Evidence-Based Complementary and Alternative Medicine

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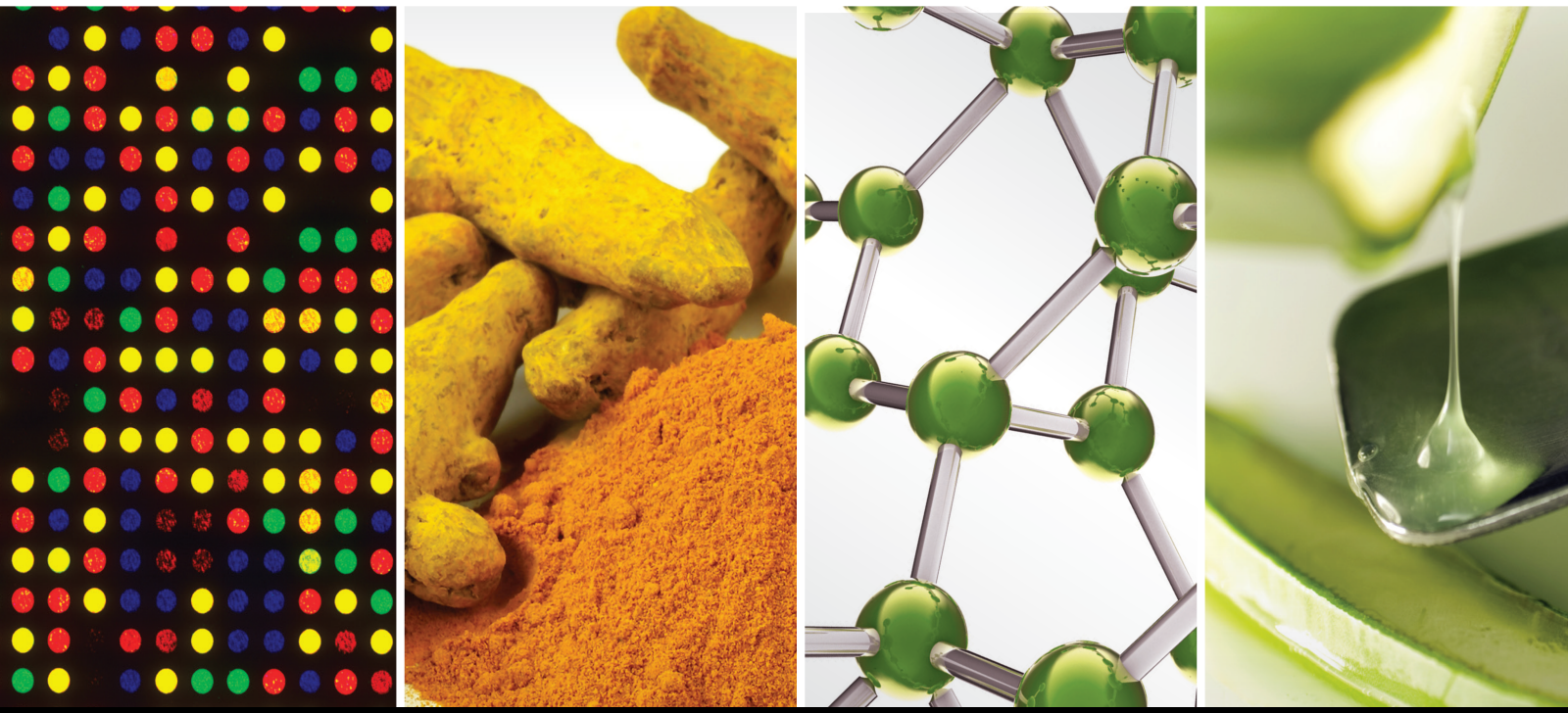

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Research Article

Exploring the Mechanism through which *Phyllanthus emblica* L. Extract Exerts Protective Effects against Acute Gouty Arthritis: A Network Pharmacology Study and Experimental Validation

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Increased uric acid levels and inflammatory reactions are the main factors considered responsible for the development of gouty arthritis. *Phyllanthus emblica* L. (PEL) has several promising pharmacological properties, including anti-inflammation and antioxidation. However, only a few studies have investigated its use for treating acute gouty arthritis (AGA), and the mechanism of action of PEL has not yet been clarified. The aim of this study was to verify the protective effects of PEL against gout and explore its underlying mechanism through network pharmacology and animal experiments. The main active components of the extract from PEL including mucic acid, mucic acid lactone, gallic acid, ethyl hexyl phthalate, and glucose were identified by UPLC-ESI-qTOF-MS. Network pharmacological analysis results revealed 13 active compounds in PEL and 85 related targets for the treatment of gout. The core mechanism of action of PEL is mainly associated with inflammation-related pathways, including the HIF-1, PI3K-Akt, TNF, and NOD-like receptor signaling pathways. Previous studies revealed that the NOD-like receptor signaling pathway, especially the NLRP3 inflammasome, plays an important role in the pathogenesis of AGA; therefore, we mainly investigated the effect of PEL on the NLRP3/ASC/caspase-1 pathway in gout rats. In the animal experiments, PEL was shown to have a satisfactory antigout effect, as it effectively reduced uric acid (UA) and xanthine oxidase (XOD) levels. In terms of inhibiting AGA-associated inflammatory reactions, our results showed that PEL significantly decreased the expression of NLRP3 and caspase-1 in ankle synoviocytes as well as the levels of downstream inflammatory factors, such as TNF-α, IL-10, and IL-1β in serum. Moreover, the results of our study show that PEL reduced MMP13 expression in the ankle synovium. Overall, the results of this study indicate that PEL exerted a therapeutic effect against AGA. Reducing uric acid levels, inhibiting inflammation, and decreasing the expression of MMP13 may be responsible for the therapeutic effect of PEL, which suggests that PEL can be further developed as a drug for the treatment of gout.

1. Introduction

Gout is a metabolic disease caused by the deposition of monosodium urate (MSU) in joints or tissues, and hyperuricemia is the main risk factor for gout [1]. Abnormally elevated serum uric acid (UA) levels (≥408 μmol/L or 6.8 mg/dL) caused by the excessive intake of purine or poor renal excretion of UA increases the risk of developing AGA. Epidemiological studies show that the global prevalence rate of gout is 0.1–10% [2]. In western developed countries, the prevalence rate of gout in recent years has been 3–6% in men and 1-2% in women [3], which is significantly higher than that in previous decades. Currently, the clinical treatments for acute gouty arthritis (AGA) mainly consist of reducing serum UA levels and alleviating inflammation. In addition, the key genes involved in uric acid excretion, such as *SLC2A9*, *ABCG2*, and matrix metalloproteinase 13 (*MMP13*), which are related to cartilage degradation, are expected to become the new therapeutic targets for AGA [4–6].

Although allopurinol is widely considered the first-line drug for the treatment of gout, it has notable side effects, such as rash, allergy, and kidney damage [7], and patients are still at risk of recurrence after treatment with allopurinol alone or in combination with other drugs. Tibetan medicine has a long history of application in the treatment of gouty arthritis. For example, "Triphala", which is prepared by mixing fruits of *P. emblica*, *Terminalia chebula*, and *T. bellerica* in equal proportions, has achieved good clinical efficacy in the treatment of hyperuricemia and gout [8]. As one of the main ingredients of these prescriptions, *Phyllanthus emblica* L. (PEL) has been considered to own the potential to treat gout [9]. Modern pharmacological studies have shown that the phenolic acids of PEL, which mainly consist of gallic acid, have anti-inflammatory and UA-lowering properties [10]. Sumantran et al. found that PEL extract exerts protective and reparative effects on cartilage injury [11]. Sarvaiya et al. also revealed the antigout activity of PEL on potassium oxonate induced gout rat model [12] Besides, according to the research of Cen, the anti-inflammatory and analgesic effect of PEL is partly due to its capacity to inhibit the release of inflammatory cytokines [13]. However, to date, only limited studies have investigated the mechanism of action of PEL in the treatment of gout.

