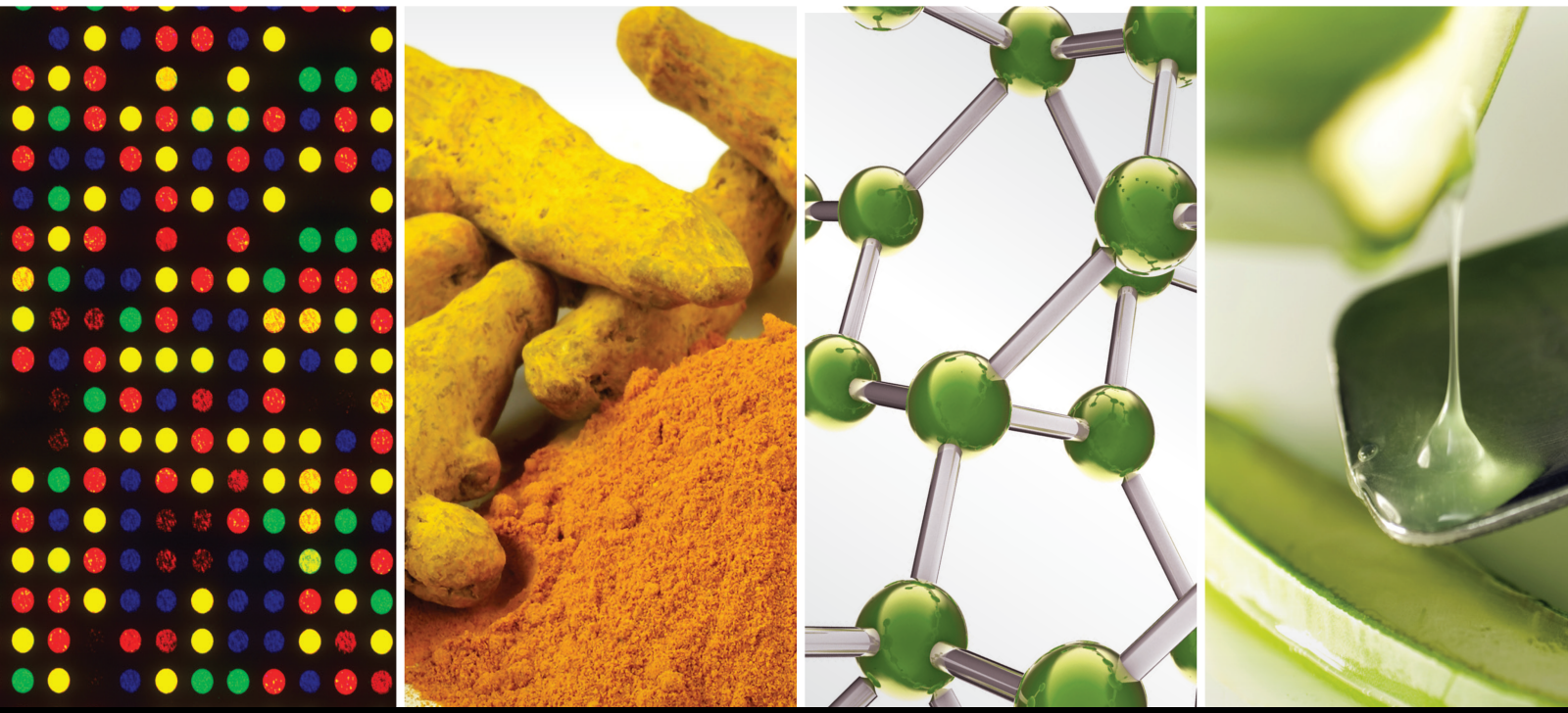
Evidence-Based Complementary and Alternative Medicine

Treatment of Hyperuricemia and Gout-related Diseases with Complementary and Alternative Medicine

Lead Guest Editor: Yafei Liu
Guest Editors: Shenghao Tu, Chunsheng Zhu, and Jingjing Cheng



Treatment of Hyperuricemia and Gout-related Diseases with Complementary and Alternative Medicine

Evidence-Based Complementary and Alternative Medicine

Treatment of Hyperuricemia and Gout-related Diseases with Complementary and Alternative Medicine

Lead Guest Editor: Yafei Liu
Guest Editors: Shenghao Tu, Chunsheng Zhu, and Jingjing Cheng

Chief Editor

Associate Editors

Academic Editors

Contents

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 3363064, 8 pages
https://doi.org/10.1155/2022/3363064

Research Article

Clinical Observation on Therapeutic Effect of Electroacupuncture Combined with Diclofenac Sodium in Treatment of Acute Gouty Arthritis: A Randomized Controlled Study

Lumin Liu, Ping Yin, Junwei Hu, Xu Li, and Yuelai Chen

Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China

Correspondence should be addressed to Yuelai Chen; chenyuelai@163.com

Received 9 June 2022; Accepted 6 August 2022; Published 29 August 2022

Academic Editor: Chunsheng Zhu

Objective. To observe the clinical effect of electroacupuncture (EA) combined with diclofenac sodium (DS) in the treatment of acute gouty arthritis (AGA). *Methods*. Patients with AGA were randomly divided into three groups: the EA + DS treatment group (i.e., EA + DS group), the low-dose DS treatment group (i.e., low-dose DS group), and the conventional-dose DS treatment group (i. e., conventional DS group). Patients in the low-dose DS group took 50 mg of DS sustained-release capsules once a day. Patients in the conventional DS group took 100 mg of DS sustained-release capsules once a day. Patients in the EA + DS group were treated with EA three times in 7 days combined with 50 mg of DS sustained-release capsules once a day. For all the three groups, 7 days were regarded as a course of treatment. Outcome indicators included pain visual analog scale (VAS), joint tenderness, joint swelling and activity limitation, and levels of inflammatory indicators (C-reactive protein (CRP)/white blood cells (WBC)/percentage of neutrophils (NE%)), level of serum uric acid (SUA), gout impact scale (GIS), and frequency of adverse reactions). *Results*. After a course of treatment, indicators regarding the VAS, joint tenderness, joint swelling, activity limitation, GIS, inflammatory indicators (CRP/WBC/NE%), and SUA were all improved ($P < 0.05$) with no adverse reactions in the EA + DS group. The EA + DS group performed better than the low-dose DS group in improving indicators regarding the VAS, joint tenderness, activity limitation, GIS, inflammatory markers (WBC/NE%), and SUA ($P < 0.05$). Similarly, the EA + DS group performed better than the conventional DS group in improving indicators regarding GIS, SUA, and adverse reactions ($P < 0.05$). *Conclusion*. EA combined with DS can improve AGA patients' joint pain and functional status, thus improving their quality of life. Moreover, this combined treatment can reduce the levels of inflammatory markers and SUA, leading to fewer adverse reactions in AGA patients.

1. Introduction

Gouty arthritis (GA) is a disease caused by the deposition of monosodium urate in joints due to disturbance of purine metabolism and/or decreased uric acid excretion. In the acute stage, GA is mostly manifested by sudden redness, swelling, heat, pain, and activity limitation of a single metatarsophalangeal joint (especially the first metatarsophalangeal joint), and the symptoms often involve other joints of the feet and the ankles [1].

Epidemiological surveys show that the prevalence of GA is increasing year-by-year [2]. The National Health and Nutrition Examination Survey found that between 2015 and 2016 there were 9.2 million adults diagnosed with GA in the United States [3]. In the United Kingdom, the prevalence of GA increased from 1.4% in 2005 to 2.5% in 2015 [4, 5]. GA has become the second-largest metabolic disease in China, with about 14 million people diagnosed every year [6]. During acute GA (AGA) attacks, the severe or unbearable pain can result in activity limitation, seriously affecting patients' physical and mental health as well as their quality of life [7, 8]. Besides, AGA imposes an economic burden on individuals and society [9].

In Western medicine, treatment of AGA is mainly based on drug therapy, including nonsteroidal anti-inflammatory drugs (NSAIDs), colchicines, and glucocorticoids [1].

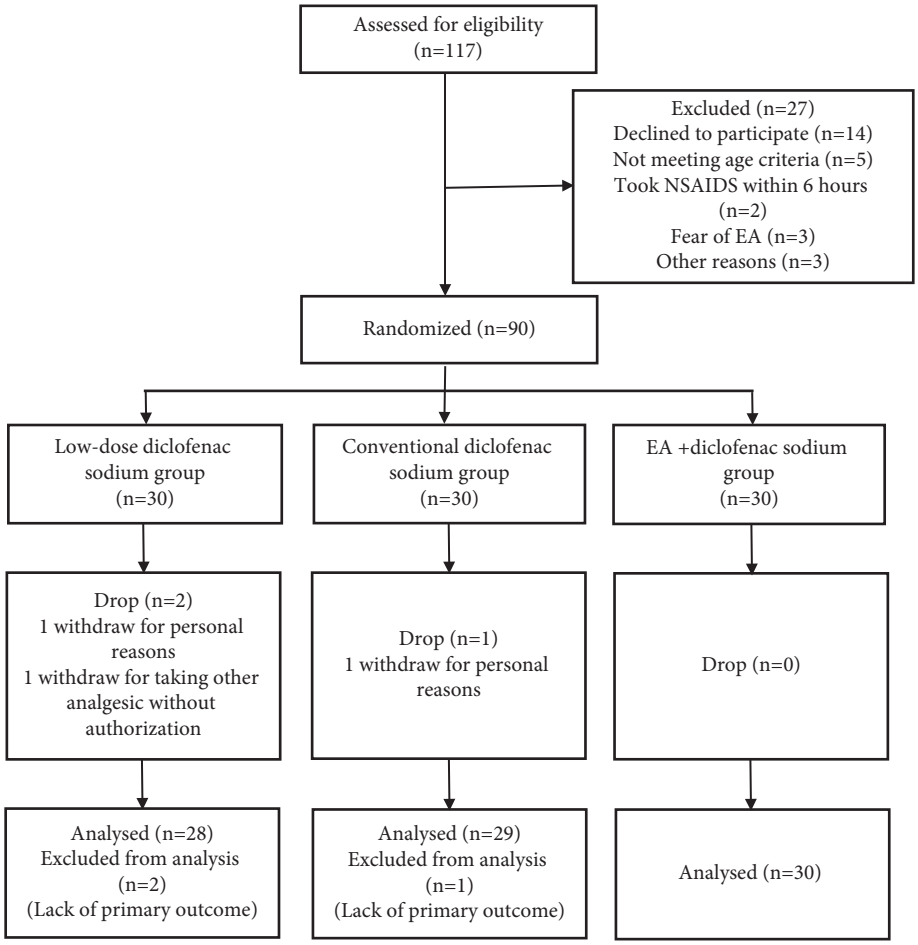


Figure 1: Flow chart of the study process.

Among them, NSAIDs are typically used as the first-line drugs, such as diclofenac sodium (DS) and indomethacin. Studies have shown that DS can improve joint pain and swelling, reduce levels of prostaglandin, interleukins, tumor necrosis factors, and other inflammatory factors in patients with AGA [10]. However, the main concern for the clinical practice of DS is the adverse reactions. A study on facet joint pain showed that adverse reactions, including nausea, vomiting, diarrhea, edema, and anaphylaxis, occurred during the administration of DS, the occurrence of which was higher in patients treated with higher doses [11]. Due to these adverse reactions, patients may stop taking the drugs. Therefore, an effective and multimodal therapy with fewer adverse reactions is urgently needed.

As a modern acupuncture therapy, electroacupuncture (EA) has been widely recognized for its analgesic effect [12, 13]. Preliminary studies have confirmed the effectiveness of EA in the treatment of AGA, including improvement of pain, swelling, and activity limitation [14]. However, the existing randomized controlled trials (RCTs) published might be biased or of low quality. For example, generation and concealment of allocation sequence and blind implementation were not mentioned or properly carried out in some of these existing RCTs. In addition, none of these RCTs explored whether EA combined with NSAIDs could reduce the dosage of analgesic drugs and its adverse reactions during AGA treatment. Considering these limitations in existing RCTs, the current research was designed to provide a more effective clinical solution for AGA treatment with fewer adverse reactions.

2. Methods

This RCT was conducted in Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated to Shanghai University of Traditional Chinese Medicine in Shanghai, China, from October 2020 to February 2021. The trial was registered at the Chinese Clinical Trial Registry (ChiCTR2000039458) and approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200279). Written informed consent was obtained from all participants. The RCT was carried out following the flow diagram shown in Figure 1.

