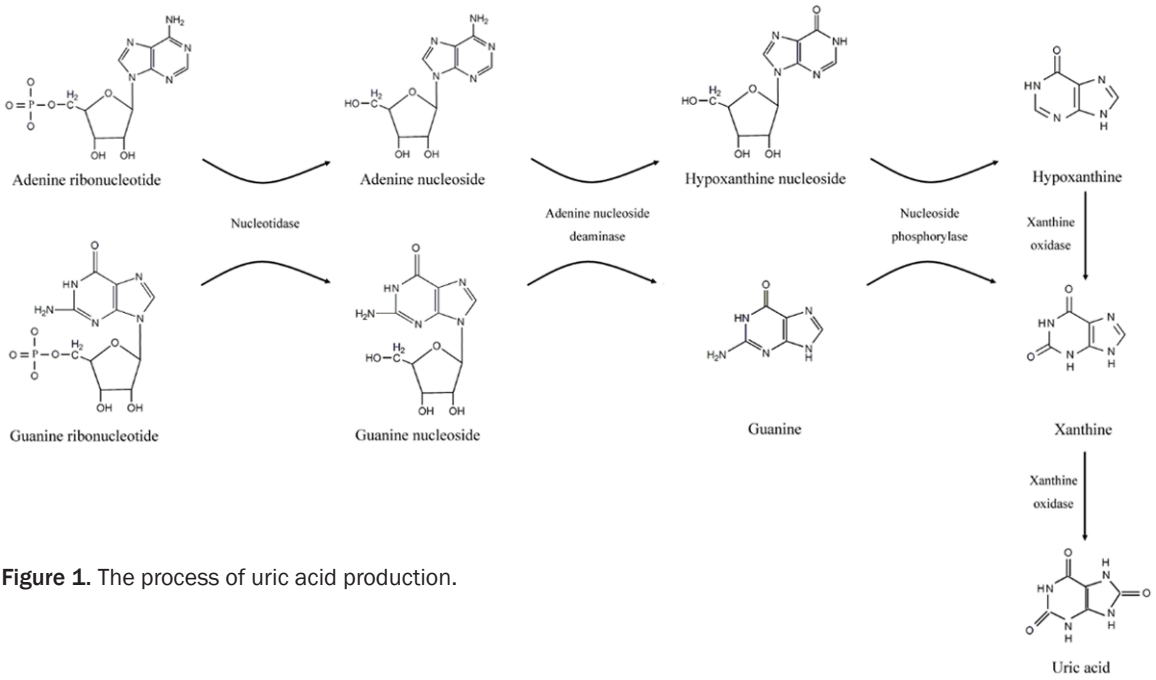

Figure 1. The process of uric acid production.

purine metabolism and excretion of uric acid in the kidney and intestine [19].

Mechanisms of reducing uric acid

Interventions that target proteases and uric acid transporters lowering uric acid inhibit uric acid synthesis by inhibiting XOD or ADA activity. Uric acid excretion can be promoted by regulating the activity of URAT1, GLUT9, ABCG2, and OATs, which affect the reabsorption and excretion of urate (**Figure 2**).

Effects and mechanisms of action of Chinese herbal components in lowering uric acid

Many components of Chinese herbal medicines can reduce uric acid. Chen *et al.* [20] isolated XOD inhibitors from a *Curcuma longa* L. extract by centrifugal ultrafiltration and identified as bisdemethoxycurcumin, demethoxy curcumin, and curcumin by liquid chromatography-mass spectrometry. Deng *et al.* [21] reported that polysaccharides of Poria cocos downregulated URAT1 expression and upregulated OAT1 expression in rats with hyperuricemia, which increased uric acid excretion and decreased serum uric acid concentration. Chen *et al.* [22], found that *Dioscorea tokoro* Makino ex Miyabe saponins reduced uric acid reabsorption, promoted urate excretion, and lowered serum uric acid level in a potassium oxonate and ethambutol-induced rat model by lowering URAT1 expression. As shown in **Table 1**, mulberry orange *Chaenomeles speciosa* (Sweet) Nakia, resveratrol from *Reynoutria japonica* Houtt., baicalin from *Scutellaria baicalensis* Georgi, and other Chinese medicine ingredients have been shown to lower serum uric acid concentrations.