Chinese medicine is a complex system with multiple components, multiple targets, and synergistic interactions among components [14], and thus, it is extremely difficult to study its role. Network pharmacology provides a novel perspective and strategy for the research of traditional Chinese medicine. The purpose of this study was to investigate the therapeutic effect of PEL on AGA as well as explore its mechanism of action. To this end, we used network pharmacology to study the active substances of PEL, determine the targets of its active components and the relationship between effective components and diseases, and construct a component-target-pathway (CTP) diagram to examine the mechanism through which PEL exerts protective effects against AGA.

2. Materials and Methods

2.1. Animals. Specific-pathogen-free (SPF) male Sprague Dawley (SD) rats weighing 200 ± 20 g were provided by the Guangdong Medical Experimental Animal Center (Guangzhou, China) [experimental animal license: SYXK (Guangdong) 2017-0125]. All rats lived in the barrier system of the Experimental Animal Center of Guangdong Pharmaceutical University. The rats were fed with pure water and standard food and housed at 24 ± 2°C under a 12 h light/12 h dark cycle. All animal experiment procedures were approved by the Ethics Committee of the Animal Experiment Committee of Guangdong Pharmaceutical University (ethical license no. gdpulacspf2017380).

2.2. Plant Materials. PEL was obtained from Puning City, Guangdong Province, China, and identified by Associate Professor Hongyan Ma (College of Traditional Chinese Medicine, Guangdong Pharmaceutical University).

2.3. Preparation of Ethanol Extract of PEL. The ethanol extract of PEL was obtained as described previously [15]. Briefly, raw PEL was washed, enucleated, and dried, and 126.0 g of the raw material was weighed. Next, we added 1,890 mL 75% ethanol to a 2 L round bottom flask for ultrasonic extraction for 25 min, with a solid/material ratio of 1 : 15. The extraction temperature was 45.8°C, and the extract was filtered and extracted three times. The experiment was repeated twice, the filtrate was concentrated to 252 mL at 45°C using a rotary evaporator, and the ethanol extract of PEL with a concentration of 0.5 gmL^{-1} was obtained.

2.4. Model Preparation and Drug Therapy. One week after adaptive feeding, SD rats were weighed and divided into five groups ($n = 9$): Control, Model, Colchicine, low-dose PEL-treated (PEL-L), and high-dose PEL-treated (PEL-H). AGA models were established for the Model, Colchicine, PEL-L, and PEL-H groups, and the Control group was given the same amount of normal saline as the other groups.

The method used to establish the AGA model was as follows [16–18]: 3% potassium oxycyanate was prepared and injected intraperitoneally into the rats with a dosage of 1 $mL{\cdot}100\,g^{-1}$ twice for 7 days. On day 4 after the beginning of modeling, the urate crystals were injected into the medial side of the tibiotarsal joint (ankle) of the rats, while they were under ether anesthesia. A small incision was created over the ankle on the dorsal side of the hind limb, and the needle was inserted into the medial side of the tendon of the tibialis anterior. Next, 0.05 mL of sodium urate solution ($25\,mg{\cdot}mL^{-1}$) was injected into the articular cavity using a 21-gauge needle with its tip beveled to 45°, and the contralateral bulging of the articular capsule was used as the injection standard to establish the AGA model. After injection, the rats showed lameness and joint swelling and could not bear weight, which was an indicator of the successful establishment of the model. The Control group was injected with the same volume of normal saline at the same site.

The administration procedure was as follows: after the first injection of potassium oxycyanate, the drug was administered intragastrically for 7 days. The Control and Model groups were administered the same volume of normal saline, and the Colchicine group was administered 0.05 $mg{\cdot}100\,g^{-1}$ colchicine. Referring to the Chinese Pharmacopoeia and related literature [19], the PEL-H group was fed PEL at a dose of 5 $g{\cdot}kg^{-1}{\cdot}d^{-1}$, while the low-dose group was fed PEL at a dose of 2.5 $g{\cdot}kg^{-1}{\cdot}d^{-1}$. Nine rats in each group were injected intraperitoneally with the crude drug dose corresponding to their daily body weight.

2.5. Component Analysis via High-Resolution UPLC-MS Analysis

2.5.1. UHPLC-ESI-QTOF-MS Conditions. The ultra-performance liquid chromatography-tandem mass spectrometry was performed using an Ultimate 3000 UHPLC system with a WPS-3000 autosampler, coupled to a Q-Exactive Orbitrap MS spectrometer, which is combined

with quadrupole ion selection and Orbitrap high-resolution scanning (Thermo Fisher Scientific, Waltham, MA, USA). The chromatographic separation was carried out on a Waters ACQUITY UPLC BEH C18 column (100 mm × 2.1 mm, 1.7 μm particle size; Waters, Milford, CT, USA). Chromatographic separations were performed at 25°C employing a gradient elution using 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) as mobile phase at a flow rate of 0.15 mL/min. The elution consisted of a gradient of 95% A, 0-1 min; 5%–95% A, 1–16 min; 95% A, 16–18 min; and 5% B, 18–20 min, and the initial condition was maintained for 5 min. The sample injection volume was 10 μL.

For MS detecting, a Q-Exactive Orbitrap-MS spectrometer was fitted with a heated electrospray ionization (ESI) ion source in both negative and positive ionization mode at full-scan mode ranging m/z 100–1000. The optimal MS parameters were as follows: spray voltage −2.8 kV/+3.5 kV; sheath gas flow rate, 35 arbitrary units; auxiliary gas flow rate, 10 arbitrary units; capillary temperature, 320°C; and auxiliary gas heater temperature, 350°C. The resolutions of full scan and dd-ms2 were 70,000 and 35,000 FWHM (full width at half maximum), while their AGC targets were set as 3×106 and 1×105, with their maximum IT (the maximum injection time allowed to obtain the set AGC target) 100 and 50 ms, respectively. The stepped NCE (normalized collision energy) was set to 35 V for MS/MS acquisition.

2.5.2. Structure Analysis Procedure. MassLynx V4.1 software (Waters Corporation) was used to process the data. Manual identification was performed to characterize the chemical constituents from PEL by comparing the exact mass and fragmentation pattern of the compounds that were previously reported in articles.

2.6. Pharmacology Research

2.6.1. Degree of Ankle Swelling. Following the injection of MSU crystals, the width of the right ankle joint at different time intervals was measured using a vernier scale. The left and right diameters (a) and the anteroposterior diameter (b) of the ankle joint were measured before establishing the arthritis model, 12 h, 24 h, and 48 h after the administration of the MSU crystals [20]. The ankle joint volume was calculated using the following formula: ankle joint volume = $1/2 \times ab^2$.

2.6.2. Inflammation Index and Dysfunction Index. The progression of acute arthritis was evaluated by the macroscopic scoring of the ankle joint. Data were recorded prior to establishing the arthritis model and 24 h after the administration of the MSU crystals. The inflammation and dysfunction scores of the rats were visually determined by two independent observers.

The following criteria were used to score dysfunction [21]:

Grade 0 (0 points): there is normal gait and both feet are evenly grounded.

Grade 1 (1 points): toes are not unfolded and foot is slightly limp.

Grade 2 (2 points): foot is bent and clearly limping and toes are on the ground.

Grade 3 (3 points): foot is completely lifted off the ground and there is three-legged gait.

The following criteria were used to score inflammation [22]:

Grade 0 (0 points): ankle joint is normal without any inflammatory reaction.

Grade 1 (2 points): joints have erythema of skin, mild swelling, and visible bony marks.

Grade 2 (4 points): joints are notably red and swollen, bony landmarks have disappeared, and swelling is limited to the joints.

Grade 3 (6 points): there is swelling outside the joint, the degree of inflammatory reaction is more severe, the ability of the foot to move is weakened, and the foot is often lifted off the ground.

2.6.3. Blood and Tissue Sample Treatment. The blood and ankle synovium samples of rats were collected. Serum UA and XOD levels were measured using ultraviolet spectrophotometry; the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 in the serum were measured using ELISA. The expression of NLRP3, MMP13, and caspase-1 in the ankle joint synovium was detected by western blotting. The pathological changes in the ankle joint were observed by hematoxylin and eosin (HE) staining.