2.1. Inclusion and Exclusion Criteria. The inclusion criteria are as follows:

(i) Those aged between 35 and 70 years

(ii) Male patients

(iii) The symptoms meet the GA diagnostic criteria jointly formulated by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2015

(iv) The symptoms comply with the diagnostic criteria of AGA in the "Traditional Chinese Medicine Syndrome Diagnosis and Efficacy Criteria" [15] promulgated by the State Administration of Traditional Chinese Medicine in 2012 and belong to the dampness-heat amassment pattern

(v) The symptoms involve unilateral first metatarsophalangeal joint and/or foot (nonfirst metatarsophalangeal) joint and/or ankle joint

(vi) The acute attack occurred within 24 hours when admitted to the hospital, and the visual analog scale (VAS) is greater than or equal to 4

The exclusion criteria are as follows:

(i) Patients allergic to NSAIDs

(ii) Patients who had a pacemaker installed, allergic to metal, or had a severe fear of needles

(iii) Patients who received acupuncture treatment within one week before treatment

(iv) Patients who have used any drugs for the treatment of AGA within one month before treatment

(v) Patients with active gastrointestinal diseases or those who had peptic ulcers within 30 days before participating in this study

(vi) Patients with primary severe diseases in the heart, brain, liver, kidney, hematopoietic system, or those with mental illness

2.2. Sample Size Calculation. According to the preliminary experimental results, the variation of VAS from baseline to treatment completion in the EA + DS group, conventional DS group, and low-dose DS group were 5.00 ± 0.38, 4.70 ± 0.82, and 3.60 ± 1.41, respectively. According to the calculation formula, $n = \varphi^2 (\sum s_i^2/g)/(\sum (\overline{X_l} - \overline{X})^2/(g-1))$ [16], each group requires 25 cases ($\alpha = 0.05$, $\beta = 0.1$). Considering the 15% dropout rate, each group requires 30 cases. Thus, a total of 90 cases are needed.

2.3. Randomization and Blinding. According to random numbers generated by SPSS 26.0 software, 90 patients were assigned to the EA + DS group, conventional DS group and low-dose DS group at a ratio of 1 : 1 : 1. All information regarding random sequence used for the grouping was sealed in a separate light-tight envelope, which could not be opened until each patient's enrollment. Criteria evaluation and clinical information collection of patients were performed by information collection personnel, and statistical data analyses were performed by specialized statisticians. The information collection personnel and statisticians were blinded to each other. Grouping was performed by special grouping personnel, and the grouping information was blinded to the information collection personnel and statisticians. Based on the characteristics of this study, patients and acupuncturists could not be blinded.

2.4. Clinical Grouping and Intervention Methods

2.4.1. Low-Dose DS Group. Patients took DS sustained-release capsules (trade name: Yingtaiqing, 50 mg, produced by Simcere Pharmaceutical Co., Ltd., batch no. H20023856) orally, 50 mg each time, once per day. 7 days were regarded as a course of treatment.

2.4.2. Conventional DS Group. The drug used and course of treatment was the same as above, except for those who took 100 mg of the capsules orally once per day.

2.4.3. EA + DS Group. For the EA + DS group, patients were treated with EA once every three days (3 times in total), while at the same time, they were treated with DS the same as in the low-dose DS group, with 7 days as a course of treatment.

All acupuncture manipulations were performed by an acupuncturist with TCM qualification and rich experience. The patients received acupuncture treatments on the affected side at the Ashi, Dadu (SP2), Taichong (LR3), Taibai (SP3), Neiting (ST44), Sanyinjiao (SP6), Zusanli (ST36), and Yinlingquan (SP9) points. In order to prevent fainting during acupuncture treatment, the acupuncturist explained the procedures to the patients and comforted them during the treatment. The acupuncture would be avoided when the patients were hungry. The skins of the acupoints were disinfected with 75% alcohol, and then two types of acupuncture needles (Huatuo disposable sterile stainless steel acupuncture needles, Suzhou Huatuo Medical Equipment Co., Ltd.) were used for acupuncture treatment. Specifically, a 0.25*25 mm needle was inserted straight into the Ashi (5–10 mm), SP2 (5–10 mm), ST44 (5–10 mm), LR3 (10–15 mm), and SP3 (10–15 mm) acupoints. A 0.25*40 mm needle was inserted straight into the SP6 (20–25 mm), ST36 (20–30 mm), and SP9 (20–30 mm) acupoints. When directly inserted into the skin, the needle was manipulated clockwise and counterclockwise to obtain a sense of "Deqi," which was then connected to the EA instrument (Huatuo G6805-II electroacupuncture instrument, Shanghai Medical Electronic Instrument Physiotherapy Branch), with LR3 and ST36 as a group and SP9 and SP6 as another group. For the EA, the wave was a continuous wave, the frequency was 2 Hz, and the current was 1–5 mA (to a degree when the skin is shaking slightly at the acupoints but the patient did not feel pain). The needles were kept in the acupoints for 30 minutes.

2.5. Outcome Indicators and Observation Time. Primary outcomes included VAS and its variation from baseline to treatment completion. Secondary outcomes included joint tenderness, joint swelling, activity limitation, gout impact scale (GIS) [17], levels of C-reactive protein (CRP), white blood cells (WBC), percentage of neutrophils (NE%), serum

uric acid (SUA), and their variation from baseline to treatment completion. All these indicators were observed before treatments (i.e., baseline) and after treatments. In addition, adverse events and safety observation of EA were documented throughout the trial.

2.6. Data Analysis. SPSS 26.0 software was used for all data analyses. For intragroup comparisons, a paired-sample *t*-test was used for measurement data that conformed to a normal distribution, and otherwise, the Wilcoxon nonparametric test was used. For intergroup comparison, one-way ANOVA was used for measurement data that conformed to a normal distribution, and otherwise, the Kruskal–Wallis nonparametric test was used. The test standard was $\alpha = 0.05$, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographics and Baseline Results. A total of 117 patients were screened in this study, and a total of 90 patients who met the inclusion criteria were finally included, with 3 patients dropping out during the treatment. The dropout reasons are shown in the flow chart (Figure 1). Thus, 87 cases were actually included in the study, including 28 cases in the low-dose DS group, 29 cases in the conventional DS group, and 30 cases in the EA + DS group. In general, there were no differences regarding age, body mass index (BMI), and disease duration among the three groups ($P > 0.05$). In terms of outcome indicators, there were no differences at baseline among the three groups ($P > 0.05$) (Table 1).

3.2. Indicators Like VAS, Joint Tenderness, Joint Swelling, and Activity Limitation. Intragroup analyses showed significant improvements regarding VAS, joint tenderness, joint swelling, and activity limitation after treatment compared to baseline in all three groups($P < 0.05$). After treatment, VAS, joint tenderness, joint swelling, activity limitation, and their variation from baseline to treatment completion in the EA + DS group and conventional DS group were all lower than those in the low-dose DS group ($P < 0.05$), except for the variation of joint swelling. There were no differences regarding these indicators between the EA + DS group and the conventional DS group ($P > 0.05$) (Table 2).

3.3. GIS. The GIS has a total of 24 questions, which can be classified into five dimensions: gout concern overall, gout concern during attack, well being during attack, unmet gout treatment need, and gout medication side effects.

Intragroup analyses showed no differences regarding gout concern overall and unmet gout treatment need in all three groups ($P > 0.05$). Gout concern during the attack in the EA + DS group was reduced ($P < 0.05$). Well-being during the attack was improved in the EA + DS group ($P < 0.05$), while it was worsened in the low-dose DS group ($P < 0.05$). Gout medication side effects in both the EA + DS group and the low-dose DS group were fewer than those at baseline ($P < 0.05$). Besides, no differences were observed regarding other indicators with the intragroup analyses.

After treatment, regarding gout concern overall, there was no difference between the three groups ($P > 0.05$). Regarding gout concern and well-being during the attack, posttreatment values and variation from baseline to treatment completion in the EA + DS group had significant differences compared to those in the conventional DS group and the low-dose DS group ($P < 0.05$). Regarding unmet gout treatment need, posttreatment value and variation from baseline to treatment completion in the EA + DS group and the conventional DS group were significantly different compared to those in the low-dose DS group ($P < 0.05$). Regarding gout medication side effects, posttreatment value and variation from baseline to treatment completion in the EA + DS group had significant differences compared to those in the conventional DS group and the low-dose DS group ($P < 0.05$), except for the variation between the EA + DS group and the low-dose DS group. Besides, no differences were observed regarding other indicators with the intergroup analyses (Table 2).

3.4. Inflammatory Indicators. Intragroup analyses showed that the levels of CRP were lower after the treatment than those at baseline in all three groups ($P < 0.05$). After treatment, no differences were observed regarding the level of CRP and its variation from baseline to treatment completion between all three groups ($P > 0.05$).

Intragroup analyses showed that the levels of WBC and NE% in the EA + DS group and the conventional DS group were lower after treatment compared to those at baseline ($P < 0.05$). After treatment, levels of WBC, NE%, and their variation from baseline to treatment completion were greater in the EA + DS and the conventional DS group than those in the low-dose DS group ($P < 0.05$), while there were no differences between the EA + DS group and the conventional DS group ($P > 0.05$) (Table 2).

3.5. SUA. Intragroup analyses showed that the level of SUA was lower after the treatment compared to that at baseline in the EA + DS group ($P < 0.05$). After treatment, no differences were observed regarding the level of SUA between all three groups ($P > 0.05$), while the variation from baseline to treatment completion was greater in the EA + DS group than that in the conventional DS group and the low-dose DS group ($P < 0.05$). Besides, there were no differences between the conventional DS group and the low-dose DS group ($P > 0.05$)(Table 2).

3.6. Adverse Reactions. During the treatment, there were 2 cases of adverse reactions in the low-dose group, both of which had the symptom of loss of appetite. There were 4 cases of adverse reactions in the conventional DS group, including 1 case with nausea and anorexia, 1 case with anorexia, 1 case with abdominal distension, and 1 case with chest tightness. Mild symptoms were monitored and treated, and all the symptoms disappeared within 4 days. There were no adverse reactions in the EA + DS group.

Table 1: Summary of demographics and baseline.

Group	EA + DS group ($n = 30$)	Low-dose group ($n = 28$)	Conventional group ($n = 29$)	P
Age	58.00 (46.00, 67.00)	58.00 (42.75, 62.00)	55.00 (44.00, 67.50)	0.609
BMI	25.15 ± 1.84	25.41 ± 1.55	25.86 ± 2.06	0.326
Disease duration	11.00 ± 6.68	9.86 ± 5.99	10.72 ± 6.57	0.782
VAS	7 (6, 7)	7 (6, 7)	7 (6, 7)	0.680
Joint tenderness	2 (2, 2)	2 (1.25, 3)	2 (2, 3)	0.527
Joint swelling	2 (1, 2.25)	2 (1, 2)	2 (1, 2)	0.974
Activity limitation	6.70 ± 2.15	6.43 ± 2.22	6.79 ± 2.72	0.835
GIS				
Gout concern overall	237.50 ± 75.93	255.36 ± 71.15	255.17 ± 58.77	0.525
Gout concern during attack	241.67 ± 56.98	252.68 ± 59.84	242.24 ± 41.24	0.681
Well-being during attack	634.17 ± 147.61	684.82 ± 148.66	646.55 ± 123.15	0.367
Unmet gout treatment need	157.50 ± 31.59	151.79 ± 26.29	155.17 ± 27.04	0.746
Gout medication side effects	150 (100, 156.25)	150 (100, 150)	150 (125, 162.5)	0.719
CRP	22.29 (10.49, 61.77)	24.66 (4.42, 75.50)	39.73 (12.62, 77.76)	0.543
WBC	9.22 ± 2.51	8.79 ± 3.09	9.43 ± 2.22	0.645
NE%	70.24 ± 7.86	68.86 ± 7.63	70.92 ± 9.56	0.651
SUA	490.38 ± 96.04	468.23 ± 108.44	470.78 ± 118.46	0.691

Table 2: Comparisons of outcome indicators and their variation from baseline to treatment completion.