Uric acid lowering by single herbs

Chinese medicines that inhibit uric acid production

Phellodendron amurense Rupr. is commonly used to clear away heat and dampness. Shen *et al.* [23] found that *Phellodendron amurense* Rupr. inhibited XOD activity in the liver of mice with potassium oxonate-induced hyperuricemia. The extent of urate-lowering was positively correlated with the dose. The components with pharmacological were berberine and phellodendrine alkaloids. Berberine has many electronegative groups, and has a high affinity for Mo-pt related molecular channels in XOD, and after the two are combined, the binding of the Mo-pt center of XOD to the substrate is blocked, and its catalytic activity is lost [23], which inhibits the two terminal catabolic reactions of purines, thereby reducing uric acid production.

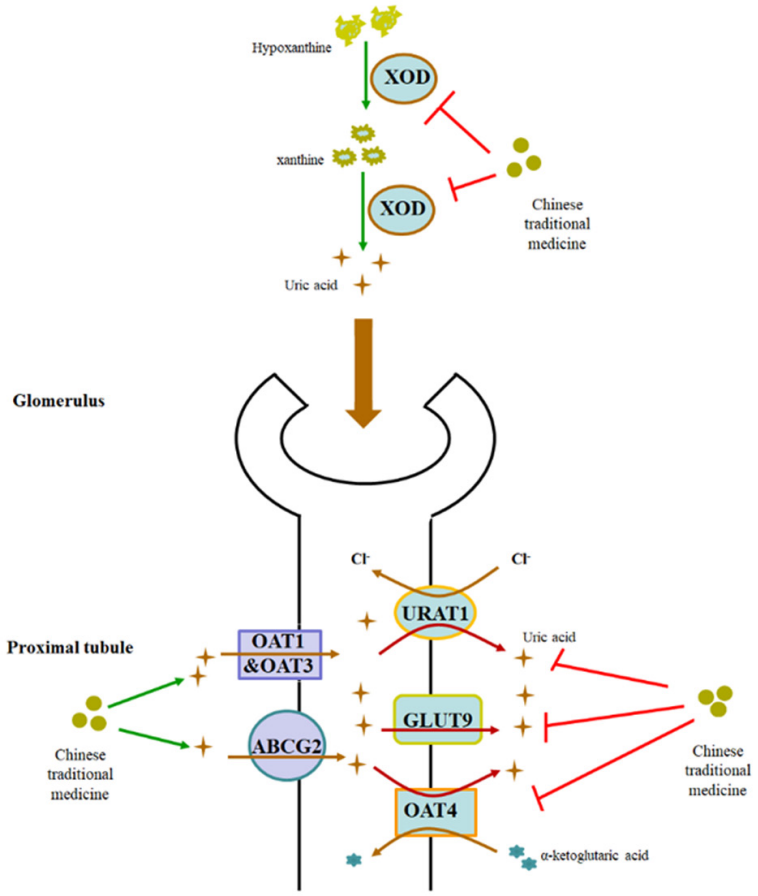

Figure 2. Uric acid-lowering mechanism. URAT1, GLUT9, and OAT4 promote uric acid reabsorption. OAT1, OAT3, and ABCG2 promoting uric acid excretion. XOD: xanthine oxidase; URAT1: urate anion transporter 1; GLUT9: glucose transporter 9; OAT1: organic anion transporter 1; OAT3: organic anion transporter 3; OAT4: organic anion transporter 4; ABCG2: ATP Binding Cassette Subfamily G Member 2.