2.6.4. HE Staining Analysis. The joint synovium tissue was incubated in 4% paraformaldehyde solution for 24 h and subjected to gradient alcohol dehydration and routine paraffin embedding. Next, the joint synovium tissue was sliced into 5 μm sections, and pathomorphological changes were observed using a microscope after HE staining.

2.6.5. Measurement of Serum UA and XOD Levels. The obtained blood samples were centrifuged for 15 min. The upper serum layer was obtained, placed in an EP tube, and stored at −80°C. Next, the serum UA and XOD levels of each group were measured using the UA Test Kit and XOD Assay Kit, respectively (Nanjing Jiancheng Bioengineering Institute, Nanjing, China), according to the manufacturer's instructions. The detection wavelength was 490 nm, and the absorbance of the sample (A), blank (A_0), and standard (A_1) holes was measured. The standard concentration was 400 μmol/L (C). The serum UA levels were calculated using the following formula:

$$\text{UA concentration}\left(\mu\text{mol} \cdot \text{L}^{-1}\right) = \frac{(A - A_0)}{(A_1 - A_0)} \times C. \quad (1)$$

XOD level was calculated using the following formula:

$$\text{XOD level}\left(\frac{U}{L}\right) = (A - 0.018) \times \frac{2.37}{(0.0126 \times 2)}. \quad (2)$$

2.7. Network Analysis

2.7.1. Identification and Screening of Active Components of PEL. Information on all components of PEL was collected from the PubMed and Traditional Chinese Medicine Database and Analysis Platform (TCMSP) databases [23]. The molecular formula and CAS number of each compound were obtained from the PubChem database [24].

Among the analyzed components, the compounds which met the conditions of OB ≥30% and DL index ≥0.18 were selected as active substances to create the database of PEL compound information. Oral bioavailability (OB) is considered one of the most important pharmacokinetic parameters in the process of absorption, distribution, metabolism, and excretion [25]. OB values greater than or equal to 30% are usually considered high OB values; high OB values are important indicators for the determination the drug-like (DL) index of active compounds. As a qualitative concept used to evaluate molecular efficacy in drug design, the DL index is often used for the rapid screening of active compounds [26]. In the DrugBank database, the average DL index is 0.18, and compounds with DL indices greater than or equal to 0.18 are considered to have high DL properties.

2.7.2. Prediction of Targets of Active Components of PEL. The similarity ensemble approach and BATMAN-TCM databases were used to predict the compounds screened (as described in Section 2.1), with "*Homo sapiens*" as the restriction condition [27]. Next, the potential targets of the components were obtained.

2.7.3. Collection of AGA-Related Disease Targets. AGA-related targets were obtained from the GeneCards, DrugBank, and OMIM databases [28–30]. After obtaining the aforementioned AGA-related disease targets, we deleted the repeated targets and constructed the disease target information database. Next, the disease targets of AGA were matched with the component targets of PEL to obtain the overlapping targets.

2.7.4. Construction of a Protein-Protein Interaction (PPI) Network. The Molecular Complex Detection (MCODE) plug-in was used to import the intersection targets, as described in Section 2.1, into the STRING database [31], and the targets with interaction values greater than 0.7 were selected to construct a PPI network. Next, the results were imported into the Cytoscape 3.7.0 software, and the degree value of the nodes in the network was analyzed by the Network Analyzer function to screen the core target. In the PPI network, the higher the degree value of the target, the more important its role.

2.7.5. GO and KEGG Pathway Enrichment Analysis. "OFFICIAL-GENE-SYMBOL," "$P \leq 0.05$," and "*Homo sapiens*" were chosen as limited conditions to obtain the data, and GO and KEGG pathway enrichment analyses were carried out using the DAVID database [32, 33]. The results were in descending order according to the enrichment degree of the target. Then, we screened the top 10 processes and pathways and visualized them.

2.7.6. Construction of a CTP Network. PEL components, intersection targets, and important pathways were imported into Cytoscape 3.7.0 to construct the CTP network of PEL.

2.8. Mechanism Validation

2.8.1. Measurement of TNF-α, IL-1β, and IL-10 Levels. TNF-α, IL-1β, and IL-10 levels in the serum of rats in each group were measured using the TNF-α, IL-1β, and IL-10 ELISA kits, respectively (Cusabio, Wuhan, China), according to the manufacturer's instructions.

2.8.2. Western Blotting of the Ankle Joint Synovium. The tissue samples were lysed on ice for 30 min using 1 × RIPA lysis buffer (Thermo Fisher Scientific, Waltham, MA, USA) containing protease inhibitor (Roche, Basel, Switzerland). The proteins in each sample were separated using sodium dodecyl sulfate–polyacrylamide gel electrophoresis on 12% polyacrylamide gels and were blotted onto a polyvinylidene fluoride membrane (Millipore Corporation, Germany). The membrane was blocked with 5% BSA in PBS for 1 h. It was then immersed in the corresponding primary antibody at 4°C overnight. On the second day, the membrane was incubated with the relevant secondary antibody (1 : 2000; Beyotime, Shanghai, China). TBST was used to rinse the strips thrice (15 min/times) throughout the whole process. Then, the developer was added, and the protein strips were detected and analyzed using ImageJ software (NIH, Bethesda, MD, USA).

2.9. Statistical Analysis. Data analysis was performed using SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA), or GraphPad Prism 6.0 software. Data are presented as the mean ± standard deviation (SD) from at least three independent experiments, and each independent experiment was repeated three times to obtain the mean. Normally distributed datasets were analyzed with the unpaired Student's *t*-test for two independent groups or paired *t*-test for two dependent groups, and the one-way analysis of variance (ANOVA) followed by the Bonferroni's multiple comparisons test was performed for more than three groups. For all statistical comparisons, $P < 0.05$ was considered statistically significant and denoted with one, two, and three asterisks when lower than 0.05, 0.01, and 0.001, respectively.

3. Results

3.1. Identification of the Compounds. UPLC-ESI-qTOF-MS chromatogram was employed to identify the main components in the ethanol extract of PEL. The total ion

chromatogram profile of the tannin fraction of PEL was presented in both negative and positive ion modes, as shown in Figure 1(a). The possible structures of 5 peaks were deduced as shown in Figures 1(b)–1(f)). Under the optimized MS conditions, the negative and positive ion modes were used to identify the peaks of 5 main compounds including gallotannins, glucose, and phthalates. Data for all of these compounds are summarized in Table 1.

3.2. Pharmacology Research

3.2.1. Protective Effect of PEL against Gout in Rats. We first confirmed the therapeutic effect of PEL on gout. The appearance of ankle joint was observed 24 h after MSU injection (Figure 2(a)). Compared with the Model group, the ankle joint swelling in the Colchicine group improved significantly, and various symptoms, such as redness, swelling, and fever, disappeared. Compared with the Model group, the PEL-L and PEL-H groups experienced significant improvements in terms of ankle swelling and redness and fever elimination, but there was no significant difference between the two different concentration groups.

As shown in Figure 2(b), the dysfunction index of gout rats was significantly lower in the PEL-H group than in the Model group ($P < 0.05$). The ankle joint diameters of the rats in each group were measured at 0 h, 2 h, 4 h, 8 h, 24 h, and 48 h after MSU injection, and the degree of ankle swelling was calculated at each time point (Figure 1(c)). The ankle joint swelling degree in the Model group continued to increase 4 h after MSU injection; however, the ankle joint swelling degree of the Control, Colchicine, PEL-L, and PEL-H groups began to decrease. The ankle joint swelling degree was lower in both PEL groups than in the Model group at 8 h, 12 h, 24 h, and 48 h after injection. Collectively, our results revealed that PEL could reduce joint swelling in acute gout rats, and its effects began to appear 4 h after MSU injection.

3.2.2. PEL Reduced the Levels of Serum Uric Acid in Gout Rats. As the high uric acid levels are often an important factor accounting for gout, we studied the effect of PEL on uric acid next. The results showed that PEL significantly decreased serum UA levels in gout rats (Figure 3(a), $P < 0.001$), indicating that PEL exerts a positive effect on reducing uric acid levels. In addition, XOD activity decreased significantly in the PEL-H group; this activity also decreased in the PEL-L group but not significantly (Figure 3(b), $P < 0.001$).

