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REVIEW ARTICLE

Traditional herbal medicine for hyperuricemia: a review of randomized clinical trials

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ABSTRACT

In the last decades, traditional herbal medicine for gout has been rapidly advanced. Numerous herbs have been identified for their hypouricidal effect. This review aims to explain the potential and mechanisms of traditional herbal medicine in reducing serum uric acid (sUA). This review included five RCTs and four traditional herbal medicine formulas from a previous systematic review. Articles published in non-English language were excluded for further analysis. Despite limited RCTs design, the formula of Chuanhu; Tufu, and ZinutriK® were beneficial for hyperuricemic individuals. While Yellow-dragon Wonderful-seed mixture showed limited hypouricemic feature. Based on these findings, traditional herbal medicine holds promising potential in treating hyperuricemia and gout. However, further studies are required.

1. Introduction

Uric acid (UA) is the final bio-product of purine catabolism. Both endogenous and exogenous purine undergo a complex degradation process, resulting in UA. One key enzyme in this process is xanthine-oxidase (XOD), which converts hypoxanthine into xanthine and xanthine into UA. Subsequently, the UA is excreted in urine and partly in feces. The production and excretion determine UA level in the serum (sUA) (Maiuolo *et al.,* 2016).

The UA has low solubility in water. A 6.8 mg/dL sUA concentration is associated with crystal formation in the tissue such as joints and kidneys (Hyndman, Liu and Miner, 2016; Maiuolo *et al.,* 2016). The most common form of crystal is monosodium urate (MSU). Deposition of MSU in the joints could initiate inflammatory state or gout. MSU deposits in the kidney are associated with kidney stone formation (Martillo, A. Recent and Crittenden, 2014). A recent study also discovered UA role in the development of metabolic diseases such as diabetes, hypertension, and metabolic syndrome.

In the last decades, traditional hahas rapidly advanced and been identified for its hypouricemic effect. In a systematic review by Chen *et al.* (2021), 194 articles were identified. Marvelously, statistical analysis of these studies concluded that traditional herbal medicine had to promise a uric acid reduction in hyperuricemic individuals (standardized mean difference: -1.65, 95%CI: -3.09—-0.22, p=0.021). Further analysis showed no substantial difference in the hypouricemic feature

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of traditional herbal medicine compared to standard Western medicine (standardized mean difference: -0.13, 95%CI: -0.99—0.74, p=0.772). Unfortunately, the study did not clearly explain the sUA-lowering mechanisms of traditional herbal medicine. This review aims to explain the potential and mechanisms of traditional herbal medicine in reducing sUA.

2. Methods

This review was constructed based on a recent systematic review published by Chen *et al.* (2021). The systematic review described numerous herbs that had been used for hyperuricemia. However, detailed mechanisms were not explained. This review only included RCT, which was published in the last ten years.

The literature search for supporting data was conducted on PubMed and Google Scholar in July 2022. The Boolean operators ("AND," "OR," and "NOT") were applied to filter the search. Due to authors' language limitation, articles published in non-English language were excluded for further analysis.

3. Results

Based on our criteria, we included five RCTs evaluating the following herbal medicine for hyperuricemia: Chuanhu, Yellow-dragon Wonderful-seed; Tufuling, and ZinutriK®

3.1. Chuanhu Mixture

Chuanhu mixture is a traditional Chinese herbal medicine developed by a research group in China. The group claimed that the Chuanhu mixture had been utilized to treat more than 1000 gout cases with high efficacy and safety since 1999. Substantially, the Chuanhu mixture received a Chinese invention patent in 2000 (CN1857317A) (Wang *et al.,* 2014; You *et al.,* 2019).

Generally, Chuanhu is composed of nine to ten different herbs. An RCT by Wang *et al.* (2019) produced Chuanhu-mixture with the following formula: Rhizome Dioscorea nipponica (15g), Rhizoma polygoni cuspidati (15 g), Caulis lonicerae (30 g), Radix saposhnikoviae (15 g), Radix clematidis (15 g), Rhizoma smilacis glabrae (15 g), Radix cyathulae (15 g), Rhizoma ligustici chuanxiong (15 g), Rhizoma dioscoreae hypoglaucae (12 g), Fructus chaenomelis (15 g), Radix glycyrrhizae (6 g), and sodium alginate (1 g). The detailed production process is described in the respective publication.

To date, two RCTs explored the Chuanhu mixture for lowering serum uric acid (sUA) in gout patients. The first RCT by Wang *et al.* in 2014 compared Chuanhu mixture with Colchicine in 176 acute gout cases (Wang *et al.,* 2014). The Chuanhu group received 250 mL of Chuanhu mixture, while the Colchicine group received an initial dose of 0.5 mg Colchicine twice a day for the first three days and once a day in further treatment. All patients received 60 mg of Etoricoxib to reduce pain for ten days and observed for 12 weeks. Interestingly, the Chuanhu mixture outperformed the Colchicine in reducing sUA with a mean reduction of 1.06 ± 0.71 mg/dL (vs 0.49 ± 0.73 mg/dL, p<0.001). Subsequently, the Chuanhu mixture showed marked reduced liver transaminases and serum creatine, yet no significant changes in blood urea nitrogen. This might indicate that the Chuanhu mixture had a protective effect on the liver and kidneys.