Lonicera japonica Thunb. is a heat-clearing and detoxifying herb. Li *et al.* [24] used high-throughput screening with ultraviolet spectrophotometry to study the XOD inhibitory activity of 20 components isolated from *Lonicera japonica* Thunb.. They identified dicaffeoylquinic acid (a polyphenol) and flavonoids that inhibited XOD activity. Luteolin, mistletoe and 3, 4-dicaffeoylquinic acid methyl ester had significant effects on reducing uric acid by inhibiting XOD activity.

Chaenomeles speciosa (Sweet) Nakai is used to expel wind and remove dampness. Tang *et al.* [25] used a variety of chromatographic separation methods to isolate components of *Chaenomeles speciosa* (Sweet) Nakai with XOD inhibitory activity. Mulberry orange, which is benzophenone derivative, reduced uric acid production by inhibiting XOD activity. The result suggests that benzophenones have potential value in inhibiting XOD activity.

Coptis chinensis Franch. [23], *Alisma plantago-aquatica* Linn. [26], *Pueraria lobata* (Willd.) Ohwi [27], *Lysimachia christinae* Hance (Lysimachiae Herba) [28], *Scutellaria baicalensis* Georgi [29], *Curcuma longa* L. [20], *Alpinia officinarum* Hance [30], *Scrophularia ningpoensis* Hemsl. [31], *Cinnamomum cassia* Presl [32], *Chrysanthemum indicum* L. [32], *Lycopus lucidus* Turcz. var. *hirtus* Regel [32], *Rheum palmatum* L. [33], *Salvia miltiorrhiza* Bunge [34, 35], and *Carthamus tinctorius* L [36] have all been found to lower uric acid by inhibiting XOD activity (**Table 2**).

Chinese medicines that promote uric acid excretion

Poria cocos (Schw.) Wolf is a diuretic and damp-permeating agent. Deng *et al.* [21] found that *Poria cocos* (Schw.) Wolf polysaccharide had a significant anti-hyperuricemia effect by downregulating the expression of reabsorption transporter URAT1 and upregulating the expression of the renal tubule secretory transporter OAT1, thereby reducing the level of uric acid in a rat model of hyperuricemia induced by potassium oxazine and ethambutol.

Dioscorea tokoro Makino ex Miyabe is used to treat gout and hyperuricemia in clinical practice, and Chen *et al.* [22] reported that saponins contained in the medicine inhibited uric acid reabsorption and promoted uric acid excretion by inhibiting the expression of URAT1 in the kidneys of rats with potassium oxazine and ethambutol-induced hyperuricemia.

Gentiana macrophylla Pall. is an antirheumatic medicine that Liu *et al.* [37] found to increase the expression of OAT1 and OAT3 and decrease URAT1 expression and uric acid excretion in

Table 1. Mechanisms of lowering uric acid by Chinese medicine components

Chinese medicine components	Source Chinese medicine	Mechanism of Action
Verbascoside [31, 41]	*Plantago asiatica* L., *Scrophularia ningpoensis* Hemsl.	XOD activity↓, URAT1↓, GLUT9↓
Berberine [23]	*Phellodendron amurense* Rupr.	XOD activity↓
Luteolin [24, 36, 41]	*Lonicera japonica* Thunb., *Plantago asiatica* L., *Carthamus tinctorius* L.	
Methyl 3, 4-dicaffeoylquinate [24]	*Lonicera japonica* Thunb.	
Mistletoe [24, 28, 36, 39]	*Lonicera japonica* Thunb., *Smilax glabra* Roxb., *Carthamus tinctorius* L., *Lysimachia christinae* Hance	
Puerarin [27]	*Pueraria lobata* (Willd.) Ohwi	
Baicalin [29]	*Scutellaria baicalensis* Georgi	
Total flavones [30]	*Alpinia officinarum* Hance	
Didemethoxycurcumin, Curcumin, Demethoxycurcumin [20]	*Curcuma longa* L.	
Mulberry orange [25]	*Chaenomeles speciosa* (Sweet) Nakai	
Emodin [33]	*Rheum palmatum* L.	
Flavonoid glycosid e [28, 39]	*Lysimachia christinae* Hance, *Smilax glabra* Roxb.	
Cassimone-8-O-β-D-glucopyranoside, Resveratrol, Polydatin [43, 44]	*Reynoutria japonica* Houtt.	
Salvianolic acid [34, 35]	*Salvia miltiorrhiza* Bunge	
Myricetin [36]	*Carthamus tinctorius* L.	
Alisol B23-acetate [26]	*Alisma plantago-aquatica* Linn.	
Polysaccharides of Poria cocos [21]	*Poria cocos* (Schw.) Wolf	URAT1↓, OAT1↑
Rhizoma Dioscoreae saponins [22]	*Dioscorea tokoro* Makino ex Miyabe	URAT1↓