3.2.3. PEL Attenuates Ankle Joint Inflammation in Gout Rats. Then, we investigate the protective effect of PEL against AGA which is mainly caused by the deposition of MSU. As shown in Figure 4(a), in the Control group, the structure of the ankle and its surrounding tissue was normal and clear, without any histopathological changes. The synovial epithelium was intact, and there was no inflammatory cell infiltration. In the Model group, inflammatory cells infiltrated the synovium and surrounding tissues. Pathological changes, such as synovium hyperemia, joint structure disorder, or incomplete joint structure, can be observed in the Model group. In the Colchicine group, the infiltration of inflammatory cells improved significantly, but pathological changes were still observed, such as a disordered and incomplete arrangement of joint structures. A small amount of inflammatory cell infiltration was observed in the PEL-L group, which was improved compared with the model group. In the PEL-H group, the joint structure was intact, and there was no exudate, dilatation, and hyperemia of the surrounding soft tissue vessels in the joint cavity. Compared with the model group, different doses of PEL could reduce synovial hyperplasia and inflammatory cell infiltration to different degrees. As shown in Figure 3(b), PEL significantly reduced the inflammatory response of ankle joints in gout rats.

3.3. Network Pharmacological Analysis

3.3.1. Active Compounds in PEL. Network pharmacological analysis was used to further investigate the mechanism of anti-inflammatory effect. A total of 93 PEL compounds were obtained through literature search and the TCMSP database. After pharmacokinetic determination, 13 active compounds were obtained by setting OB ≥30% and DL ≥0.18. The component noted with "*" was included in the construction of PEL active compound database owing to its strong biological activity and clear pharmacological effect. The results are shown in Table 2.

3.3.2. Acquisition of Disease Targets for AGA and Intersection Targets. In total, 556 gene targets of PEL active components were obtained from the similarity ensemble approach and BATMAN-TCM databases. We screened 1,815 possible AGA-related targets by using the keywords "Gout" and "Acute gouty arthritis" in the GeneCards, DrugBank, and OMIM databases. In total, 85 intersection targets were obtained by pairing the AGA-related targets with the component targets of PEL, and the Wayne diagram of the intersection targets was constructed using Venny 2.1.0 (Figure 5).

3.3.3. Construction of PPI Network. The intersection targets were analyzed using the STRING database, and the PPI network diagram was constructed using Cytoscape 3.7.0 to analyze the results (Figure 6). The nodes represented the screened active components and targets, and the connections between the nodes represented the interactions between these bioanalyses. The node value represented the number of connections between molecules and targets in the core architecture of the network. In the PPI network, the larger the degree value of the node is, the more critical the biological role it may play [34]. The PPI network showed 170 nodes and 1,105 edges, with an average node value of 13. Among them, *Akt1* (degree value: 55), *Il6r* (degree value: 51), and *Il1b* (degree value: 45) were considered the hub genes in the PPI network.

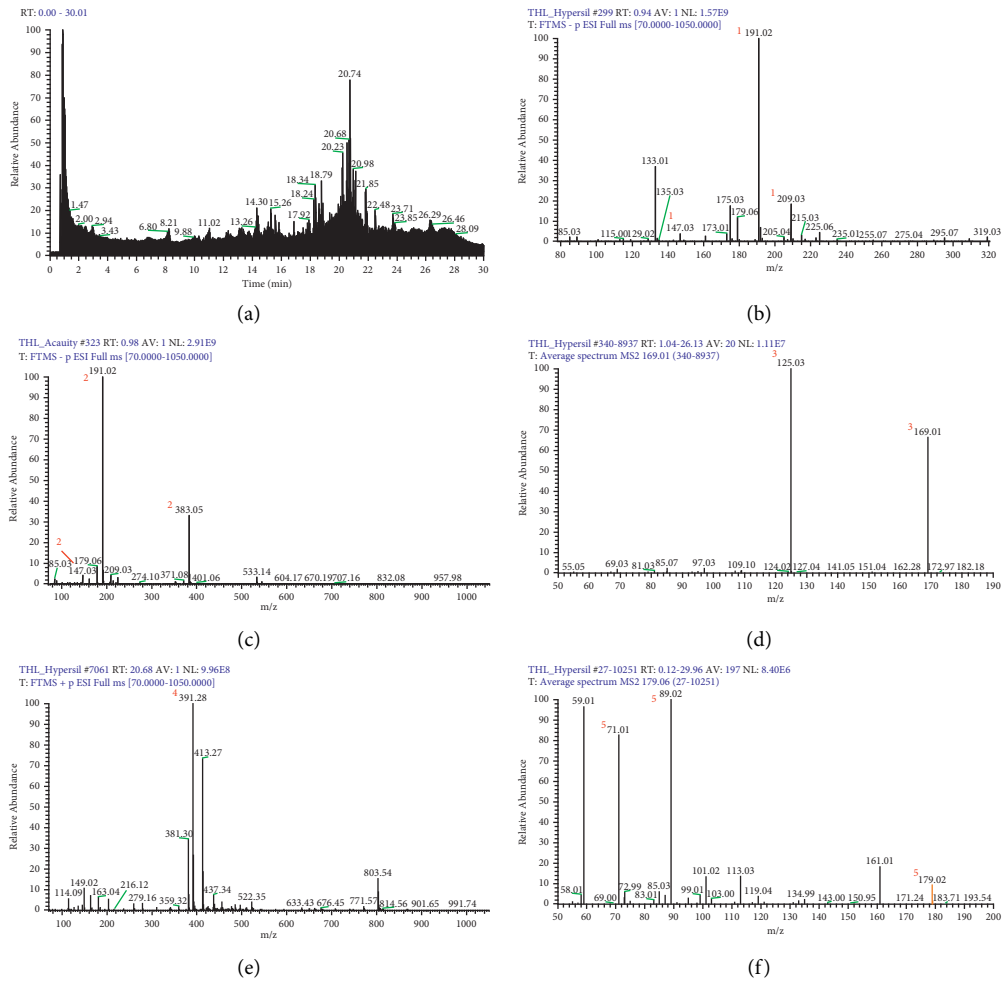


Figure 1: UPLC-MS^n chromatogram of the tannin fraction of PEL (a). Representative UPLC-QTOF-MS base peak chromatograms of mucic acid ((b) peak 1); mucic acid lactone ((c) peak 2); gallic acid ((d) peak 3); ethyl hexyl phthalate ((e) peak 4); and glucose ((f) peak 5).

Table 1: The UPLC-MS^n data and main compound names of the 5 peaks.

Peak no.	Scan mode	t R (min)	Molecular formula	[M ± H]	Identification	ppm	Identification
[a]1	Negative	0.81	$C_6H_{10}O_8$	209.0307	MS1: 209.0307 $[M-H]^-$, MS2: 191.0202 $[M\text{-}H_2O\text{-}H]^-$, 147.0302 $[M\text{-}H_2O\text{-}CO_2\text{-}H]^-$	−0.48	Mucic acid
[a]2	Negative	0.88	$C_6H_8O_7$	191.0202	MS1: 191.0202 $[M-H]^-$, 383.0477 $[2M-H]^-$ MS2: 147.0302 $[M\text{-}CO_2\text{-}H]^-$	0.52	Mucic acid lactone
[a]3	Negative	1.61	$C_7H_6O_5$	169.0149	MS1: 169.0149 $[M-H]^-$, MS2: 125.0251 $[M\text{-}CO_2\text{-}H]^-$	0.59	Gallic acid
[b]4	Positive	20.68	$C_{24}H_{39}O_4$	391.2838	MS1: 391.2838 $[M+H]^+$	−0.51	Ethyl hexyl phthalate
[c]5	Negative	2.26	$C_6H_{12}O_6$	179.0564	MS1: 179.0564 $[M-H]^-$, MS2: 101.0248 $[C_4H_5O_3]^-$, 89.0242 $[C_3H_5O_3]^-$, 71.01382 $[C3H_2O_2]^-$	−2.78	Glucose

a: Gallotannins, b: Phthalates, c: Glucose.