The later RCT by Wang *et al.* (2019) compared Chuanhu mixture with Allopurinol and Placebo in 195 chronic gout cases. Like the previous RCT, the Chuanhu mixture received 125 mL of the mix twice daily. The allopurinol group received 100 mg of Allopurinol three times a day, and the placebo group received a placebo agent mimicking the Chuanhu mixture and Allopurinol. All patients received the intervention for eight weeks and 30 mg of Etoricoxib. The sUA reduction by the Chuanhu mixture was superior to the Allopurinol and Placebo group. The average decrease in sUA by Chuanhu in 8 weeks was 2.86 ± 0.82 mg/dL, while Allopurinol and Placebo were 1.18 ± 0.35 and 0.44 ± 0.39 mg/dL, respectively (p<0.05). In addition, the eGFR in the Chuanhu mixture was higher than in other groups (p<0.05).

Along with its efficacy, the Chuanhu mixture also had fewer side effects. The rate of gastrointestinal side effects was significantly lower in participants receiving Chuanhu compared to Colchicine (2.27% vs 28.41%, p<0.001) (Wang *et al.,* 2014). The notable adverse effects of the Chuanhu mixture are its bitter taste, mild diarrhea, and nausea in some patients. Therefore, a granule formulation was developed to enhance patient adherence. The latest study on animal models gracefully showed the possible mechanism of the Chuanhu mixture in reducing sUA (You *et al.,* 2019). A high dose of Chuanhu mixture (10.75 g/mL) significantly suppressed hepatic xanthine-oxidase (XOD) levels in the hyperuricemic model. In addition, a medium (5.4 g/mL) and high dose of Chuanhu mixture significantly reduced URAT1 mRNA levand with lower serum creatinine than the control group. These findings indicated that the Chuanhu mixture suppressed the production and promoted the excretion of uric acid.

3.2. Yellow-dragon Wonderful-seed Mixture

Based on TCM theory, gout is caused by "dampness-heat pouring downward." Followingly, a diuretic is considered a method to relieve this dampness. The typical TCM formula for diuretic is "Two Wonderful Herbs Powder" (2WHP) consisting of Phellodendron chinense cortex (15 g) and Atractylodes

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lancea rhizome (15 g) (Kong *et al.,* 2004). Later, three and four WHPs were developed by adding Cyathula officinalis radix and Cyathula officinalis radix-Coix lacryma-jobi seeds, accordingly.

Yellow-dragon Wonderful-seed (YW) mixture is a modification of 4WHP formulation (Phellodendron chinense cortex [10 g], Atractylodes lancea rhizome [9 g], Cyathula officinalis radix [10 g], and Coix lacryma-jobi seeds [20 g]) with the addition of Pheretima (10 g) and Cardamom (6 g). The authors named this mixture yellow-dragon since the bark of Phellodendron is yellowish, and Pheretima is called "earth dragon" in Chinese (Yu *et al.,* 2018).

A pilot RCT was conducted in 72 hyperuricemic individuals and randomly enrolled into three groups: YW, YW + gypsum, and Allopurinol. The YW mixture was given orally three times daily (decoction of 100 mL) for four weeks with/without adding 15 g of gypsum fibrosum daily. The Allopurinol group received an initial dose of 100 mg/24 hours for one week, followed by 200 mg/24 hours during the follow-up period. Unfortunately, the YW and YW + gypsum groups exhibited no significant hypouricemic effect (p>0.05). However, the urate concentration in the urine was decreased in all groups (p<0.05). This reduction was more prominent in the YW + gypsum group compared to the YW group (p<0.05) (Yu *et al.,* 2018).

On the contrary, a meta-analysis on Simiao (type of 4WHP) showed different findings. The Simiao comprises Atractylodis rhizome, the Phellodendri cortex, Achyranthis Bidentatae radix, and Coix lacryma-jobi. A minor modification of Simiao was made based on the TCM principle to treat other comorbidity of gout. The overall analysis demonstrated the superiority of modified Simiao decoction towards anti-inflammatory medication, urate-lowering drugs, and combined therapy in reducing sUA (mean difference: -68.02, 95%CI: -90.97—-45.07, p<0.001). The hypouricemic effect of Simiao was more prominent compared to anti-inflammatory medication (mean difference: -90.62, 95%CI: -128.38—-52.86, p<0.001) and urate-lowering drugs (mean difference: -91.43, 95%CI: -122.38—-60.49, p<0.001). Despite this extraordinary outcome, the included studies had poor methodology based on risk of bias assessment (Liu *et al.,* 2017).

A study in the gout animal model revealed the possible mechanism of Simiao in sUA regulation. Simiao had unique regulation in uric acid production. Low- and medium-dose Simiao significantly reduced XOD, while high-dose Simiao negatively affected adenosine deaminase (ADA) activity (Lin *et al.,* 2020). Inversely, another in vivo study revealed the hypouricemic effect of Simiao was not associated with significant XOD suppression (Xu *et al.,* 2022). Further studies are required to elucidate this inconsistent result.