XOD: xanthine oxidase; URAT1: urate anion transporter 1; GLUT9: glucose transporter 9; OAT1: organic anion transporter 1.

Table 2. Mechanisms of single Chinese medicine for lowering uric acid

Single Chinese medicine	Model/Method	Mechanism of Action
Smilax glabra Roxb. [39]	Hypoxanthine, potassium oxonate model	XOD activity↓, URAT1↓, GLUT9↓
Scutellaria baicalensis Georgi [29]		XOD activity↓
Reynoutria japonica Houtt. [43, 44]	Potassium oxonate, adenine model	XOD activity↓, OAT3↑, URAT1↓, GLUT9↓
Plantago asiatica L. [41]	Potassium oxonate model	XOD activity↓, ADA activity↓, URAT1↓
Phellodendron amurense Rupr. [23]		XOD activity↓
Rheum palmatum L. [33]		
Lysimachia christinae Hance [28]		
Alisma plantago-aquatica Linn. [26]		
Scrophularia ningpoensis Hemsl. [31]		
Lonicera japonica Thunb. [24]	High-throughput screening method based on spectrophotometric principle	
Cinnamomum cassia Presl, *Chrysanthemum indicum* L., *Lycopus lucidus* Turcz.var. *hirtus* Regel [32]		
Carthamus tinctorius L. [36]		
Poria cocos (Schw.) Wolf [21]	Potassium Oxonate, ethambutol model	URAT1↓, OAT1↑
Dioscorea tokoro Makino ex Miyabe [22]		URAT1↓
Gentiana macrophylla Pall. [37]	Adenopurinol, ethambutol model	URAT1↓, OAT1↑, OAT3↑
Pueraria lobata (Willd.) Ohwi [27]	Yeast extract, potassium oxonate model	XOD activity↓
Alpinia officinarum Hance [30]	Potassium oxonate model + in vitro inhibition of xanthine oxidase activity test	
Curcuma longa L. [20]	Centrifugal ultrafiltration and liquid chromatography-mass spectrometry	
Chaenomeles speciosa (Sweet) Nakai [25]	In vitro inhibition assay of xanthine oxidase activity	
Salvia miltiorrhiza Bunge [34, 35]	Potassium oxonate and xanthine model	

XOD: xanthine oxidase; ADA: Adenosine deaminase; URAT1: urate anion transporter 1; GLUT9: glucose transporter 9; OAT1: organic anion transporter 1; OAT3: organic anion transporter 3.

hyperuricemic rats, as measured by western blotting and immunohistochemistry.

Chinese medicine that inhibit uric acid production and promote uric acid excretion

Smilax glabra Roxb. is a heat-clearing and detoxifying medicine. A study by Kuang *et al.* [38] included 116 patients with acute gouty arthritis of the dampness-heat accumulation type who were either given conservative treatment with diclofenac sodium and prostanol tablets, or conservative treatment plus (*Smilax glabra* Roxb.) decoction 100 g. Fasting serum uric acid levels decreased in both groups ($P < 0.05$), and was lower in the Chinese medicine group than in the conventional group ($P < 0.01$). Ding *et al.* [39] reported that *Smilax glabra* Roxb. Significantly reduced XOD activity, uric acid production, and serum uric acid concentration in a hypoxanthine and potassium oxonate induced mouse hyperuricemia model. The medicine also downregulated messenger RNA (mRNA) and protein expression of URAT1 and GLUT9 in the mouse kidneys, suggesting that it promoted uric acid excretion by downregulating the expression of URAT1 and GLUT9. Xu *et al.* [40] found that quercetin in *Smilax glabra* Roxb. inhibited XOD activity.