3.3.4. GO and KEGG Enrichment Analyses. Gene ontology (GO) enrichment analysis was used to further investigate the intersection targets, and the pathways involved in the top 10 intersection targets were constructed in a GO enrichment analysis path map (Figure 7): (1) 347 biological processes (BP) were involved in obtaining the active components of PEL, mainly comprising the positive regulation of transcription from RNA polymerase II promoter, signal transduction, and inflammatory response; (2) 47 related cellular components (CC) were obtained, including the nucleus, cytoplasm, and cytosol; and (3) 78 molecular functions (MF) related to the intersection targets were enriched, including protein binding, ATP binding, and protein homodimerization activity.

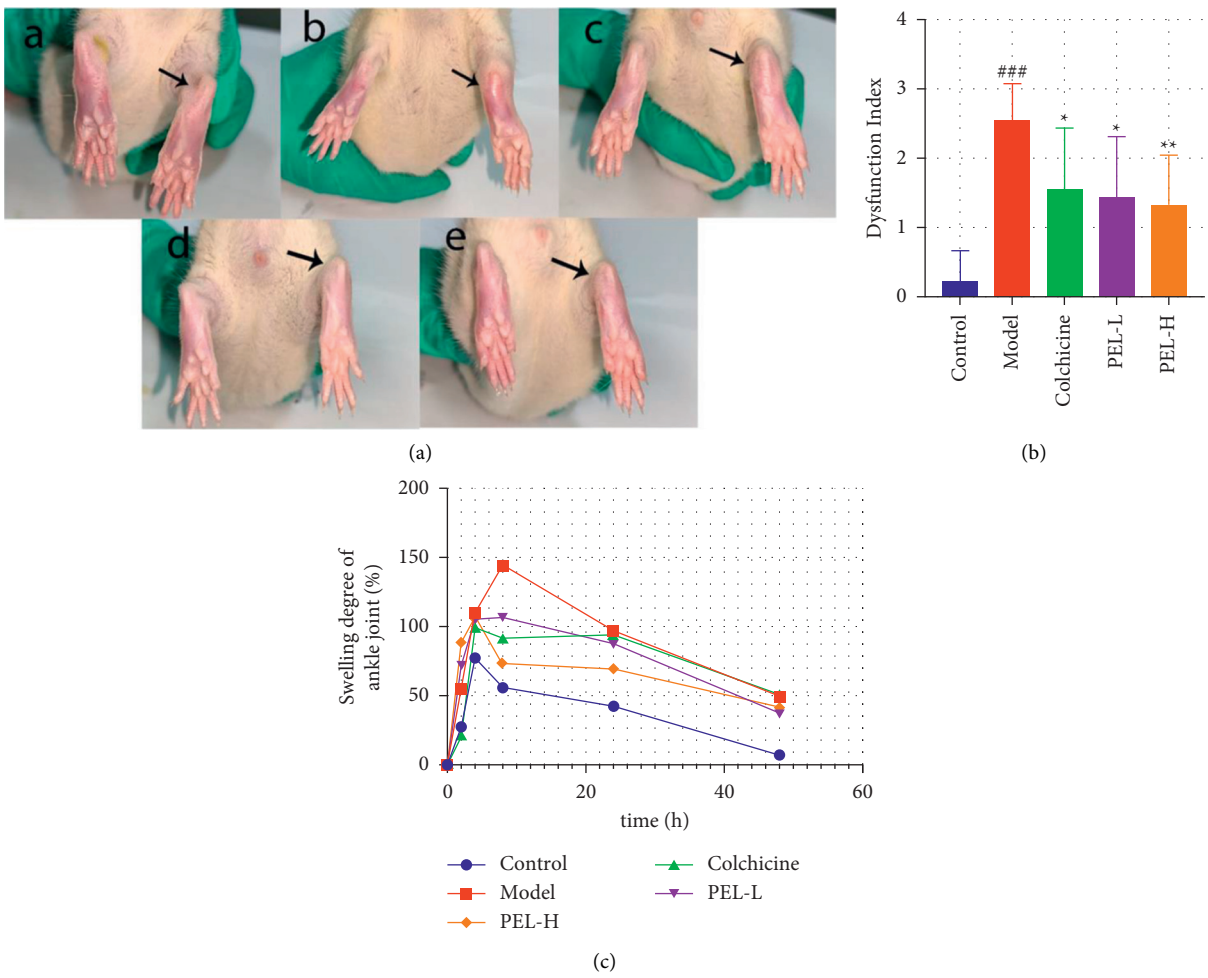


Figure 2: Changes in ankle joints of rats in each group after treatment ($\bar{x} \pm s$, $n = 9$). (a) Ankle morphology of rats in each group, including a for Control group, b for Model group, c for Colchicine group, d for PEL-L group, and e for PEL-H group. The arrow indicates the injection site of MSU. (b) Step score of rats in each group. (c) Joint swelling degree of rats in each group. Compared with the blank group, $^{###}P < 0.001$; compared with the model group, $^{*}P < 0.01$, $^{**}P < 0.05$.

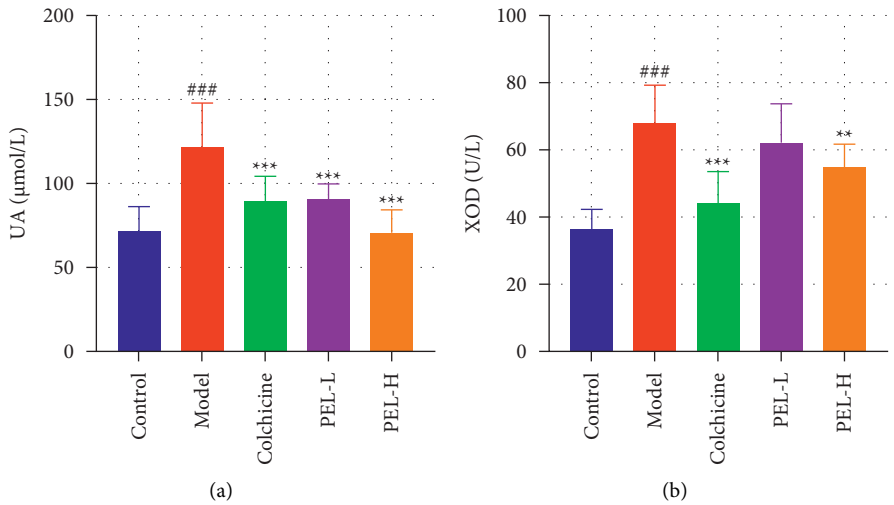
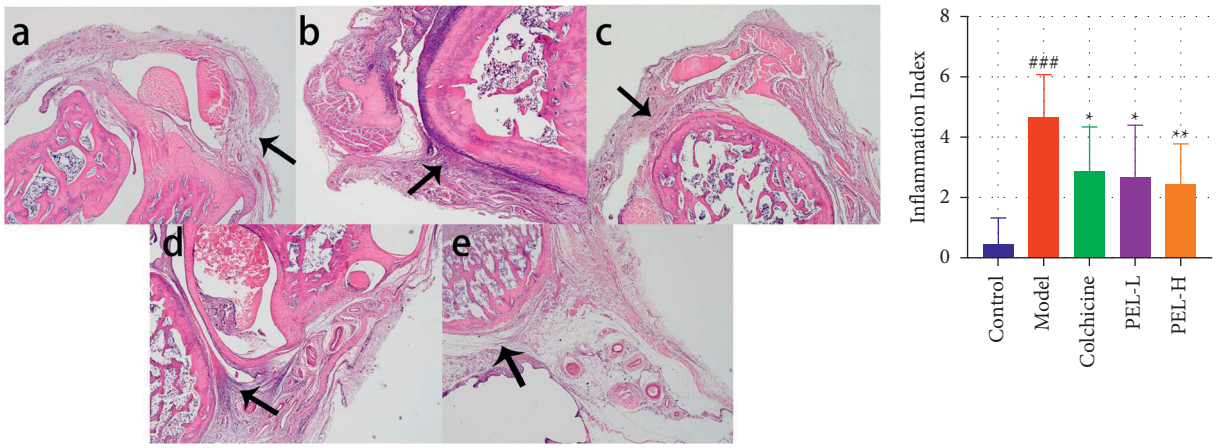


Figure 3: Changes in UA and XOD in serum of rats in each group after treatment ($\bar{x} \pm s$, $n = 9$). (a) Rat serum UA value. (b) Rat serum XOD activity value. Compared with the blank group, $^{###}P < 0.001$; compared with the model group, $^{**}P < 0.01$, $^{***}P < 0.001$.