Group	EA + DS group ($n = 30$)	Low-dose group ($n = 28$)	Conventional group ($n = 29$)	P		
				EA + DS vs. low-dose	EA + DS vs. conventional	Low-dose vs. conventional
VAS	0 (0, 0)*	1 (0, 2*	0 (0, 0.5*	0.001	0.692	0.005
Variation+	6 (5, 7)	5 (5, 6)	7 (6, 7)	0.026	0.512	0.004
Joint tenderness	0 (0, 0)*	0 (0, 1*	0 (0, 0*	0.008	0.529	0.044
Variation+	2 (1, 2)	1 (1, 2)	2 (1, 3)	0.049	0.603	0.014
Joint swelling	0 (0, 1)*	1 (0, 1*	0 (0, 1*	0.018	0.869	0.028
Variation+	2 (1, 2)	1 (0.25, 2)	2 (1, 2)	0.163		
Activity limitation	0 (0, 0)*	0.5 (0, 2*	0 (0, 0*	0.001	0.916	0.001
Variation+	6.53 ± 2.21	5.21 ± 1.99	6.59 ± 2.70	0.034	0.931	0.028
GIS						
Gout concern overall	227.50 ± 73.80	260.71 ± 55.87	256.90 ± 56.65	0.092		
Variation+	0 (0, 6.25)	0 (0, 0)	0 (0, 0)	0.272		
Gout concern during attack	219.17 ± 68.76*	262.50 ± 67.87	250.86 ± 40.91	0.008	0.048	0.470
Variation+	0 (0, 50)	0 (0, 0)	0 (0, 0)	<0.001	<0.001	0.780
Well-being during attack	570.00 ± 128.05*	786.61 ± 146.01*	660.34 ± 99.44	<0.001	0.007	<0.001
Variation+	25 (0, 100)	-62.5 (-231.25, 0)	−25 (−75, 62.5)	<0.001	<0.001	0.075
Unmet gout treatment need	168.33 ± 19.62	135.71 ± 31.50	157.76 ± 20.16	<0.001	0.098	0.001
Variation+	0 (-25, 0)	25 (0, 50)	0 (-12.5, 12.5)	0.003	0.374	0.042
Gout medication side effects	100 (100, 125*	125 (125, 125*	125 (125, 150)	0.013	<0.001	0.104
Variation+	25 (0, 50)	25 (0, 25)	0 (−12.5, 25)	0.194	0.007	0.171
CRP	4.27 (2.07, 11.51)*	3.30 (0.83, 11.54)*	3.86 (2.34, 9.50)*	0.350		
Variation+	11.83 (5.45, 44.73)	12.48 (2.51, 65.00)	33.66 (2.72, 60.81)	0.527		
WBC	6.93 ± 2.25*	8.51 ± 2.55	7.20 ± 1.76*	0.008	0.635	0.028
Variation+	2.29 ± 2.54	0.27 ± 2.91	2.22 ± 2.39	0.004	0.917	0.006
NE%	62.43 ± 9.28*	68.47 ± 8.72	63.26 ± 9.48*	0.014	0.728	0.035
Variation+	7.81 ± 8.52	0.42 ± 8.34	7.66 ± 9.31	0.002	0.947	0.002
SUA	411.18 ± 83.66*	458.76 ± 112.46	465.84 ± 89.74	0.078		
Variation+	79.19 ± 131.11	9.46 ± 111.38	4.97 ± 135.12	0.039	0.027	0.893

+The variation value from baseline to treatment completion. *There was significant difference ($P < 0.05$) in intragroup comparison from baseline to treatment completion.

3.7. Safety of EA. During the treatment, one patient in the EA + DS group developed local subcutaneous hematoma after acupuncture. The hematoma subsided after 2 days, and there were no other side effects or complications. All the patients in the EA + DS group had a good tolerance to the acupuncture treatment.

4. Discussion

Acupuncture treatment for AGA has been gradually recognized due to advantages such as anti-inflammatory and analgesic effects and the capacity to decrease the uric acid level [14]. Severe pain and activity limitation in AGA patients significantly affect their physical and mental health. However, only a few studies explored how different therapies affect the quality of life for AGA patients. Therefore, in this study, we aimed to explore whether EA combined with DS could be effective while at the same time improving the quality of life for AGA patients and reducing their dosage of analgesic drugs and adverse reactions during the treatment.

The study revealed that after a course of treatment, the clinical symptoms of joint pain, joint tenderness, joint swelling, and activity limitation in patients in the EA + DS group were improved. The performance of treatment in the EA + DS group was better than that in the low-dose DS group and was comparable to that in the conventional DS group. These results showed that combined EA and DS could synergistically relieve pain and improve the functionality of joints of AGA patients. However, the detumescence advantage of EA combined with DS was unconspicuous. It might be that the observation time was after the whole course of treatment, but a previous study found that the detumescence advantage of acupuncture was reflected immediately after a one-time treatment [18].

Through the investigation with GIS on the quality of life of AGA patients, it was found that the patients in the EA + DS group were less worried, had better health status during the attack period, and had a higher satisfaction with treatment. The "gout concern overall" is an indicator reflecting a long-term effect (usually 3 months), and thus results regarding this indicator were of little significance to the current study, which was carried out for only 1 week. In conclusion, this evaluation demonstrated the efficacy of the combined approach in treating AGA subjectively. A previous study reported a higher occurrence of depression, bipolar affective disorder, and other emotional disorders in people affected by AGA [19]. The two indicators, "gout concern during attack" and "well-being during attack," reflected patient's psychological status, and the length of time or severity of the impact of gout on their work, mood, sleep, entertainment, social interaction, self-care ability, and activity ability [20]. Our study indicated that EA combined with DS could also improve the accompanying symptoms such as insomnia, negative emotions, and low quality of life. In addition, patients in the EA + DS group reported being less affected by the side effects of gout drugs, which was consistent with the observation that there were fewer adverse reactions for patients in the EA + DS group. DS, as a nonselective NSAID, can inhibit cyclooxygenase-1 and prostacyclin, thus causing adverse reactions in the digestive system, cardiovascular system, and kidney [21]. Thus, the current study showed that EA combined with DS could not only achieve a good curative effect but could also reduce the adverse reactions caused by the sole use of DS.

Increased counts of WBC and NE and levels of CRP are all contributing factors that facilitate urate crystals in activating downstream inflammatory factors under the action of phagocytes, thereby triggering AGA [22–24]. The anti-inflammatory effect of acupuncture on AGA may be achieved through the downregulation of interleukins and tumor necrosis factors [25, 26]. In this study, indicators including the levels of WBC, NE%, and CRP were comparable between the EA + DS group and the conventional DS group, which were better than those in the low-dose DS group. In addition, the three groups showed significant differences regarding the levels of WBC and NE% but not CRP, which might relate to the sensitivity of the indicators such as the level of CRP, which has a high sensitivity and thus, a large variation. The results regarding CRP should be comprehensively interpreted in combination with other indicators [27].

SUA is closely related to the onset and prognosis of GA. When the level of SUA in the blood exceeds its saturated solubility, the precipitated urate crystals are deposited in the joint gap, thereby triggering an inflammatory response [28]. Previous clinical studies have shown that EA can downregulate the uric acid level and its effect was superior to the DS treatment [29]. It was found that EA may achieve this effect by regulating related processes, such as purine metabolism and uric acid excretion [30, 31]. This study found that the levels of SUA were only reduced in the EA + DS group. Although the decline was not significant due to the short treatment period, it can still indicate that EA was the main factor in reducing the levels of SUA in the EA + DS combined treatment.

The efficacy of EA + DS in the treatment of AGA has been shown for the first time, but this study also has certain limitations. Firstly, owing to the characteristics of acupuncture, the acupuncturist and patients could not be blinded in this study, which might have affected the results. Secondly, these participants were recruited from only one hospital, which might lead to a lack of representativeness.

Current study used a treatment course of 5–7 days. As acupuncture treatment displays both immediate and long-term effects in AGA patients, it would be advisable to set follow-up observations to find the impact on patients' level of SUA and the recurrence rate. As the dose-effect relationship of acupuncture is also a decisive part in the curative effect of AGA treatment, the operation time or the interval between two acupuncture sessions can be further explored to optimize the therapeutic strategy during the AGA treatment [32].

5. Conclusion

EA combined with DS can improve AGA patients' joint pain and functional status, thus improving their quality of life. Moreover, this combined treatment can reduce levels of inflammatory markers and SUA, thus leading to fewer adverse reactions in AGA patients during treatments.

Data Availability

The data used to support the findings of this study are included within the article and available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was supported by Shanghai Leading Talent Program (2021-013).

References

[1] J. D. FitzGerald, N. Dalbeth, T. Mikuls et al., "2020 American college of rheumatology guideline for the management of gout," *Arthritis Care & Research*, vol. 72, no. 6, pp. 879–895, 2020.

[2] E. Roddy and M. Doherty, "Epidemiology of gout," *Arthritis Research and Therapy*, vol. 12, p. 223, 2010.

[3] M. Chen-Xu, C. Yokose, S. K. Rai, M. H. Pillinger, and H. K. Choi, "Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the national health and nutrition examination survey, 2007-2016," *Arthritis & Rheumatology*, vol. 71, no. 6, pp. 991–999, 2019.

[4] C. F. Kuo, M. J. Grainge, C. Mallen, W. Zhang, and M. Doherty, "Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study," *Annals of the Rheumatic Diseases*, vol. 74, pp. 661–667, 2015.

[5] L. Annemans, E. Spaepen, M. Gaskin et al., "Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005," *Annals of the Rheumatic Diseases*, vol. 67, pp. 960–966, 2008.

[6] J.-W. Yu, T.-G. Yang, W.-X. Diao et al., "Epidemiological study on hyperuricemia and gout in Foshan areas, Guangdong province," *Chinese Journal of Epidemiology*, vol. 31, no. 8, p. 860, 2010.

[7] E. Roddy, W. Zhang, and M. Doherty, "Is gout associated with reduced quality of life? A case-control study," *Rheumatology*, vol. 46, pp. 1441–1444, 2007.

[8] M. A. Becker, H. R. Schumacher, K. L. Benjamin et al., "Quality of life and disability in patients with treatment-failure gout," *Journal of Rheumatology*, vol. 36, pp. 1041–1048, 2009.

[9] A. Wertheimer, R. Morlock, and M. A. Becker, "A revised estimate of the burden of illness of gout," *Current Therapeutic Research*, vol. 75, pp. 1–4, 2013.

[10] S.-B. Zhang, Y.-B. Zhang, P. Liu, W. Zhang, J. Ma, and J. Wang, "Efficacy and safety of etoricoxib compared with NSAIDs in acute gout: a systematic review and a meta-analysis," *Clinical Rheumatology*, vol. 35, pp. 151–158, 2016.

[11] K. Ma, Y.-Q. Mi, T. Wu et al., "Efficacy of diclofenac sodium in pain relief after conventional radiofrequency denervation for chronic facet joint pain: a double-blind randomized controlled trial," *Pain medicine (Malden, Mass)*, vol. 12, no. 1, pp. 27–35, 2011.

[12] J.-F. Tu, J.-W. Yang, G. X. Shi et al., "Efficacy of intensive acupuncture versus sham acupuncture in knee osteoarthritis: a randomized controlled trial," *Arthritis & Rheumatology*, vol. 73, pp. 448–458, 2021.

[13] Z.-T. Lv, L.-L. Shen, B. Zhu et al., "Effects of intensity of electroacupuncture on chronic pain in patients with knee osteoarthritis: a randomized controlled trial," *Arthritis Research and Therapy*, vol. 21, p. 120, 2019.

[14] W. B. Lee, S. H. Woo, B. I. Min, and S. H. Cho, "Acupuncture for gouty arthritis: a concise report of a systematic and meta-analysis approach," *Rheumatology*, vol. 52, pp. 1225–1232, 2013.

[15] National Administration of Traditional Chinese Medicine, *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine*, China Medical Science Press, Beijing, China, 2012.

[16] M. M. Desu and D. Raghavarao, *Sample Size Methodology*, p. 57, Academic Press, New York, NY, USA, 1990.

[17] J. D. Hirsch, S. J. Lee, R. Terkeltaub et al., "Evaluation of an instrument assessing influence of gout on health-related quality of life," *Journal of Rheumatology*, vol. 35, pp. 2406–2414, 2008.

[18] K. Y. Huang, S. Liang, J. J. Wang, and Y. Wu, "Influence of electric-acupuncture combined with ermiao san for acute gouty arthritis model rats' gait and joint," *Journal of liaoning University of traditional Chinese medicine*, vol. 17, no. 8, pp. 134–136, 2015.

[19] T. C. Changchien, Y. C. Yen, C. L. Lin, M. C. Lin, J. A. Liang, and C. H. Kao, "High risk of depressive disorders in patients with gout: a nationwide population-based cohort study," *Medicine*, vol. 94, p. 2401, 2015.

[20] C. H. Pao and Y. Ko, "An assessment of the psychometric properties of the Chinese version of the Gout Impact Scale," *Current Medical Research and Opinion*, vol. 36, pp. 17–21, 2020.

[21] L. Wilson and J. J. Saseen, "Gouty arthritis: a review of acute management and prevention," *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, vol. 36, pp. 906–922, 2016.

[22] C. Schiltz, F. Lioté, F. Prudhommeaux et al., "Monosodium urate monohydrate crystal-induced inflammation in vivo: quantitative histomorphometric analysis of cellular events," *Arthritis & Rheumatism*, vol. 46, pp. 1643–1650, 2002.