Plantago asiatica L. is a diuretic and damp-permeating agent, and Zeng *et al.* [41] reported that an extract lowered uric acid by inhibiting XOD activity and downregulating the expression of mURAT1 (mouse urate anion transporter 1) mRNA to promote uric acid excretion in mice. The extract also inhibited the activity of ADA in the liver of hyperuricemic mice, which suggests that *Plantago asiatica* L. interfered with purine conversion by inhibiting ADA activity, which decreased xanthine and hypoxanthine synthesis and uric acid production. It has also been found that mullein and isomullein, which are active components of *Plantago asiatica* L., can lower uric acid by inhibiting XOD activity and downregulating renal expression of URAT1 and GLUT9 [42].

Reynoutria japonica Houtt. is a diuretic and damp-permeating agent that was found by Ye *et al.* [43] to inhibit the expression of GLUT9, URAT1, and to increase OAT3 mRNA and promote uric acid excretion in a potassium oxyzincate plus adenine-induced model of hyperuricemia in rats. Chen *et al.* [44] found that polydatin, an active component of *Reynoutria japonica* Houtt., reduced serum uric concentration acid by inhibiting XOD activity and the expression of renal transporter proteins. Kong *et al.* [32] confirmed, by high-throughput screening and spectrophotometry, that resveratrol and cassimone-8-O-β-D-glucopyranoside, in a water extract of *Reynoutria japonica* Houtt., inhibited XOD [34].

Chinese herbal compounds to lower uric acid concentration

Wuling powder

Wuling Powder is a formula used to treat hyperuricemia. In a potassium oxonate-induced mouse hyperuricemia model, Ding *et al.* [14] showed that Wuling Powder reduced uric acid concentration by inhibiting mURAT1 and mGLUT9 (mouse glucose transporter 9) expression and reducing urate absorption. Wuling powder also increased urate secretion by upregulating mOAT1 (mouse organic anion transporter 1) expression.

Simiao powder

Simiao Powder is specifically used to treat the symptom of damp-heat downward injection. Qi *et al.* [45] collected 60 cases of gouty arthritis in patients and used clinical control observation. The control group was administered febuxostat tablets and the experimental group were administered febuxostat tablets supplemented with Simiao Powder. The control and experimental groups had a treatment effectiveness of 86.67% and 96.67%, respectively ($P < 0.05$). Zhang *et al.* [46] used adenine and yeast paste to establish a mouse model of hyperuricemia by gavage. Simiao Powder promoted uric acid excretion by upregulating the expression of ABCG2 and inhibiting uric acid reabsorption by downregulating the expression of GLUT9, thus producing a lowering uric acid effect. It also inhibited XOD activity and downregulated the mRNA and protein expression of XOD to improve hyperuricemia.

Danxi Tongfeng formula

Danxi Tongfeng Formula is used to treat gout, and was compared with celecoxib capsules by Shen *et al.* [47] in 68 gout patients. Blood sedi-

mentation rates and serum uric acid concentration were significantly reduced by both treatments. The duration of pain relief was significantly longer and the onset of action was significantly shorter with the Danxi Tongfeng Formula. However, the differences in the effectiveness between the two treatments were significant ($P < 0.05$). In an experimental potassium oxonate-induced hyperuricemia model, Duan *et al.* [48] showed that low, medium, and high doses of an aqueous extract of Danxi Tongfeng Formula significantly reduced serum uric acid in hyperuricemic mice compared with normal controls. The effect was dose-dependent and probably associated with inhibition of XOD activity.