(a) (b)

Figure 4: Changes in pathological tissue and inflammation of ankle joints of rats in each group after treatment. (a) Paraffin pathological sections of rat ankle joints stained by HE (×200), in which a is Control group, b is Model group, c is Colchicine group, d is PEL-L group, and e is PEL-H group. The arrow refers to the site of severe inflammation or therapeutic effect. (b) Inflammation index score of rats 24 h after MSU injection. Compared with the blank group, $^{###}P < 0.001$; compared with the model group, $^{*}P < 0.05$, $^{**}P < 0.01$.

Table 2: Basic information on the active compounds of PEL.

MOLID	Compound	CAS number	MW	OB (%)	DL
MOL006812	Phyllanthin	10351-88-9	418.58	33.31	0.42
MOL000006	Luteolin	491-70-3	286.25	36.16	0.25
MOL000358	Beta-sitosterol	83-46-5	414.79	36.91	0.75
MOL006824	α-Amyrin	638-95-9	426.8	39.51	0.76
MOL000422	Kaempferol	520-18-3	286.25	41.88	0.24
MOL001002	Ellagic acid	476-66-4	302.2	43.06	0.43
MOL005983	Leukoefdin	491-52-1	322.29	43.45	0.31
MOL000098	Quercetin	117-39-5	302.25	46.43	0.28
MOL006793	Mucic acid 1, 4-lactone 2-0-gallate	—	358.28	49.56	0.31
MOL006821	(-)-Epigallocatechin-3-gallate	989-51-5	458.4	55.09	0.77
MOL000569	Digallate	536-08-3	322.24	61.85	0.26
MOL006826	Chebulic acid	23725-05-5	356.26	72	0.32
MOL000513	Gallic acid*	149-91-7	170.13	31.69	0.04

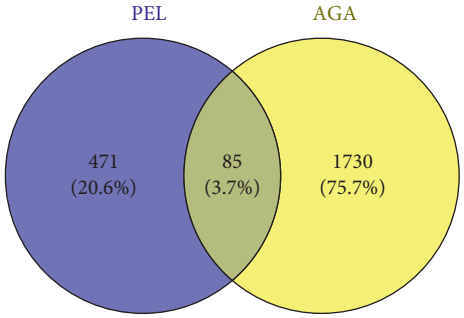


Figure 5: Venny diagram of ingredients-disease intersection targets. There are 471 targets of ingredients (left), 1730 disease targets (right), and 85 ingredients-disease intersection targets (middle).

Kyoto Encyclopedia of Genes and Genome (KEGG) enrichment analysis was used to determine the signaling pathways related to anti-AGA, and 20 pathways were selected to map according to the number of genes involved. The main pathways were the PI3K-Akt, HIF-1, TNF, and NOD-like receptor signaling pathways. The results are shown in Figure 8.

3.3.5. Construction of a CTP Network. PEL components, intersection targets, and important pathways were used to construct the CTP network of PEL with Cytoscape 3.7.0 (Figure 9). We consulted the literature to rule out the pathways that were not related to gout, such as cancer and hepatitis B, and selected the relatively important pathways [e.g., the HIF-1 (degree value: 15), PI3K-Akt (degree value: 12), TNF (degree value: 11), and NOD-like receptor signaling pathways (degree value: 7)] using the network analysis function in Cytoscape 3.7.0 (Table 3).

3.4. Mechanism Validation

3.4.1. PEL Can Inhibit Inflammation in Gout Rats. As shown in Figure 10, PEL significantly reduced the expression of the proinflammatory cytokines, IL-1β and TNF-α, and increased

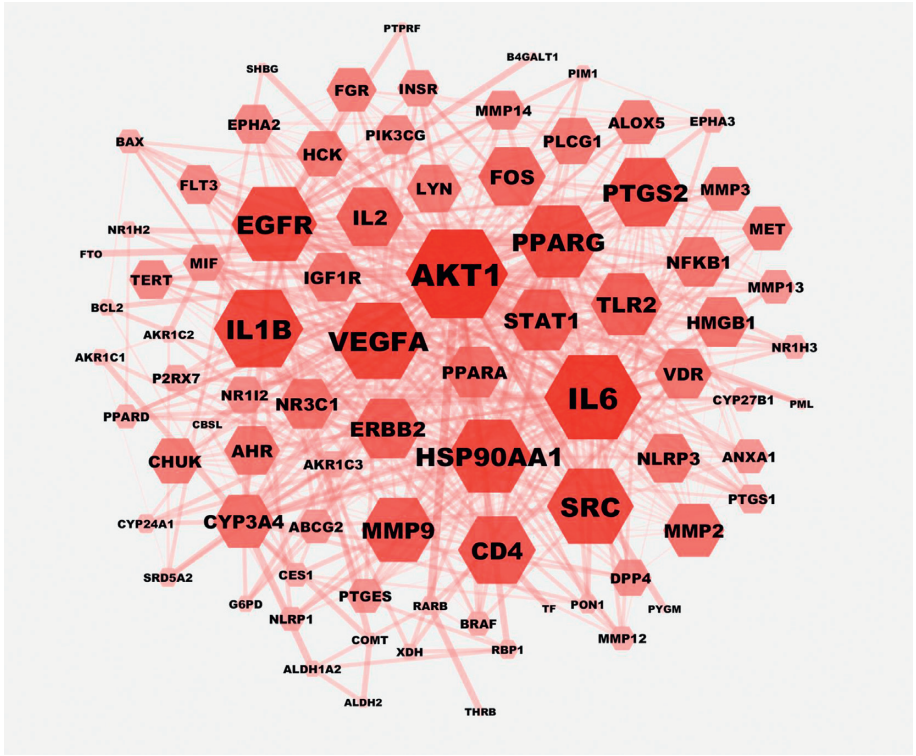


Figure 6: Network of protein-protein interactions. The hexagon represents the gene target, and the color depth and area size are positively correlated with the node value. Darker color and bigger size reflected the higher degree value.

the expression of the anti-inflammatory factor, IL-10, in gout rats, although there was no significant difference in IL-10 expression between the Model and PEL groups.

3.4.2. PEL Can Inhibit the Expression of MMP13 and NLRP3. As shown in Figure 11, PEL-H significantly reduced the expression of NLRP3, MMP13, and caspase-1 in the ankle joint synovium. The expression of NLRP3, MMP13, and caspase-1 also decreased in the PEL-L group, but there was no significant difference in the expression of NLRP3 and caspase-1 between the PEL-L and Model groups.

4. Discussion

In the present study, the potential components and action targets of PEL in the treatment of AGA were analyzed by network pharmacology, and 11 components, 41 action targets, and 20 action pathways were found. Ellagic acid is one of the active components of PEL with suitable antioxidant and anti-inflammatory properties [35]. Gallic acid has also been shown to play a therapeutic role in inflammation and related diseases by targeting the MAPK and NF-κB pathways [36]. The KEGG and CTP networks showed that PEL played a role in the treatment of AGA mainly through the HIF-1, PI3K-Akt, TNF, and NOD-like receptor signaling pathways.