[23] A. K. Wessig, L. Hoffmeister, A. Klingberg et al., "Natural antibodies and CRP drive anaphylatoxin production by urate crystals," *Scientific Reports*, vol. 12, p. 4483, 2022.

[24] C. Schauer, C. Janko, L. E. Munoz et al., "Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines," *Nature Medicine*, vol. 20, pp. 511–517, 2014.

[25] Z. Jin, Z.-Y. Zhang, and S.-S. Jiang, "Effect of acupuncture combined with medication on the contents of interleukin-1β and interleukin-8 in synovium of rat models of acute gouty arthritis," *Shanghai Journal of Acupuncture and moxibustion*, vol. 31, no. 12, pp. 923-924, 2012.

[26] T.-L. Long, T.-J. Huang, and Q.-L. Gao, "Effect of dredging channels and eliminating turbid acupuncture on the level of TNF-α in mice with acute gouty arthritis: an experimental study," *World Chinese Medicine*, vol. 11, no. 2, pp. 219–221, 2016.

[27] M. Harrison, "Erythrocyte sedimentation rate and C-reactive protein," *Australian Prescriber*, vol. 38, pp. 93-94, 2015.

[28] Y. Shi, A. D. Mucsi, and G. Ng, "Monosodium urate crystals in inflammation and immunity," *Immunological Reviews*, vol. 233, pp. 203–217, 2010.

[29] J.-H. Zhang, Y.-R. Chen, K. Lan, H. U. Liyu, and Y. U. Haibo, "Clinical, anti-hyperuricemic, and pain-relief effects of five acupuncture and moxibustion therapies in acute gouty arthritis:a network meta-analysis," *Chinese General Practice*, vol. 24, no. 8, pp. 1001–1010, 2021.

[30] R.-L. Li, X.-L. Lu, Y. Xiong et al., "Effects of combined acupuncture-drug on uric acid and xanthine oxidase activity in hyperuricemia rats with renal damage," *Shanghai Journal of Traditional Chinese Medicine*, vol. 52, no. 2, pp. 95–98, 2018.

[31] X.-F. Liu, H.-Y. Chen, J. Wang, and S. Yun, "Effect of acupuncture stimulation of "Shenshu" (BL23)-Taixi (KI3) on levels of serum uric acid and renal URAT1 and OAT1 protein expression in hyperuricemia rats," *Acupuncture Research*, vol. 44, no. 5, pp. 319–323, 2019.

[32] X.-M. Shi, "Study of the relationship between acupuncture dose and effect," *Acupuncture and Herbal Medicine*, vol. 1, no. 1, pp. 3–9, 2021.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 7873426, 13 pages
https://doi.org/10.1155/2022/7873426

Research Article

Efficacy and Safety of Qinpi Tongfeng Formula in the Treatment of Acute Gouty Arthritis: A Double-Blind, Double-Dummy, Multicenter, Randomized Controlled Trial

Yihua Fan,[1,2,3] **Wei Liu**,[1,2] **Hang Lu**,[1,2] **Jian Liu**,[4] **Rui Wu**,[5] **Jun Zhao**,[5] **Aihua Wang**,[1,2] **and Xianheng Zhang**[4]

[1]*First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China*
[2]*National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China*
[3]*Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, Sichuan, China*
[4]*The First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei 230031, Anhui, China*
[5]*The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi, China*

Correspondence should be addressed to Wei Liu; fengshiliuwei@163.com

Received 11 May 2022; Accepted 25 June 2022; Published 12 July 2022

Academic Editor: Chunsheng Zhu

Objective. Traditional Chinese medicine (TCM) has certain curative effect against acute gouty arthritis (AGA), but it lacks high-quality evidence-based studies. In this randomized controlled trial, we try to evaluate the clinical efficacy and safety of Qinpi Tongfeng Formula (QPTFF) in the treatment of AGA. *Methods*. One hundred and fourteen patients with AGA (damp heat accumulation syndrome) who met the inclusion and exclusion criteria were randomly divided into treatment group and control group in a ratio of 1 : 1. Patients in the treatment group were treated with QPTFF, and patients in the control group were treated with diclofenac sodium sustained-release tablets for 7 days. The primary outcome measure was the change in visual analog scale (VAS) score for pain from the baseline to day 8. The secondary outcome measures were joint symptom score, TCM syndrome score, total effective rate, pain cure rate, complete pain relief time, patient satisfaction score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum uric acid level. The safety outcome measures were routine blood test, urinalysis, liver function including alanine aminotransferase and aspartate aminotransferase, renal function including blood urea nitrogen and serum creatinine, and the rate of treatment-related adverse events (TRAEs). *Results*. 105 patients with 53 in the treatment group and 52 in the control group completed the 7-day treatment. There was no significant difference between two groups in demographic characteristics, VAS score for pain, joint symptom score, TCM syndrome score, ESR, CRP, and serum uric acid level before enrollment at baseline (based on both the full analysis set (FAS) and per protocol set (PPS), $P > 0.05$). The 95% confidence interval of the difference between the eighth and first VAS score for pain of the two groups was (−0.57, 0.42) in FAS and (−0.48, 0.47) in PPS. The lower bound of both FAS and PPS is greater than the bound value of −0.7. On day 8, there was no significant difference between the two groups in joint symptom score, TCM syndrome score, total effective rate, pain cure rate, complete pain relief time, patient satisfaction score, ESR, and CRP (FAS and PPS, $P > 0.05$). The serum uric acid level and TRAEs in the treatment group were significantly lower than those in the control group (FAS and PPS, $P < 0.05$). *Conclusions*. QPTFF could alleviate the symptoms of patients with AGA, which is not inferior to diclofenac sodium sustained-release tablets in analgesic. Moreover, QPTFF overmatches diclofenac sodium sustained-release tablets in decreasing serum uric acid level and TRAEs. Therefore, the results provide reliable foundation for QPTTF in the treatment of AGA. *Trial Registration*. This study protocol was registered in Chinese Clinical Trial Registry (registration number: ChiCTR2100050638).

1. Introduction

Gout is a metabolic rheumatism caused by abnormal purine metabolism, increased synthesis, and/or decreased excretion of uric acid, resulting in increased serum uric acid. With the high serum uric acid level, urate will be deposited into crystals to gather in joints, cartilage, and kidney [1]. Urate crystals in joints can lead to bone injury by repeated inflammation stimulation further to influence the daily activities of gout patients. Urate crystals in kidney can lead to gouty nephropathy which will develop into renal failure and endanger life, once poorly controlled [2]. In addition, long-term high serum uric acid level can increase the risk of cardiovascular events and cerebrovascular diseases [3].

Acute gouty arthritis (AGA) is a common acute arthritis with clinical features of severe arthralgia with swelling, recurrence, and poor prognosis [4]. For AGA, 2021 Asia Pacific League of Associations for Rheumatology [5] recommended anti-inflammatory and analgesic therapy. Colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs for the treatment of AGA. Although colchicine can alleviate the patient's condition in a short time, there will be different adverse reactions such as damage to the liver, kidney, gastrointestinal, and bone marrow suppression after the treatment [6]. NSAIDs can also effectively reduce joint pain, but they are lack in reducing serum uric acid level with certain side effects [7]. Hence, it is important to seek a safe and effective treatment method.

In traditional Chinese medicine (TCM), the clinical manifestations of AGA, such as joint swelling and tenderness and local skin redness, constitute the "damp heat accumulation syndrome" of "Bi syndrome" (joint pain) similar to the acute stage of gouty arthritis. The treatment of AGA with TCM has a history of thousand years in China. A preliminary systematic study [8]found that TCM compound has good curative effect with less adverse reactions in the treatment of AGA. However, the included research studies were lack in strictness and poor in quality. More high-quality randomized controlled trials are needed to furnish evidence for the efficacy of TCM. Qinpi Tongfeng Formula (QPTFF) is a TCM treatment for AGA. It has been used clinically in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine for at least 12 years. Both QPTFF combined with western medicine or bloodletting therapy have good curative effects in the treatment of gout [9, 10]. Nevertheless, rigorous randomized controlled trials have not been carried out to compare the efficacy and safety of QPTFF and NSAIDs. Thus, the purpose of this study is to evaluate the effects and safety of QPTFF in the treatment of AGA.

2. Materials and Methods

2.1. Study Design. This is a double-blind, double-dummy, multicenter, randomized, noninferiority clinical trial. The study was conducted under the *Declaration of Helsinki* and the *Good Clinical Practice Guidelines of the International Conference on Harmonization*. Meanwhile, the study followed consort (Table S1). The protocol of the study has been approved by the Ethics Committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (ethics number: TYLL2021[Z] 017), and it has been registered in Chinese Clinical Trial Registry (registration number: ChiCTR2100050638).

2.2. Participants. Men and women aged 18–70 years were considered for enrollment if met the diagnostic criteria of AGA of the American College of Rheumatology in 2015 [11] as well as diagnostic criteria of dampness heat accumulation syndrome in the *Guidelines for the Combined Diagnosis and Treatment of Gout and Hyperuricemia* [12]. All participants signed informed consent. We conducted this clinical trial in three centers, including the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, The First Affiliated Hospital of Anhui University of Chinese Medicine, and The First Affiliated Hospital of Nanchang University.

2.2.1. Inclusion Criteria

(1) Patients within 72 hours of AGA attack
(2) Patients with at least one attack of gout in the past
(3) Patients with moderate or above arthralgia, and the visual analog scale (VAS) score for pain is ≥4
(4) Patients without taking other oral traditional Chinese medicine or western medicine for AGA 72 hours before enrollment
(5) Patients without taking uric-acid-lowering drugs in recent 2 weeks

2.2.2. Exclusion Criteria

(1) Patients diagnosed with secondary AGA caused by other diseases or drugs
(2) Patients diagnosed with chronic gout
(3) Patients with inflammatory arthritis such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and knee osteoarthritis
(4) Patients with polyarthralgia (>4 joints)
(5) Patients complicated with serious primary diseases such as cardiovascular, cerebrovascular, lung, and kidney
(6) Alanine aminotransferase, aspartate aminotransferase, or serum creatinine greater than 1.5 times upper limit of normal [13]
(7) Patients allergic to test drug ingredients
(8) Patients currently preparing for pregnancy, being pregnant, or breastfeeding
(9) Patients with active digestive ulcer or bleeding, or who have suffered or suffering from digestive ulcer or bleeding
(10) Patients in other intervention studies in recent 1 month

(11) Patients with mental illness or abnormal intelligence, unable to accurately express the condition or take medicine on time, and unable to finish follow-up cooperatively

2.2.3. Discontinued

(1) In case of intolerable adverse events, complications, or physiological changes, the researcher considered that the trial should be stopped and patients would be treated accordingly after evaluation.

(2) The condition of participant did not alleviate or even got worsen within a certain period of time. Although the study was not completed, the researcher should stop the trial and take effective treatment in order to protect the participant. The curative effect of this case was determined to be invalid.

(3) The participant proposed to the researcher to withdraw from the experiment voluntarily.

(4) The participants who demonstrated poor compliance and were unwilling to continue participating in the study or lost to follow-up. Researchers should try to complete the last laboratory test of all withdrawn or lost cases in order to analyze their efficacy and safety. The reasons for the shedding of all shedding cases in detail and the records of the indicators that met the test requirements should be filled in the case report form (CRF). The unfinished indicators should be also filled in by the last carry forward method.

2.2.4. Exclusion. During the study period, participants who used a series of combined medications at will, which will affect the assessments of curative effect, should be excluded and recorded in the CRF.

2.3. Methods

2.3.1. Sample Size. The primary outcome measure of this study was the change in VAS score for pain from the baseline to day 8. According to the preliminary clinical trial, the mean values of VAS score changes of QPTFF and diclofenac sodium sustained-release tablets were 3.67 and 3.75, with the standard deviation of 1.22 and 0.97. For sample size estimation, PASS 15.0 software was used and noninferiority design was adopted with one-sided test selected, taking $\alpha = 0.025$, $\beta = 0.2$, the ratio of the treatment group and the control group = 1 : 1, and the boundary value = −0.7. The calculated sample size for the two groups was 102 cases. Considering the potential dropout rate of about 10%, a total of 114 cases were finally included, with 57 cases in each group. According to the situation, 114 drug packaging bags were numbered, so that each center could distribute drugs according to the numbers.

2.3.2. Randomization and Blinding. Excel 2013 software was used for stratified randomization for the three centers. There were 74 AGA patients in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, 20 in the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, and 20 in the First Affiliated Hospital of Nanchang University.