Clinical studies of Jinlong Jiangniaosuan granule [49], Fufang Tufuling Keli [50], modified wuling powder [51], Tongfengyin granule [52], Baimao decoction [53], and modified Bixiefenqing decoction [54] have shown some clinical effect in lowering uric acid levels (**Table 3**). Ermiao pill [55], Liuwei Tongfeng decoction [56], Compound Tufuling Granules [57], Tongfengning [58], Qushi-Dizhuo decoction [59], Lonicera Japonica Gout Grain [60], Fangji Huangqi decoction [61], Qingxie Zhuodu formula [62], Cangzhu Baihu decoction [63], Gui-Zhi decoction [64], Bixiecheqianfuyi decoction [65], Wuzi Chengqi decoction [66], Huoxue Simiao decoction [67], Upper Middle Lower Generic Gout decoction [68] and modified Yinchen Wuling Powder [69] were found to have uric acid reducing effects in animal studies (**Table 4**).

Discussion

A literature search revealed some shortcomings of the published studies of Chinese medicine for lowering uric acid. First, the clinical reports are not standardized, there is a lack of multicenter clinical trials, and there are no systematic reviews, which limits the strength of the evidence to support clinical treatment guidelines. Research efforts should be increased to provide a richer and stronger basis for the use Chinese medicine to lower uric acid. Second, the research on the mechanism of lowering uric acid is not systematic. Systematic study of the proteases and transport proteins active in uric acid metabolism should be conducted to clarify the specific targets of Chinese medicine, especially the monomers, and to add to what we know of the mechanisms of action. Finally, comparative studies of Chinese and Western medicines are lacking. Western medicines have well-described mechanisms and curative effect for the lowering of uric acid. The medications have a fast onset, but problems such as rapid recurrence and serious side effects cannot be ignored. A few studies suggest that Chinese medicine has the advantages of long-lasting efficacy, low recurrence rates, and safety. However, there is a lack of in-depth studies on the effectiveness of Chinese medicine compared with Western medicine, for example, what is the specific onset of action time of the Chinese medicine? How long does the benefit last after discontinuation? What is the safety of long-term use? These questions should be explored in order to take advantage of the respective strengths of Chinese and Western medicines and to achieve better results in clinical use.

Syndrome differentiation and treatment are the embodiment and essence of Chinese medicine. With the modernization of Chinese medicine and the advancement of chemical separation methods, it is no longer possible to meet the needs of modernization of Chinese medicine by relying solely on compound research. Studies of small monomer components of Chinese medicine monomer may be a developmental trend in the future. By systematically studying the target of lowering uric acid and the effects of Chinese medicine monomers on uric acid metabolism, we can develop small compounds with greater efficacy and better safety. To take full advantage of Chinese medicine, clearly defined targets and substances are expected to bring a breakthrough in modernizing Chinese medicines for lowering uric acid [70].

In summary, a review of the efficacy and mechanisms of action of available studies shows that the advantages of Chinese medicine for lowering uric acid are becoming increasingly clear, and the clinical application of Chinese medicine is becoming more extensive. With the increasing annual incidence of hyperuricemia, we should expand our study of Chinese medicine for lowering uric acid. We look forward to more Chinese medicines that are effective