Among these signaling pathways, HIF-1 has been confirmed to play an important role in hypoxic cells, while the latest research emphasizes the close relationship between hypoxia and inflammation. IL-1β is a key factor in acute gout inflammation [37]. Gupta et al. have shown that chitin can reduce the secretion of IL-1β by inhibiting the expression of HIF-1α and NLRP3 in macrophages, thus exerting therapeutic effects on AGA [38]. Related studies have also confirmed that HIF-1α can regulate the expression of NLRP3 in a venous thrombosis model [39]. This suggests that HIF-1α may have an effect on AGA by regulating the NLRP3 pathway. However, there are no studies to confirm that the HIF pathway has a definite effect on AGA; therefore, the complexity of the relationship between the HIF pathway and AGA needs to be studied further. The PI3K-Akt pathway plays an important role in the inflammatory response by activating NF-κB, while NF-κB is also one of the upstream signals for activating the NLRP3 inflammasome [40]. Related studies have shown that PI3K inhibitors can reduce neutrophil apoptosis and chondrocyte inflammation in osteoarthritic rats [41]. However, the pathogenesis of AGA through the PI3K-Akt pathway has not been completely elucidated to date.

Recent studies have shown that MSU deposition in the joints of patients with gout can trigger the formation of NLRP3 inflammasomes. NLRP3 inflammasomes activate IL-1β by activating caspase-1 and then activate the NOD receptor family signaling pathway to induce gout inflammation [42]. Given the essential role of the NLRP3/ASC/caspase-1 pathway in AGA development as well as the targets and pathways obtained using network pharmacological analysis, we finally selected the NLRP3 pathway to study the protective effect of PEL. In the present study, we

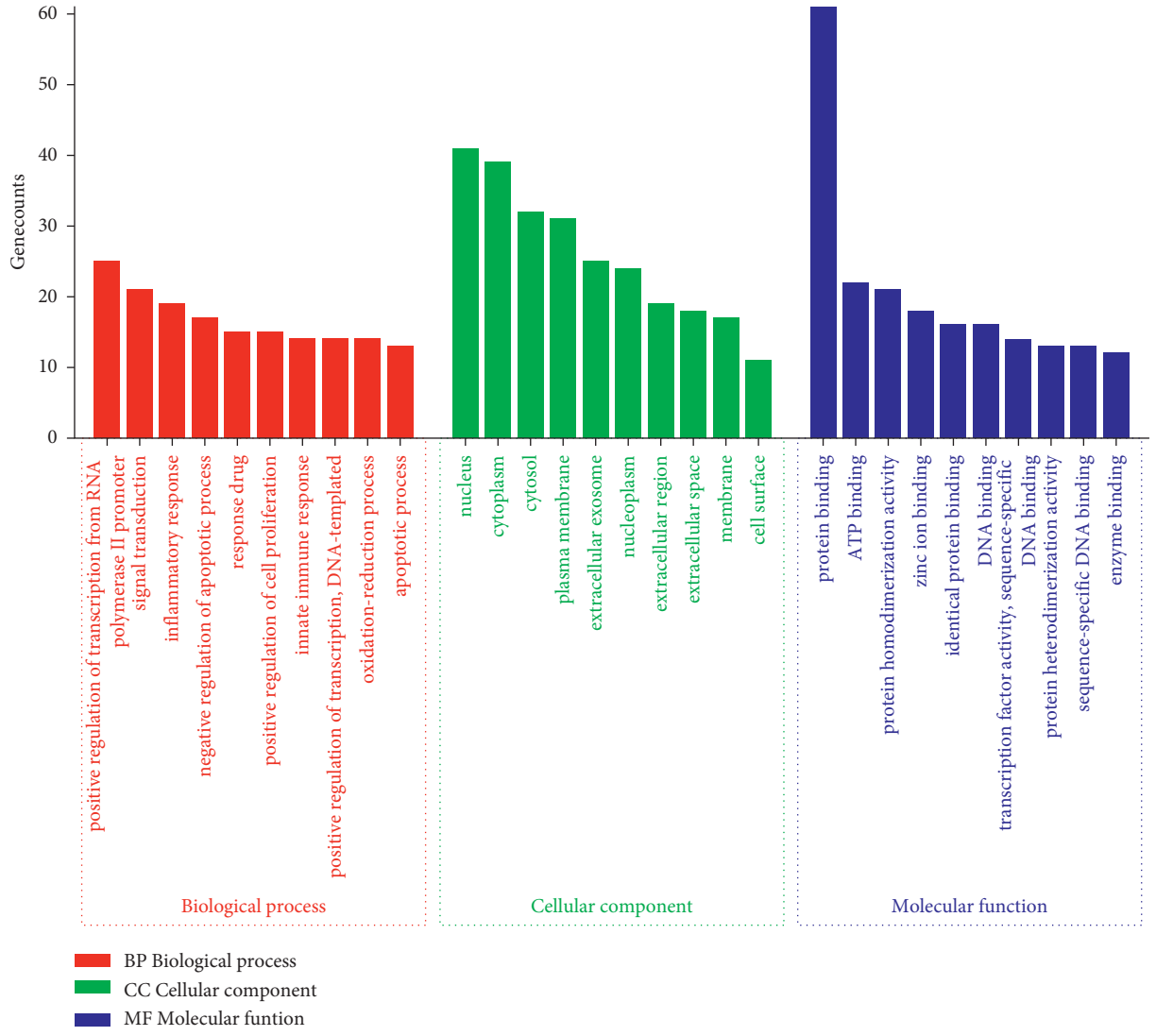


Figure 7: GO enrichment analysis of intersection targets.

established an experimental model of AGA by injecting rats with potassium oxycyanate and MSU. Unlike in humans, uricase is expressed in rats, and it results in the self-healing of acute inflammation in the AGA model within approximately three days [43]. Therefore, to obtain an adequate drug concentration in a short experimental time, each group of model rats was treated with corresponding drugs before and after injection with MSU.

At present, the pathological process of gout can be roughly divided into four stages: (1) hyperuricemia (HUA), but no MSU deposition or gout; (2) MSU deposition, but no gout symptoms; (3) MSU deposition accompanied by late AGA; (4) gout with various complications, such as gouty stone deposition, chronic gouty arthritis, and radiological erosion [44]. The clinical treatment of gout is mainly focused on reducing uric acid levels and inflammation in the third stage. The results of the current study showed that the alcohol extract of PEL could improve the appearance of ankle in the model group and reduce the gait score of gout rats and their degree of ankle swelling. These results show that the alcohol extract of PEL can reduce the pathological changes associated with gout arthritis in rats and exert a therapeutic effect on AGA.

Reducing uric acid levels plays a key role in the prevention and treatment of gout. The alcohol extract of PEL was confirmed to reduce uric acid levels in this experiment, and this result is consistent with that reported by Sato [15]. There are many reasons accounting for HUA. Excessive uric acid production or relatively insufficient uric acid excretion are the two main reasons for abnormal increase in uric acid levels in the body. As a key enzyme in purine metabolism pathway, XOD can convert hypoxanthine and xanthine into uric acid; this is also the most important pathway of uric acid production in vivo. We speculated that the alcohol extract of PEL could reduce uric acid levels by inhibiting the activity of XOD, which was successfully confirmed by measuring the activity of XOD in the serum of rats in each group. The American Rheumatic Society guidelines recommend that serum uric acid levels of all patients receiving uric acid–lowering therapy should remain below 360 μmol/L or 6 mg/

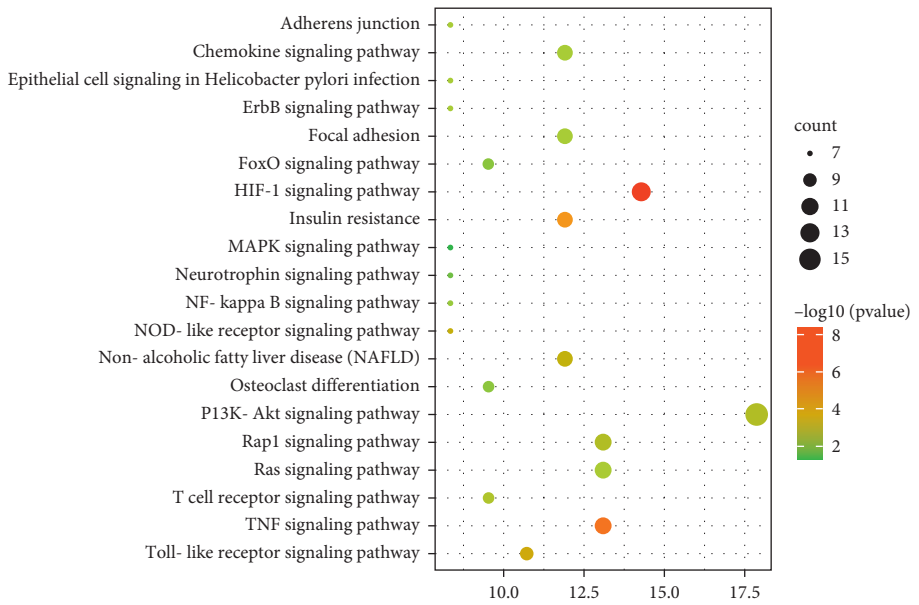


Figure 8: KEGG path enrichment diagram of intersection targets. The *X* axis shows the count of enriched genes, *Y* axis shows the KEGG pathways, and color represents the adjusted *P* value.