The study was designed to be double-blinded and double-dummied. The treatment group used the QPTFF granule + diclofenac sodium sustained-release tablets simulant (the color, texture, taste, and smell were the same as the actual drug), while the control group used diclofenac sodium sustained-release tablets + QPTFF granule simulant (the color, texture, taste, and smell were the same as the actual drug):

(1) Blinding: a trained statistician not involved with the study completed the blinding of the test medications. This study adopted a two-stage blind design. The first stage was the group code corresponding to each drug number, which was group A or group B, and the second stage was the treatment scheme adopted by group A and group B. The two-stage blind data should be placed in an opaque envelope and should not be opened during the study. All researchers who were responsible for recruiting, distributing drugs, testing indexes, and evaluating efficacy, all participants were blind to the randomization. The expert statisticians who were also blind to the randomization would conduct statistical analysis after completing the study.

(2) Emergency unblinding: each drug with a number had a corresponding emergency letter, so that the patient could carry out emergency unblinding in case of serious adverse reaction events.

2.4. Treatment. Basic treatment: (1) avoiding cold and wet stimulation of joints, (2) no drinking, (3) low purine diet, (4) drinking more than 2000 mL water every day, and (5) prohibiting medications that affect uric acid metabolism.

2.4.1. Medications. Patients in the treatment group were treated with QPTFF as granule, provided by Sichuan New Green Pharmaceutical Technology Development Company, Chengdu, China (batch no. 2107705). QPTFF has 8 components: 30 g Cortex *Fraxini* (Qin Pi), 10 g *Rhizoma Coptidis* (Huang Lian), 20 g *Semen Plantaginis* (Che Qian Zi), 30 g *Rhizome Dioscoreae Hypoglaucae* (Bi Xie), 80 g *Rhizoma Smilacis Glabrae* (Tu Fu Ling), 20 g *Radix Clematidis* (Wei Ling Xian), 30 g *Herba Siegesbeckiae* (Xi Xian Cao), and 10 g *Radix Saposhnikoviae* (Fang Feng). QPTFF was taken one bag each time, three times daily, boiled in water for each dose. The simulant of diclofenac sodium sustained-release tablets was manufactured by Tiandi Hengyi Pharmaceutical Company, Changsha, China (batch no. 201101), and was taken 0.1 g each time orally, once daily. Patients in the control group were treated with diclofenac sodium sustained-release tablets provided by Hunan Warner Pharmaceutical Company in Liuyang, China (H200677776), which was taken 0.1 g orally, once daily; QPTFF simulant (made by Sichuan New Green Pharmaceutical Technology

Development Company, Chengdu, China, batch no. 2107705) was taken one bag each time, three times daily, boiled in water for each dose. The simulant was similar to the original drug in appearance, smell, and taste. All participants were treated for 7 days.

2.4.2. Emergency Treatment. If the pain of participants was severe and intolerable during the study, they would be given colchicine tablets (obtained by Guangdong Pidi Pharmaceutical Company, Kaiping, China, H20113208) to assist in emergency pain relief, 0.5 mg each time, three times a day. At the same time, the medication administration would be recorded in the CRF.

2.5. Indicators

2.5.1. Baseline Demographic Characteristics of Patients. Record the participant's name, gender, age, height, weight, body mass index (BMI), nationality, course of gout disease, allergy history, smoking history, drinking history, past medical history, and family history of gout.

2.5.2. Safety Indicators

(1) Vital sign: temperature, heart rate, blood pressure, and respiration were recorded on day 1 and day 8

(2) Laboratory examination: routine blood test, urinalysis, liver function including alanine aminotransferase and aspartate aminotransferase, and renal function including blood urea nitrogen and serum creatinine were examined on day 1 and day 8

(3) Treatment-related adverse events (TRAEs): researchers refer to the incidence of Common Terminology Criteria for Adverse Events version 5.0 [14] to record the adverse events and treatment measures in the whole process

2.5.3. Primary Outcome Measure

(1) Changes in VAS Score for Pain. The pain degree of the participant was evaluated by VAS [15]. Researchers should record VAS score for pain before each treatment and the VAS score for final pain on day 8. A total of 8 scores were obtained.

2.5.4. Secondary Efficacy Index

(1) Joint Symptom Score. The participant's joint tenderness, redness, swelling, and mobility were evaluated by Likert scale [16] (Table S2) at the baseline and day 8.

(2) TCM Syndrome Score. Researchers would evaluate the TCM syndrome score, including the main and concurrent symptoms of AGA patients (Table S3), referring to the *Guiding Principles for Clinical Research of New Traditional Chinese Medicine* [17], the quantitative integral evaluation of TCM syndrome was adopted. The higher the score, the worse the condition of AGA was. The TCM syndrome score would be recorded at the baseline on day 8.

(3) Total Effective Rate. The efficacy was evaluated according to the *Guiding Principles for Clinical Research of New Traditional Chinese Medicine* [18] (efficacy index = (pretreatment TCM syndrome score−posttreatment TCM syndrome score)/pretreatment TCM syndrome score × 100%) [19]. Recovery: curative effect index ≥95%; markedly effective: 70%≤ curative effect index <95%; effective: 30%≤ efficacy index <70%; ineffective: efficacy index <30%. Total effective rate = (the number of people cured + the number of people in markedly effective + the number of people in effective)/total number of people × 100%.

(4) Pain Cure Rate. Definition of pain cure: within 24 hours during the treatment, the VAS score for pain was 0, and the VAS score was still 0 24 hours after the treatment. The pain cure rate refers to the proportion of cured patients in the total number of patients within 7 days of treatment.

(5) Complete Pain Relief Time. Complete pain relief time indicated the duration of the VAS score turning to 0.

(6) Patient Satisfaction Score. On day 8, the participant would get an overall evaluation of the treatment, which was rated as 5 points (1 point: poor treatment effect; 2 points: slightly effective; 3 points: acceptable curative effect; 4 points: good; and 5 points: extremely good) [16].

(7) Laboratory Index. The levels of CRP, ESR, and serum uric acid of participants were measured at baseline on day 8.

2.6. Statistical Analysis.

All outcome measures in this study were analyzed by the full analysis set (FAS) and per protocol set (PPS). In the FAS, for the indicators with missing data, the last observation value carry forward method was used to fill in the data. Safety indicators were analyzed by a safety set. SPSS 22.0 was used to carry out statistical analysis on the data. The quantitative data were described by mean, standard deviation, or interquartile interval M (P_{25}, P_{75}). For normal distributed data, the independent sample t-test or paired t-test was used for comparison between groups or within groups before and after the treatment, while data in skewed distribution nonparametric test should be adopted. The repeated measurement data in this study were skewed distribution, so the mixed linear model was used. The counting data were expressed by frequency and composition ratio, and the chi-square test was used for statistics; the Kaplan–Meier survival curve was used to describe the time of complete pain relief, and the log-rank test was used for comparison between groups. $P < 0.05$ indicated the difference was statistically significant. The change of VAS score was taken as the main efficacy index, and the noninferiority test was carried out according to the confidence interval method. SAS software was used to calculate the 95% confidence interval (CI) of the difference between the changes value of VAS score for pain between the treatment group and the control group before

and after treatment. If the lower limit of the CI was greater than the limit value, the noninferiority was established [20]. GraphPad Prism 8 software was used to make graphics.

3. Results

3.1. Case Collection and Completion. According to the registered protocol, 114 eligible AGA patients were included in this study from August 2021 to February 2022. In the course of the study, the clinical symptom indexes (VAS score for pain, TCM syndrome score, and joint symptom score) were measured. 105 participants completed the 7-day treatment, and 105 were finally included in the PPS, including 53 in the treatment group and 52 in the control group; 89 participants finally finished the laboratory indexes and were included in the PPS, including 45 in the treatment group and 44 in the control group (Figure 1).

3.2. Baseline Characteristic Analysis. There was no significant difference between the two groups in gender, age, course of gout disease, weight, height, and BMI ($P > 0.05$), as shown in Table 1. There was no significant difference in allergy history, smoking history, drinking history, past history, and family history of gout between the two groups ($P > 0.05$). There was no significant difference in temperature, heart rate, systolic blood pressure, diastolic blood pressure, and respiration between the two groups ($P > 0.05$). There was no significant difference between the two groups in VAS score for pain, joint symptom score, TCM syndrome score, ESR, CRP, and serum uric acid level ($P > 0.05$), as shown in Table 2, indicating that the two groups were comparable at baseline.

3.3. Clinical Efficacy

3.3.1. VAS Score for Pain. The VAS score for pain of the two groups decreased gradually, and the changes are shown in Figures 2 and 3. The mixed linear model was used to compare the measurement results of VAS score at different time points between the two groups. The fixed effect analysis results of mixed linear model showed that there was no interaction effect at group * time point ($P > 0.05$), and the overall curative effect difference between the two groups was not statistically significant ($P > 0.05$), as shown in Table 3. There was no significant difference in VAS score between the two groups at different time points ($P > 0.05$), as shown in Table 4. In the FAS, the 95% CI of the difference between the eighth time and baseline VAS scores of the two groups was (−0.57, 0.42), and its lower limit was greater than the boundary value of −0.7, so the noninferiority was established. In the PPS set, the 95% CI of the difference between the eighth time and the baseline VAS scores the two groups was (−0.48, 0.47), and its lower limit was greater than the boundary value of −0.7, so the noninferiority was established. In conclusion, the noninferiority test of this study is qualified.

3.3.2. Joint Symptom Score. The joint symptom scores of the two groups after the treatment were better than those before the treatment (FAS and PPS, $P < 0.05$). After the treatment, there was no significant difference in the joint symptom scores between the treatment group and the control group ($P > 0.05$), as shown in Table 5.

3.3.3. TCM Syndrome Score. In FAS and PPS, the TCM syndrome scores of the two groups after the treatment were better than those before the treatment and the difference was statistically significant ($P < 0.05$). After the treatment, there was no statistically significant difference between the TCM syndrome scores of the treatment group and the control group ($P > 0.05$), as shown in Table 6.

3.3.4. Total Effective Rate. In FAS, the total effective rate was 89.47% in the treatment group and 87.72% in the control group, and there was no significant difference between the two groups ($P > 0.05$). In PPS, the total effective rate was 96.23% in the treatment group and 96.15% in the control group, and there was no significant difference between the two groups ($P > 0.05$), as shown in Table 7.

3.3.5. Pain Cure Rate. In FAS, the pain cure rate was 35.09% in the treatment group and 38.60% in the control group, and there was no significant difference between the two groups ($P > 0.05$). In PPS, the pain cure rate was 35.84% in the treatment group and 38.46% in the control group, and there was no significant difference between the two groups ($P > 0.05$), as shown in Table 8.

3.3.6. Comparison of Complete Pain Relief Time between the Two Groups. In FAS, the median time of complete pain relief time in both the treatment group and the control group was 7.65 days (Figure 4). Using the log-rank test, there was no significant difference between the two groups ($P = 0.701$). In PPS, the median time of complete pain relief time in the treatment group and the control group was 7.65 days. The survival curve of the two groups is shown in Figure 5. Using the log-rank test, there was no significant difference between the two groups ($P = 0.85$).

3.3.7. Patient Satisfaction Score. The patient satisfaction score adopted PPS. The results showed that there was no statistical difference between the two groups ($P > 0.05$) (see Table 9).

3.3.8. Laboratory Index. In FAS and PPS, the levels of ESR and CRP in the two groups after the treatment were lower than those before the treatment and the differences within the two groups were statistically significant ($P < 0.001$). After the treatment, there was no statistically significant difference in the levels of ESR and CRP between the treatment group and the control group ($P > 0.05$), as shown in Tables 10 and 11. In FAS and PPS, the level of serum uric acid in the treatment group after the treatment was significantly lower

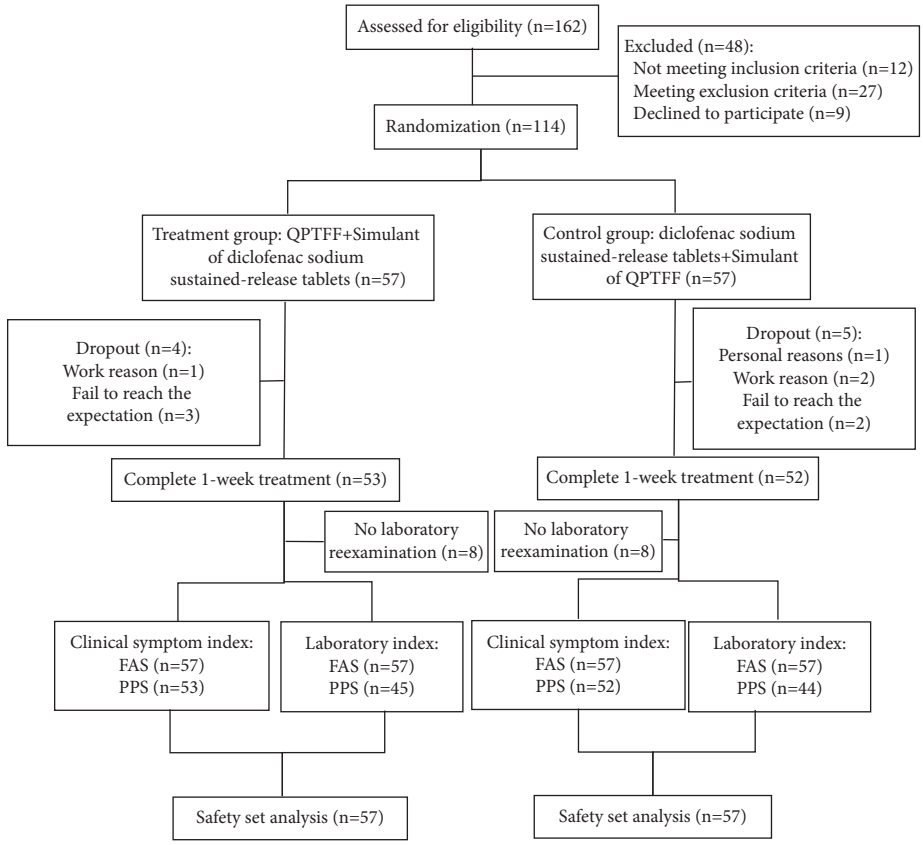


Figure 1: Flow diagram of AGA patients.