3.3. Tufuling Mixture

Smilax glabra, or Tufuling in Chinese, is a common medicinal herb for various diseases such as infection, kidney inflammatory diseases, and gout. Tufuling mixture, well-known as Qu-Zhuo-Tong-Bi, is made from the following herbs: Smilax glabra rhizome (30 g), Dioscoreae collettii rhizome (30 g), Curcuma longa (12 g), Herba siegesbeckiae (18 g), Corydalis rhizome (18 g), Coix seeds (30 g), Loranthus parasiticus (15 g), and Stigma maydis (15 g) (Xie *et al.,* 2017). In another study, sixty grams of Tufuling were used instead of thirty grams (Lv *et al.,* 2019).

A double-blind RCT was carried out in 2012-2013 to explore the hypouricemic feature of the Tufuling mixture. A total of 210 patients were included and randomly assigned to the Tufuling and placebo group with a ratio of 2:1. The Tufuling mixture was decocted (1:8 water/volume) and given twice daily (each 250 mL). At the end of week 12, the mean sUA reduction of the Tufuling group was 12.76% or 1.25 mg/dL compared to the placebo group, with 4.57% or 0.48 mg/dL reduction (p=0.004). The ruling mixture also showed fewer adverse events and fewer leukopenia events than the placebo group (p=0.033) (Xie *et al.,* 2017).

Studies in hyperuricemic mice demonstrated two possible mechanisms of Tufuling mixture in ameliorating hyperuricemia. First, the Tufuling mixture rebalances the intestinal microbiota, specifically butyrate-producing bacteria, which upregulates ABCG2 (urate transporter in the intestine). Therefore, it facilitates uric acid fecal excretion (Wen *et al.,* 2021). The second mechanism relates to the primary active compound in Smilax glabra, Astilbin (0.1174 mg/g). The hypouricemic activity of Astilbin was associated with the alteration of XOD activity and enhancement of uric acid transporters in the kidney, such as OAT1, OCTN2, and their associated mRNAs (Huang *et al.,* 2019).

3.4. ZinutriK®

ZinutriK® is an antioxidant nutraceutical product by Akademy Pharma. Each ZinutriK® contains a fixed dry extract dose of 250 mg Gingko Biloba leaf, 167 mg Scutellaria baicalensis root, 100 mg green coffee seeds, and 50 mg rutin. Focusing on the active compounds, each pill is equivalent to 10 mg kaempferol, 50 mg baicalin, 10 mg chlorogenic acid, and 4.5 mg caffeine. One small RCT, PICONZ-UA Study, examined the effect of ZinutriK® towards sUA among individuals with hyperuricemia. The study used a cross-over design with sixteen hyperuricemic individuals. Administration of ZinutriK® for four weeks significantly reduced the

Table 1. The mechanisms of uric acid reduction by traditional herbs

Name of Herbs/Formula	Mechanisms of Action	Effect on Serum Uric Acid
Chuanhu	Inhibition of hepatic xanthine-oxidase (XOD) and reduced uric acid reabsorption in the kidney by reduced URAT1 activity.	Significant reduction compared to Colchicine, Allopurinol, and placebo.
Yellow-dragon Wonderful-seed	Inhibition of XOD and possibly adenosine deaminase (ADA) at higher doses.	No significant reduction in serum uric acid compared to Allopurinol.
Tufuling	Uric acid fecal excretion via ABCG2 transporter, inhibition of XOD, and promoting urine excretion by OAT1 and OCTN2 transporters.	Significant reduction compared to placebo.
ZinutriK®	Inhibition of XOD, fecal excretion via ABCG2, and urinary excretion by SLC2A9v2, RST, OAT1, and UAT transporters.	Significant reduction compared to placebo. Yet, the final serum uric acid remained high.

sUA level from 7.9 ± 0.9 mg/dL to 7.0 ± 0.7 mg/dL (p=0.006) (Rozza *et al.,* 2016). Despite a significant reduction, the sea level was still high.

A study in hyperuricemic mice showed that 5 mg/kg Kamferol inhibited XOD activity by 31.32% (Haidari *et al.,* 2011). Similarly, baicalin also inhibits the activity of XOD. The computational model suggested that baicalin binds to XOD in a dose-dependent fashion, yet baicalin did not influence the expression of XOD (Meng *et al.,* 2017). Meanwhile, chlorogenic acid affected both the production and excretion of uric acid. The chlorogenic acid inhibited XOD activity and enhanced OAT1 and ABCG2 transporter expression (Zhou *et al.,* 2021). Finally, rutin was known to regulate uric acid transporters in the kidney, such as renal SLC2A9v2, RST, OAT1, and UAT (Hu *et al.,* 2009). All mechanisms are summarized in Table 1.

4. Conclusions

Based on published RCTs, Chuanhu mixture, Tufuling, and ZinutriK® can potentially reduce sUA among hyperuricemic individuals. Yet, most RCTs had a low sample size and included only Chinese descendants. Further, RCT with a larger sample size and more diverse individuals are needed to validate the findings.

Conflict of interest

All authors have no conflict of interest in this article.

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