Table 3. The effect of compound on lowering uric acid in clinical research

Compound	Grouping	Observation indicators	Lowering uric acid efficacy
Jinlong Jiangniaosuan granule [49]	Control group (n=30): allopurinol 0.1 g once a day for 8 weeks; Treatment group (n=30): allopurinol + Jinlong Jiangniaosuan granule once a day for 8 weeks	serum uric acid, fasting blood glucose, blood lipids, routine blood, urine, blood rheology, body mass index and traditional Chinese medicine syndrome score were recorded before treatment and at week 4 and 8 after treatment	Treatment group↓ ($P < 0.05$)
Fufang Tufuling Keli [50]	Control group (n=20): health education, diet control; Short course group (n=20): 1 course of treatment in 20 days with 10 days between courses for 3 months, followed by 9 months of basic treatment; Long course group (n=20): In addition to the short course of treatment, one course of 10 days from month 4, with an interval of 20 days between courses, and a further 9 courses of oral treatment at the same dose as in the short course group, for a total of 12 months	serum uric acid level, blood and urine routine, liver and kidney function were measured at the 3rd and 12th months after treatment	Long course group↓
modified wuling powder [51]	Control group (n=40): benzbromarone 50 mg once a day for 12 weeks; Treatment group (n=40): modified wuling powder; for 12 weeks; follow-up	Serum uric acid levels were measured before treatment, at 4 weeks, 8 weeks, 12 weeks and at 4 weeks and 12 weeks after discontinuation of treatment. Blood, urine, stool and liver and kidney function were checked once before and after treatment	A short period: benzbromomarone > modified wuling powder; Stable and lasting: modified wuling powder > benzbromomarone.
Tongfengyin Granule [52]	Control group (n=50): benzbromarone 50 mg once a day for 4 weeks; Treatment group (n=50): Tongfengyin Granule for 4 weeks	Serum uric acid levels were measured before and after treatment and liver and kidney function was reviewed regularly on a monthly basis	Tongfengyin Granule = benzbromarone
Baimao decoction (as a tea substitute) [53]	Before medication: lifestyle intervention; After medication: lifestyle intervention + Baimao decoction	Traditional Chinese medicine symptom score, uric acid, liver function, kidney function, blood lipid and glycosylated haemoglobin test before and after medication, followed up after 1 month and 3 months respectively	after medication > before medication ($P < 0.05$)
modified Bixiefenqing decoction [54]	Control group (n=25): allopurinol tablets, 100 mg, 2 times a day; 6 weeks/a course Treatment group (n=25): modified Beixiefenqing decoction; 6 weeks/a course	Changes of serum uric acid before and after treatment and after 3 and 6 months of drug withdrawal; changes of liver function, blood routine, urine routine, etc. before and after treatment	treatment group > control group ($P < 0.005$)

Table 4. The mechanism of compound for lowering uric acid in basic research

Compound	Model	Mechanism of Action
Ermiao pill [55]	Potassium oxonate model	XOD activity↓, URAT1↓
Wuling powder [14]		URAT1↓, GLUT9↓, OAT1↑
Gui-Zhi decoction [64]		XOD activity↓, URAT1↓, GLUT9↓, ABCG2↑
Danxi Tongfeng formula [47]		XOD activity↓
Qingxie Zhuodu formula [62]		XOD activity↓
Fangji Huangqi decoction [61]		OAT1↑, OAT3↑, ABCG2↑
Huoxue Simiao decoction [67]	Adenine, ethambutol model	XOD activity↓
Upper Middle Lower Generic Gout decoction [68]		XOD activity↓, ADA activity↓
Modified Yinchen Wuling powder [69]		
Tongfengning [58]		URAT1↓, GLUT9↓, OAT1↑, ABCG2↑, OAT3↑
Lonicera Japonica Gout Grain [60]		XOD activity↓
Cangzhu Baihu decoction [63]		
Compound Tufuling Granules [57]	Potassium oxonate, yeast extract model	XOD activity↓, GLUT9↓
Bixiecheqianfuyi decoction [65]		XOD activity↓
Qushi-Dizhuo decoction [59]	Adenine, potassium oxonate model	XOD activity↓, URAT1↓, GLUT9↓, OAT1↑, ABCG2↑
Wuzi Chengqi decoction [66]		XOD activity↓
Simiao San [46]	Adenine, yeast extract model	XOD activity↓, GLUT9↓, ABCG2↑
Liuwei Tongfeng decoction [56]	Adenine model	XOD activity↓

XOD: xanthine oxidase; URAT1: urate anion transporter 1; GLUT9: glucose transporter 9; OAT1: organic anion transporter 1; OAT3: organic anion transporter 3; ABCG2: ATP Binding Cassette Subfamily G Member 2.

and safe for treating patients with hyperuricemia.

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Disclosure of conflict of interest

None.

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