Table 1: Basic characteristics (FAS) of AGA patients ($\overline{x} \pm s/M$ (P_{25}, P_{75})/n (%)).

	Characteristics		Treatment group	Control group	P value
FAS	Gender	Male	56 (98.2%)	56 (98.2%)	1.000
		Female	1 (1.80%)	1 (1.80%)	
	Age (years)		41.68 ± 11.51	31.50 (26, 52)	0.247
	Course of disease (months)		50.00 (15.50, 77)	30.5 (0.25, 61.75)	0.852
	Weight (kg)		86.65 ± 15.80	82.56 ± 16.82	0.184
	Height (cm)		175.00 ± 6.07	173.47 ± 6.30	0.190
	BMI (kg/m^2)		28.24 ± 4.74	27.29 ± 4.54	0.275
PPS	Gender	Male	52 (98.11%)	51 (98.08%)	1.000
		Female	1 (1.89%)	1 (1.89%)	
	Age (years)		41 ± 11.65	29.5 (25.75, 48.25)	0.487
	Course of disease (months)		59.50 (17.50, 89.00)	26 (0.00, 61.25)	0.430
	Weight (kg)		86.58 ± 15.74	83.00 ± 17.42	0.272
	Height (cm)		176.02 ± 6.17	173.62 ± 6.20	0.248
	BMI (kg/m^2)		28.21 ± 4.73	27.36 ± 4.62	0.353

than that before the treatment ($P < 0.001$), and there was no significant difference in the level of serum uric acid in the control group before and after the treatment ($P > 0.05$). After the treatment, the level of serum uric acid in the treatment group was significantly lower than that in the control group ($P < 0.05$), as shown in Table 12.

3.4. Safety Evaluation. During the treatment, routine blood test and urinalysis did not show abnormalities in the two groups. Only 23 patients had elevated leukocytes stimulated by inflammation before the treatment, but they all returned to normal level after the treatment. Another 9 patients had elevated platelet count before the treatment, but decreased after the treatment. There was no abnormal increase or decrease in vital signs in the two groups after the treatment. The TRAEs were 7.02% in the treatment group and 26.32% in the control group. The TRAEs of the treatment group were significantly lower than those of the control group ($P < 0.05$), as shown in Table 13.

4. Discussion

AGA is caused by the deposition of urate crystals in the articular cavity, manifested as redness, swelling, and severe pain of the joints [21]. International guidelines recommend NSAIDs as the first-line treatment of AGA [22, 23], and diclofenac sodium sustained-release tablets are commonly used as positive controlled medicines in the treatment of AGA [24–26]. Therefore, diclofenac sodium sustained-release tablet was chosen as the controlled medicine in this study. VAS score for pain is the most widely used tool to measure pain intensity in clinic [27, 28], which is often used

Table 2: Baseline comparison of clinical efficacy indicators ($\overline{x} \pm s/M$ (P_{25}, P_{75})).

	Characteristics	Treatment group	Control group	P value
FAS	VAS score for the pain	6.00 (5.00, 6.00)	5.00 (5.00, 6.00)	0.292
	Joint symptom score	7.00 (5.00, 7.50)	7.00 (7.00, 8.00)	0.371
	TCM syndrome score	26.73 ± 5.26	27.26 ± 4.46	0.566
	ESR (mm/h)	24.79 ± 14.49	22.95 ± 13.48	0.484
	CRP (mg/L)	40.18 ± 24.36	25.08 (11.66, 49.45)	0.854
	Serum uric acid (μmol/L)	565.97 ± 129.96	572.01 ± 119.20	0.796
PPS	VAS score for the pain	5.50 (5.00, 6.75)	5.00 (4.75, 6.00)	0.346
	Joint symptom score	7.00 (5.25, 7.75)	7.00 (7.00, 8.00)	0.377
	TCM syndrome score	26.75 ± 5.39	27.29 ± 4.60	0.587
	ESR (mm/h)	23.31 ± 13.24	22.50 (13, 30.75)	0.912
	CRP (mg/L)	15.93 (7.28, 44.25)	18.07 (11.54, 51.58)	0.453
	Serum uric acid (μmol/L)	565.39 ± 136.39	577.51 ± 120.78	0.659

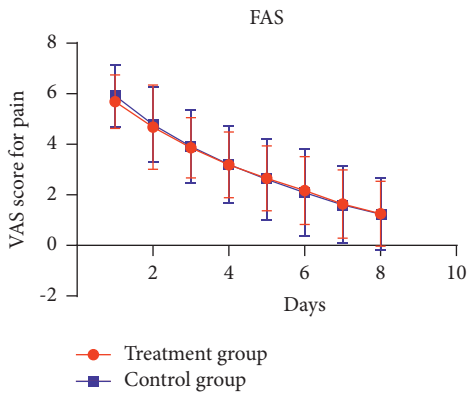


Figure 2: Changes in VAS score for pain between the two groups (FAS).

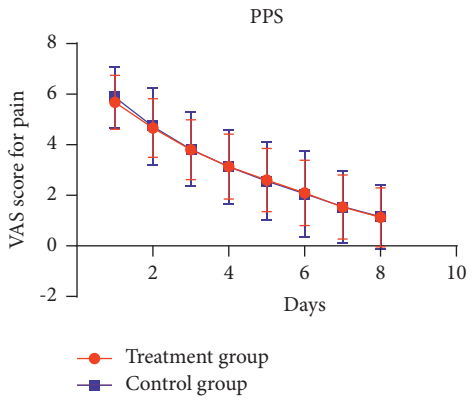


Figure 3: Changes in VAS scores for pain between the two groups (PPS).

Table 3: Analysis of mixed linear models of VAS scores for pain between the two groups.

	Characteristics	Statistics (F)	P value
FAS	Group	0.091	0.762
	Time point	148.619	<0.001
	Group * time point	0.148	0.994
PPS	Group	0.087	0.768
	Time point	148.950	<0.001
	Group * time point	0.092	0.999

to evaluate the condition changes in joint pain of AGA [29]. In addition, the joint symptom score scale in this study includes the condition of joint tenderness, joint redness, joint swelling, and joint activity, which can comprehensively reflect the clinical manifestations of affected joints. Meanwhile, according to the requirements of the *Guiding Principles for Clinical Research of New Traditional Chinese Medicine* [17], the TCM syndrome score scale is used to evaluate the TCM syndrome of patients, which is widely used in the efficacy evaluation of TCM therapy [9, 19]. ESR and CRP are commonly used as inflammatory indicators in clinic and play an important guiding role in judging the progress of inflammation [30]. Serum uric acid level is not only a diagnostic indicator of AGA but also an indicator of its prognosis. The level of serum uric acid is closely related to the recurrence rate of gouty arthritis [31], so we also listed serum uric acid as the outcome measure. Nevertheless, the main aim of the treatment to AGA is to control inflammation and relieve pain, and serum uric acid was set as the secondary outcome measure.

In this study, the improvement of patients' pain is the primary outcome measure of the study. The VAS score for pain of participants on day 8 was significantly lower than that at baseline, indicating that both treatments could effectively reduce the pain of patients. The noninferiority test proved that the lower confidence interval of the difference value of VAS score for pain (from baseline to day 8) between the two groups is greater than the lower limit (FAS and PPS, lower limit >−0.7). There was no significant difference in complete pain relief time and pain cure rate between the two groups, which suggested that the analgesic effect of QPTFF was not inferior to that of diclofenac sodium sustained-release tablets. The results of secondary outcome measures showed that both treatments had a great improvement in the joint symptom score, TCM syndrome score, ESR, and CRP, but without significant difference, indicating that QPTFF and diclofenac sodium sustained-release tablets could significantly improve the patients' symptoms and inflammatory indicators with equal effects. However, QPTFF had more advantages than diclofenac sodium sustained-release tablets in reducing the serum uric acid level. After the treatment, the satisfaction survey was carried out on the patients, and the results showed that the

Table 4: Comparison of VAS scores for pain at each time point between the two groups.

	Characteristics	Group (*I*)	Group (*J*)	Mean difference (*I*–*J*)	*P* value
FAS	Baseline	Treatment group	Control group	0.02	0.946
	2nd	Treatment group	Control group	0.04	0.887
	3rd	Treatment group	Control group	0.07	0.781
	4th	Treatment group	Control group	0.05	0.855
	5th	Treatment group	Control group	−0.01	0.968
	6th	Treatment group	Control group	−0.05	0.839
	7th	Treatment group	Control group	−010	0.694
	8th	Treatment group	Control group	−0.23	0.374
PPS	Baseline	Treatment group	Control group	−0.20	0.939
	2nd	Treatment group	Control group	−0.01	0.980
	3rd	Treatment group	Control group	0.40	0.877
	4th	Treatment group	Control group	0.40	0.871
	5th	Treatment group	Control group	0.01	0.973
	6th	Treatment group	Control group	−0.02	0.936
	7th	Treatment group	Control group	−0.06	0.827
	8th	Treatment group	Control group	−0.21	0.432

Table 5: Comparison of joint symptom scores between the two groups (M (P_{25}, P_{75})).

	Group	*N*	Before treatment	After treatment	Comparison between groups *P* value
FAS	Treatment group	57	6.00 (7.00, 8.00)	0.00 (0.00, 1.00)	<0.001
	Control group	57	6.00 (7.00, 8.00)	0.00 (0.00, 0.00)	<0.001
	Comparison between groups		*P* value	0.542	
PPS	Treatment group	53	7.00 (5.25, 7.75)	0.00 (0.00, 1.00)	<0.001
	Control group	52	7.00 (7.00, 8.00)	0.00 (0.00, 0.00)	<0.001
	Comparison between groups		*P* value	0.397	

Table 6: Comparison of TCM syndrome scores between the two groups ($\overline{x} \pm s/M$ (P_{25}, P_{75})).

	Group	*N*	Before treatment	After treatment	Comparison between groups *P* value
FAS	Treatment group	57	26.74 ± 5.26	3 (2, 5)	<0.001
	Control group	57	27.26 ± 4.46	10.21 ± 7.54	<0.001
	Comparison between groups		*P* value	0.325	
PPS	Treatment group	53	26.75 ± 5.39	2.5 (2, 4)	<0.001
	Control group	52	27.29 ± 4.60	8.60 ± 5.60	<0.001
	Comparison between groups		*P* value	0.329	

Table 7: Comparison of total effective rate between the two groups (*n* (%)).

Curative effect index	FAS		PPS	
	Treatment group ($n = 57$)	Control group ($n = 57$)	Treatment group ($n = 53$)	Control group ($n = 52$)
Cured	3 (5.26%)	2 (3.51%)	3 (5.66%)	2 (3.85%)
Markedly effective	28 (49.12%)	26 (45.61%)	28 (52.83%)	26 (50.00%)
Effective	20 (35.09%)	22 (38.60%)	20 (37.74%)	22 (42.31%)
Ineffective	6 (10.53%)	7 (12.28%)	2 (3.77%)	2 (3.85%)
Total effective rate	89.47%	87.72%	96.23%	96.15%
P value	0.789		0.809	

subjective feeling of the patients in the two groups was equal.

In terms of safety evaluation, the rate of TRAEs in the treatment group was significantly lower than that in the control group and the patients in the treatment group had no liver and kidney function injury, but discomfort in the stomach. To timely monitor the changes of liver and renal function, we set the abnormal liver and renal function as higher than the upper limit of the normal, or abnormal liver and renal function before treatment, while further increased after treatment to protect the patient's health. Although the reported percentage of abnormal liver and renal function

Table 8: Comparison of pain cure rate between the two groups (n (%)).

	Group	N	Pain cure rate	P value
FAS	Treatment group	57	20 (35.09%)	0.698
	Control group	57	22 (38.60%)	
PPS	Treatment group	53	19 (35.84%)	0.597
	Control group	52	20 (38.46%)	

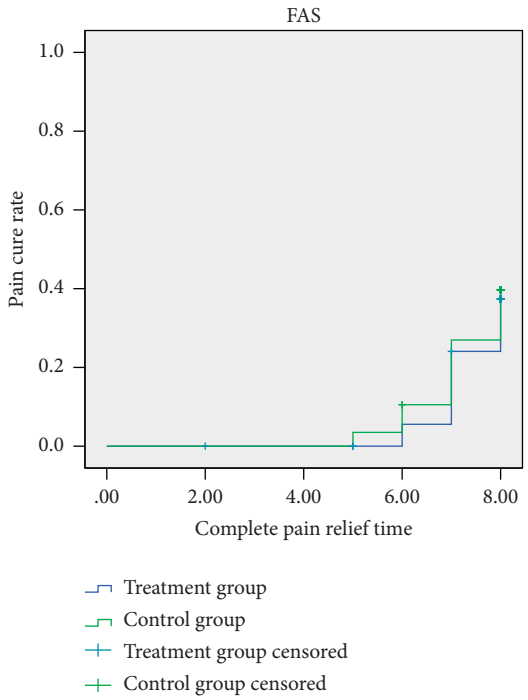


Figure 4: Survival curves for complete pain relief time (FAS).

Table 9: Patient satisfaction score between the two groups (M (P_{25}, P_{75})).

	Group	N	Score	Statistics	P value
PPS	Treatment group	53	4 (4, 4)	$Z = -1.850$	0.064
	Control group	52	5 (4, 5)		

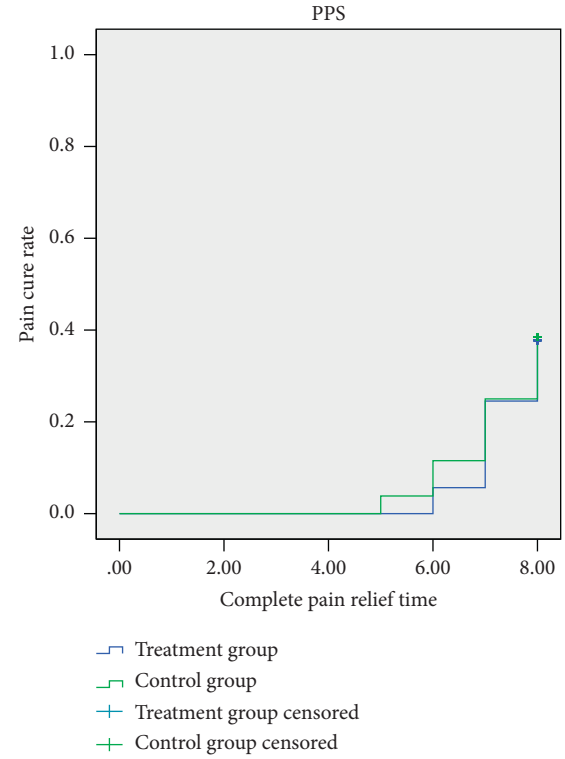


Figure 5: Survival curves for complete pain relief time (PPS).

was higher in the control group, there was no serious liver and renal injury occurred in the patients. The side effects of nonsteroidal drugs on the digestive system have been widely concerned by clinical workers. Clinical studies have shown that they will increase the risk of digestive tract, cardiovascular, and kidney disease [32]. Although the treatment course of this study was short, it has been observed that patients in the control group had abnormal liver and kidney function and adverse reactions of digestive tract. Moreover, clinical studies have pointed out that long-term use of diclofenac sodium could increase the risk of upper digestive tract, especially in elderly patients [33]. Our study suggests that QPTFF is safer than diclofenac sodium sustained-release tablets.

QPTFF is optimized and improved from Qinpi powder in the ancient Chinese book *Taiping Shenghui recipe* (AD 992). This compound contains *Cortex Fraxini* (Qin Pi), *Rhizoma Coptidis* (Huang Lian), *Semen Plantaginis* (Che Qian Zi), *Rhizome Dioscoreae Hypoglaucae* (Bi Xie), *Rhizoma Smilacis Glabrae* (Tu Fu Ling), *Radix Clematidis* (Wei Ling Xian), *Herba Siegesbeckiae* (Xi Xian Cao), and *Radix Saposhnikoviae* (Fang Feng). QPTFF has the functions of clearing heat and detoxification, removing dampness and turbidity, dredging arthralgia, and relieving pain. The total coumarin of Qinpi in *Cortex Fraxini* can reduce uric acid by inhibiting the activity of xanthine oxidase [34]. *Cortex Fraxini* extract can reduce the level of urate anion transporter 1 (URAT1), so it has the effect of reducing uric acid [35]. Aesculetin B and Aesculetin A can also inhibit the release of inflammatory factors [36]. The components in *Rhizoma Smilacis Glabrae*, such as colchicine, syringic acid, and catechin, can inhibit the expression of inflammatory factors and have strong anti-inflammatory effects [37]. *Rhizoma Smilacis Glabrae* can reduce the serum uric acid concentration of mouse hyperuricemia model by inhibiting xanthine oxidase activity [38]. Berberine is an important component of *Rhizoma Coptidis*, which could inhibit the activation of NLRP3 inflammatory bodies and prevent IL-1β to resist inflammation [39]. Berberine in *Rhizoma Coptidis* can reduce the serum uric acid level and protect renal function by inhibiting the activation of NLRP3 inflammatory bodies and the abnormal expression of URAT1 [40]. There are sesquiterpenoids, diterpenoids, flavonoids, and other compounds in *Herba Siegesbeckiae*, which have anti-inflammatory and analgesic effects [41]. The extract of *Herba Siegesbeckiae* can also inhibit the activity of xanthine oxidase and reduce serum uric acid [42]. *Rhizome Dioscoreae Hypoglaucae* has anti-inflammatory and analgesic effects

Table 10: Comparison of ESR levels between the two groups ($\overline{x} \pm s/M$ (P_{25}, P_{75})).

	Group	N	Before treatment	After treatment	Comparison between groups P value
FAS	Treatment group	57	24.79 ± 14.49	8 (5, 16.5)	<0.001
	Control group	57	22.95 ± 13.48	14 (4.5, 23)	<0.001
	Comparison between groups		P value	0.656	
PPS	Treatment group	45	23 (12, 35)	5.5 (3, 11.5)	<0.001
	Control group	44	22.50 (13, 30.75)	5.5 (3, 13.5)	<0.001
	Comparison between groups		P value	0.297	

Table 11: Comparison of CRP levels between the two groups ($\overline{x} \pm s/M$ (P_{25}, P_{75})).

	Group	N	Before treatment	After treatment	Comparison between groups P value
FAS	Treatment group	57	40.18 ± 24.36	5.37 (3.13, 8.45)	<0.001
	Control group	57	25 (10.99, 50.41)	5.39 (3.13, 16.00)	<0.001
	Comparison between groups		P value	0.353	
PPS	Treatment group	45	15.93 (7.28, 44.25)	3.13 (3.13, 4.42)	<0.001
	Control group	44	18.07 (11.54, 51.58)	3.13 (3.13, 4.05)	<0.001
	Comparison between groups		P value	0.309	

Table 12: Comparison of serum uric acid levels between the two groups ($\overline{x} \pm s$).

	Group	N	Treatment group	Control group	Comparison between groups P value
FAS	Treatment group	45	565.97 ± 126.96	523.33 ± 100.64	0.004
	Control group	44	572.01 ± 119.20	562.20 ± 101.68	0.419
	Comparison between groups		P value	0.043	
PPS	Treatment group	45	565.39 ± 136.39	511.38 ± 96.47	0.003
	Control group	44	577.51 ± 120.78	564.80 ± 98.25	0.420
	Comparison between groups		P value	0.011	

Table 13: Comparison of adverse reactions between the two groups (n (%)).

The treatment-related adverse events	Treatment group ($n = 57$)		Control group ($n = 57$)	
	N	Adverse reaction classification	N	Adverse reaction classification
Abnormal liver function	0 (0%)	No	4 (7.02%)	Grade 2
Abnormal renal function	0 (0%)	No	2 (3.51%)	Grade 1
Nausea	0 (0%)	No	2 (3.51%)	Grade 1
Vomit	2 (3.51%)	Grade 1	0 (0%)	No
Acid reflux	0 (0%)	No	1 (1.75%)	Grade 1
Diarrhea	2 (3.51%)	Grade 1	3 (5.26%)	Grade 1
Stomachache	0 (0%)	No	2 (3.51%)	Grade 2
Dizzy	0 (0%)	No	1 (1.75%)	Grade 1
Total	4 (7.02%)		15 (26.32%)	
P value			0.012	

[43, 44]. The extract of *Rhizome Dioscoreae Hypoglaucae* can promote the excretion of uric acid by regulating the levels of organic anion transporter 1, murat1, and organic cation transporter 2 and has the effect of reducing uric acid [45]. There are many components with xanthine oxidase inhibitor effect in *Semen Plantaginis*, such as luteolin, mullein glycoside, golden sage grass flavin, so it has the effect of reducing uric acid [46]. *Plantain polysaccharide* may have renal protective effect by downregulating the expression of NLRP3, ASC, and caspase-1 protein and inhibiting the release of downstream inflammatory factors [47]. *Radix Clematidis* inhibits NF-κB and MAPK pathways in macrophages to reduce the production of proinflammatory factors, to function in anti-inflammatory and analgesic [48]. Polysaccharide of *Radix Saposhnikoviae* has anti-inflammatory and analgesic effects by regulating the expression of p53 and inhibiting the release of inflammatory factors [49]. The extract of *Radix Saposhnikoviae* can reduce blood uric

acid by inhibiting the activity of xanthine oxidase [50]. Therefore, these drugs can exert the clinical efficacy of anti-inflammatory and analgesic, reduce serum uric acid, and improve the symptoms of gout patients.

However, our study still has some limitations. This study only uses common efficacy indicators for observation, without the observation of the changes of immune indicators and images in AGA. Although the sample size of this study was estimated by the PASS 15.0 software, it was only the minimum sample size required by clinical practice, and there were only 3 hospitals in the study. In the future, more high-quality multicenter, large-sample randomized controlled trials should be carried out to observe the changes of immune indicators and images with AGA.

5. Conclusions

QPTFF can improve the symptoms and signs of patients with AGA, as well as the inflammatory indexes and serum uric acid level. Its analgesic effect is not inferior to diclofenac sodium sustained-release tablets, but it has more advantages in reducing the serum uric acid level and the rate of treatment-related adverse events. Therefore, QPTFF is an effective clinical treatment for AGA.

Abbreviations

TCM: Traditional Chinese medicine
AGA: Acute gouty arthritis
QPTFF: Qinpi Tongfeng Formula
VAS: Visual analog scale
ESR: Erythrocyte sedimentation rate
CRP: C-reactive protein
TRAEs: Treatment-related adverse events
FAS: Full analysis set
PPS: Per protocol set
NSAIDs: Nonsteroidal anti-inflammatory drugs
CRF: Case report form
BMI: Body mass index
CI: Confidence interval.

Data Availability

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request (Wei Liu: fengshiliuwei@163.com).

Ethical Approval

This study has been approved by the ethics committee of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (TYLL2021[Z]017).

Disclosure

Yihua Fan, Wei Liu, and Hang Lu are the co-first authors. The funded organization only provided financial support and did not play any role in the design, patient recruitment, data collection, statistical analysis, and paper writing of this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yihua Fan and Hang Lu conceived the study and developed the first trial protocol. Hang Lu, Wei Liu, and Yihua Fan designed the study and drafted the original manuscript. Hang Lu, Jian Liu, Rui Wu, Jun Zhao, and Xianheng Zhang collected the data. Wei Liu and Aihua Wang have revised the manuscript. All authors have read and approved the final version of the manuscript. Yihua Fan, Wei Liu, and Hang Lu equally contributed to this work and are co-first authors.

Acknowledgments

The authors thank Chen Yang (Tianjin University of Traditional Chinese Medicine) for his help with the English language. This study was supported by the National Natural Science Foundation of China (No. 82074377) and the Traditional Chinese Medicine Inheritance and Innovation "Hundred Million" Talent Project (Qihuang Project) (Chinese Medicine People's Education Letter [2018] No. 12)-Liu Wei Qihuang Scholar Studio Construction Project and Tianjin Key Specialty Program (20210602-1).

Supplementary Materials

Table S1: the CONSORT 2010 checklist. Table S2: joint symptom score. Table S3: TCM syndrome score. (*Supplementary Materials*)

References

[1] G. A. Johannsdottir, O. Palsson, H. Jonsson, and B. Gudbjornsson, "Gout—a treatable condition," *Laeknabladid*, vol. 104, no. 4, pp. 177–186, 2008.

[2] F. Piani and R. J. Johnson, "Does gouty nephropathy exist, and is it more common than we think?" *Kidney International*, vol. 99, no. 1, pp. 31–33, 2021.

[3] A. A. Ejaz, T. Nakagawa, M. Kanbay et al., "Hyperuricemia in kidney disease: a major risk factor for cardiovascular events, vascular calcification, and renal damage," *Seminars in Nephrology*, vol. 40, no. 6, pp. 574–585, 2020.

[4] L. Kaly, I. Bilder, M. Rozenbaum et al., "Acute gout sacroiliitis," *The Israel Medical Association Journal: The Israel Medical Association Journal*, vol. 23, no. 3, pp. 191-192, 2021.

[5] J. P. P. Lorenzo, M. H. M. Z. Sollano, E. O. Salido et al., "2021 Asia-pacific league of associations for rheumatology clinical practice guideline for treatment of gout," *International Journal of Rheumatic Diseases*, vol. 25, no. 1, pp. 7–20, 2021.

[6] M. Gottlieb, W. Rabah, and B. Long, "Colchicine for acute gout," *Academic Emergency Medicine*, vol. 29, 2022.

[7] K. E. G. Blake, J. L. Saag, and K. G. Saag, "What's new on the front-line of gout pharmacotherapy?" *Expert Opinion on Pharmacotherapy*, vol. 23, no. 4, pp. 453–464, 2022.

[8] N. Xiao, H. Chen, S.-Y. He et al., "Evaluating the efficacy and adverse effects of clearing heat and removing dampness method of traditional Chinese medicine by comparison with western medicine in patients with gout," *Evidence-Based*

Complementary and Alternative Medicine, vol. 2018, 18 pages, Article ID 8591349, 2018.

[9] W. Liu, Y.-H. Wu, B. Xue et al., "Effect of integrated traditional Chinese and western medicine on gout," *Journal of Traditional Chinese Medicine*, vol. 41, no. 5, pp. 806–816, 2021.

[10] H. Lu, W. Liu, Y. Fan et al., "Efficacy and safety of Qinpi Tongfeng formula combined with bloodletting therapy in the treatment of acute gouty arthritis: a study protocol for a randomized controlled trial," *Evidence-Based Complementary and Alternative Medicine*, vol. 20228 pages, Article ID 3147319, 2022.

[11] T. Neogi, T. L. T. A. Jansen, N. Dalbeth et al., "2015 gout classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative," *Arthritis & Rheumatology*, vol. 67, no. 10, pp. 2557–2568, 2015.

[12] Q. Jiang, M. Han, X. Tang, C. Luo, and X. Gong, "Guidelines for combined diagnosis and treatment of gout and hyperuricemia," *Journal of Traditional Chinese Medicine*, vol. 62, no. 14, pp. 1276–1288, 2021.

[13] X. N. Yu, H. Y. Wu, Y. P. Deng et al., "Yellow-dragon wonderful-seed formula for hyperuricemia in gout patients with dampness-heat pouring downward pattern: a pilot randomized controlled trial," *Trials*, vol. 19, no. 1, p. 551, 2018.

[14] A. Schoenfeld, K. Arbour, H. Rizvi et al., "Severe immune-related adverse events are common with sequential PD-(L) 1 blockade and osimertinib," *Annals of Oncology*, vol. 30, no. 5, pp. 839–844, 2019.

[15] M. D. Reed and W. Van Nostran, "Assessing pain intensity with the visual analog scale: a plea for uniformity," *Journal of Clinical Pharmacology*, vol. 54, no. 3, pp. 241–244, 2014.

[16] N. Dalbeth, C. S. Zhong, R. Grainger et al., "Outcome measures in acute gout: a systematic literature review," *Journal of Rheumatology*, vol. 41, no. 3, pp. 558–568, 2014.

[17] X. Zheng, *Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine*, China Pharmaceutical Science and T echnology Press, Beijing, China, 2002.

[18] X. Zheng, *Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine*, China Pharmaceutical Science and Technology Press, Beijing, China, 2002.

[19] S. Wang, Y. Zhang, M. Dai et al., "Efficacy of rebixiao Chinese herbal tablets and Chinese formula granules in acute gout arthritis patients: a randomized, multicenter, double-blind, controlled trial," *Journal of Traditional Chinese Medicine*, vol. 40, no. 4, pp. 664–673, 2020.

[20] B. L. Wiens, "Multiple comparisons in non-inferiority trials: reaction to recent regulatory guidance on multiple endpoints in clinical trials," *Journal of Biopharmaceutical Statistics*, vol. 28, no. 1, pp. 52–62, 2018.

[21] N. Dalbeth, H. K. Choi, L. A. Joosten et al., "Gout (primer)," *Nature Reviews: Disease Primers*, vol. 5, 2019.

[22] J. D. FitzGerald, N. Dalbeth, T. Mikuls et al., "2020 American College of Rheumatology guideline for the management of gout," *Arthritis Care & Research*, vol. 72, no. 6, pp. 744–760, 2020.

[23] M. Hui, A. Carr, S. Cameron et al., "The British society for rheumatology guideline for the management of gout," *Rheumatology*, vol. 56, no. 7, p. 1246, 2017.

[24] E. Jia, Y. Zhang, W. Ma et al., "Initiation of febuxostat for acute gout flare does not prolong the current episode: a randomized clinical trial," *Rheumatology*, vol. 60, no. 9, pp. 4199–4204, 2021.

[25] Y. K. Zhang, H. Yang, J. Y. Zhang, L. J. Song, and Y. C. Fan, "Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout," *International Journal of Clinical Practice*, vol. 68, no. 5, pp. 633–638, 2014.

[26] S. Zhang, Y. Zhang, P. Liu, W. Zhang, J.-l. Ma, and J. Wang, "Efficacy and safety of etoricoxib compared with NSAIDs in acute gout: a systematic review and a meta-analysis," *Clinical Rheumatology*, vol. 35, no. 1, pp. 151–158, 2016.

[27] I. S. K. Thong, M. P. Jensen, J. Miró, and G. Tan, "The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure?" *Scandinavian journal of pain*, vol. 18, no. 1, pp. 99–107, 2018.

[28] Z. C.-X. Y. Zi-Han, X. Gui-Xing, Y. Cheng, and H. Ai-Ling, "Acupuncture and/or moxibustion for the treatment of lumbar disc herniation: quality assessment of systematic reviews," *Traditional Medicine Research*, vol. 5, no. 4, p. 282, 2020.

[29] X. Zhang, Y. Tang, M. Wang, D. Wang, and Q. Li, "The clinical efficacy of urate-lowering therapy in acute gout: a meta-analysis of randomized controlled trials," *Clinical Rheumatology*, vol. 40, no. 2, pp. 701–710, 2021.

[30] C. Bray, L. N. Bell, H. Liang et al., "Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine," *WMJ*, vol. 115, no. 6, pp. 317–321, 2016.

[31] A. Shiozawa, S. M. Szabo, A. Bolzani, A. Cheung, and H. K. Choi, "Serum uric acid and the risk of incident and recurrent gout: a systematic review," *Journal of Rheumatology*, vol. 44, no. 3, pp. 388–396, 2017.

[32] S. Harirforoosh, W. Asghar, and F. Jamali, "Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications," *Journal of Pharmacy & Pharmaceutical Sciences*, vol. 16, no. 5, p. 821, 2013.

[33] W. S. Wan Ghazali, W. M. K. B. Wan Zainudin, N. K. Yahya, A. Mohamed Ismail, and K. K. Wong, "Older age and diclofenac are associated with increased risk of upper gastrointestinal bleeding in gout patients," *PeerJ*, vol. 9, Article ID e11468, 2021.

[34] Y. Wang, M. Zhao, H. Ye et al., "Comparative pharmacokinetic study of the main components of cortex fraxini after oral administration in normal and hyperuricemic rats," *Biomedical Chromatography*, vol. 31, no. 8, Article ID e3934, 2017.

[35] Y. Zhou, X. Zhang, C. Li et al., "Research on the pharmacodynamics and mechanism of fraxini cortex on hyperuricemia based on the regulation of URAT1 and GLUT9," *Biomedicine & Pharmacotherapy*, vol. 106, pp. 434–442, 2018.

[36] B.-y. Yang, Y. Ming-yu, J. Pan, Y. Liu, and K. Hai-xue, "Research progress on chemical constituents and pharmacological effects of qinpi," *Information of traditional Chinese Medicine*, vol. 33, no. 6, pp. 116–119, 2016.

[37] F. Xu, F. Xu, F. C. Li et al., "Discovery of the active compounds of smilacis glabrae rhizoma by utilizing the relationship between the individual differences in blood drug concentration and the pharmacological effect in rats," *Journal of Ethnopharmacology*, vol. 258, Article ID 112886, 2020.

[38] D. Zhang, M. Zhao, Y. Li, D. Zhang, Y. Yang, and L. Li, "Natural xanthine oxidase inhibitor 5-O-caffeoylshikimic acid ameliorates kidney injury caused by hyperuricemia in mice," *Molecules*, vol. 26, no. 23, p. 7307, 2021.

[39] J. Wu, Y. Luo, Q. Jiang et al., "Coptisine from coptis chinensis blocks NLRP3 inflammasome activation by inhibiting caspase-1," *Pharmacological Research*, vol. 147, Article ID 104348, 2019.

[40] Q. Li, Z. Huang, D. Liu et al., "Effect of berberine on hyperuricemia and kidney injury: a network pharmacology analysis and experimental validation in a mouse model," *Drug Design, Development and Therapy*, vol. 15, pp. 3241–3254, 2021.

[41] Q. Wang, Y.-Y. Liang, K.-W. Li et al., "Herba siegesbeckiae: a review on its traditional uses, chemical constituents, pharmacological activities and clinical studies," *Journal of Ethnopharmacology*, vol. 275, Article ID 114117, 2021.

[42] T. D. Nguyen, P. T. Thuong, I. H. Hwang et al., "Anti-hyperuricemic, anti-inflammatory and analgesic effects of Siegesbeckia orientalis L. resulting from the fraction with high phenolic content," *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, p. 191, 2017.

[43] Y. Zhang, H.-Y. Yu, L.-P. Chao et al., "Anti-inflammatory steroids from the rhizomes of dioscorea septemloba thunb," *Steroids*, vol. 112, pp. 95–102, 2016.

[44] L. Liu, D. Wang, M. Liu et al., "The development from hyperuricemia to gout: key mechanisms and natural products for treatment," *Acupuncture and Herbal Medicine*, vol. 2, no. 1, pp. 25–32, 2022.

[45] Y. Chen, X.-l. Chen, T. Xiang et al., "Total saponins from dioscorea septemloba thunb reduce serum uric acid levels in rats with hyperuricemia through OATP1A1 up-regulation," *Journal of Huazhong University of Science and Technology - Medical sciences*, vol. 36, no. 2, pp. 237–242, 2016.

[46] Y. Guan, T. Ye, Y. Yi, H. Hua, and C. Chen, "Rapid quality evaluation of plantaginis semen by near infrared spectroscopy combined with chemometrics," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 207, Article ID 114435, 2022.

[47] H. Zhao, J. Xu, R. Wang et al., "Plantaginis semen polysaccharides ameliorate renal damage through regulating NLRP3 inflammasome in gouty nephropathy rats," *Food & Function*, vol. 12, no. 6, pp. 2543–2553, 2021.

[48] L. Cai, S.-Y. Shao, S.-W. Han, and S. Li, "Sesquiterpenoids, phenolic and lignan glycosides from the roots and rhizomes of Clematis hexapetala Pall. and their bioactivities," *Bioorganic Chemistry*, vol. 104, Article ID 104312, 2020.

[49] B. Ci, W. Wang, and Y. Ni, "Inhibitory effect of saposhnikovia divaricate polysaccharide on fibroblast-like synoviocytes from rheumatoid arthritis rat in vitro," *Pakistan Journal of Pharmaceutical Sciences*, vol. 31, pp. 2791–2798, 2018.

[50] C. W. Kim, J. H. Sung, J. E. Kwon et al., "Toxicological evaluation of saposhnikoviae radix water extract and its antihyperuricemic potential," *Toxicological Research*, vol. 35, no. 4, pp. 371–387, 2019.