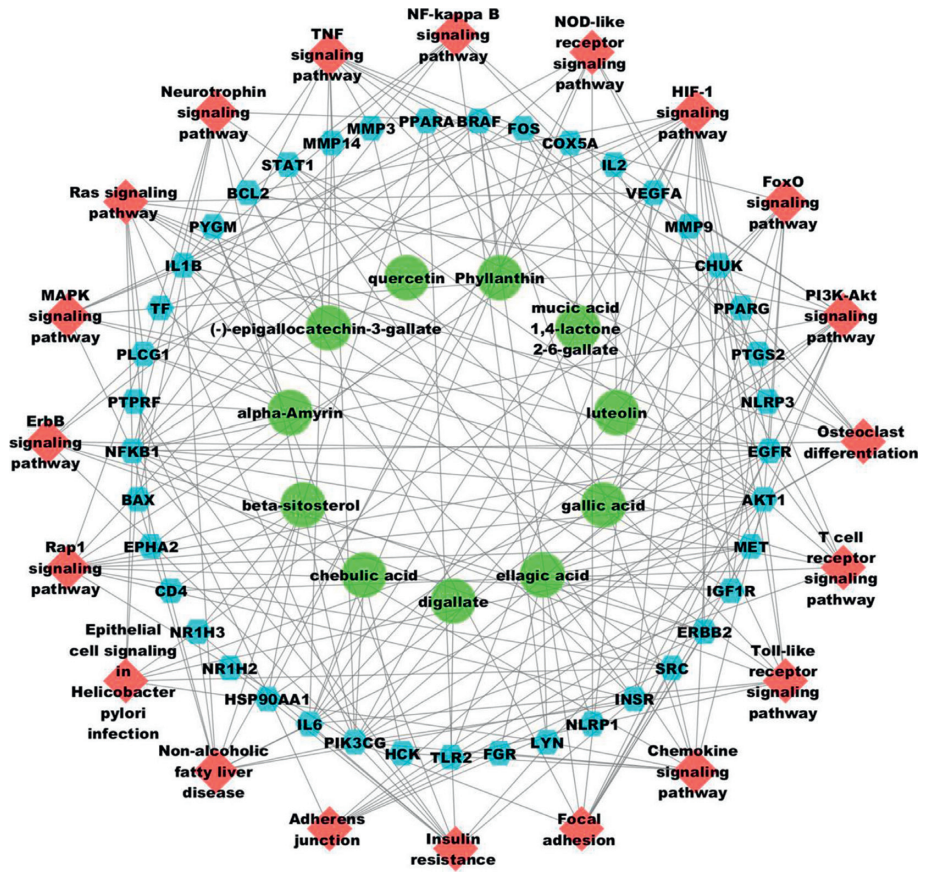


Figure 9: PEL component-target-pathway network diagram. The green circular nodes represent the active components of PEL, blue hexagons represent intersection targets, and red diamond nodes represent important paths. The edges represent the relationship among components, targets, and pathways.

Table 3: Degree value analysis of pathways in CTP network.

Pathways	Betweenness centrality	Closeness centrality	Degree
HIF-1 signaling pathway	0.10670956	0.44099379	15
PI3K-akt signaling pathway	0.06644801	0.4251497	12
TNF signaling pathway	0.13508328	0.42011834	11
Ras signaling pathway	0.03548477	0.41520468	11
Rap1 signaling pathway	0.03281526	0.41040462	11
Nonalcoholic fatty liver disease	0.09957878	0.41040462	10
Insulin resistance	0.08416535	0.40571429	10
Focal adhesion	0.02776726	0.40112994	10
Chemokine signaling pathway	0.06689398	0.41040462	10
Toll-like receptor signaling pathway	0.04355976	0.40571429	9
T-cell receptor signaling pathway	0.04668759	0.40112994	8
Osteoclast differentiation	0.0411098	0.39664804	8
FoxO signaling pathway	0.01449155	0.39226519	8
NOD-like receptor signaling pathway	0.03845429	0.37566138	7
NF-kappaB signaling pathway	0.02278709	0.38378378	7
Neurotrophin signaling pathway	0.01906849	0.38797814	7
MAPK signaling pathway	0.01459004	0.38797814	7
ErbB signaling pathway	0.01213661	0.38378378	7
Epithelial cell signaling in helicobacter pylori infection	0.01438965	0.38378378	7
Adherens junction	0.01115371	0.33023256	7

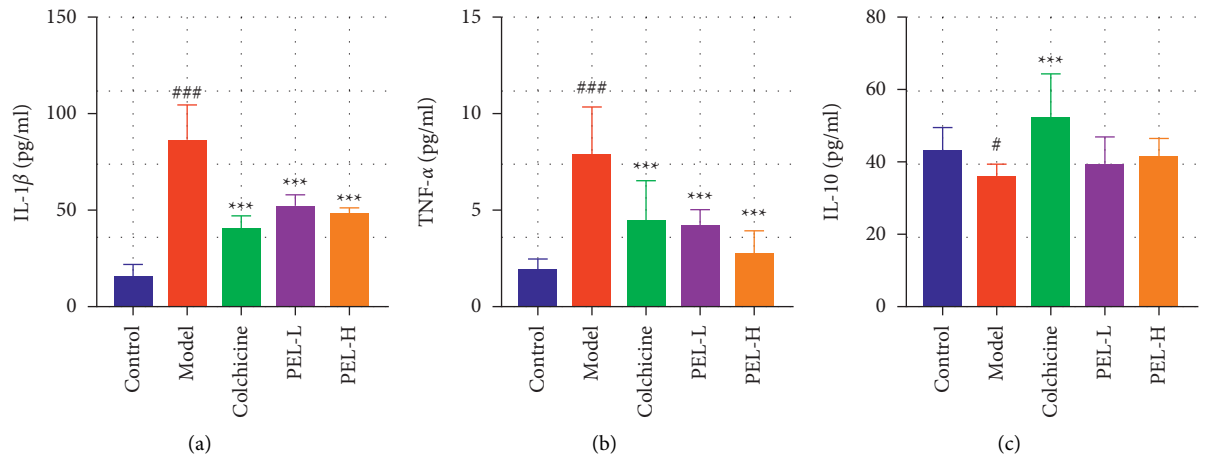


Figure 10: Changes in serum related factors of rats in each group after treatment ($\bar{x} \pm s$, $n = 9$). The expression levels of proinflammatory cytokines IL-1β (a), TNF-α (b), and IL-10 (c). Compared with the blank group, $^{\#}P < 0.05$, $^{\#\#\#}P < 0.0001$; compared with the model group, $^{***}P < 0.001$.

dL [45], because long-term levels below this critical level may dissolve MSU, inhibit inflammation, and eliminate gout [46]. However, the dosage of alcohol extract of PEL needed to achieve this uric acid–lowering effect in clinical settings still needs to be elucidated.

In AGA patients, the local inflammatory response induced by MSU deposited in the joint is a crucial cause of joint tissue injury. For example, colchicine, the positive drug used in this experiment, is one of the first-line drugs for the treatment of gout because of its outstanding anti-inflammatory effects [47, 48]. Our results show that the alcohol extract of PEL can reduce the severity of inflammatory reactions in gout rats, decrease the degree of neutrophil infiltration in the ankle joints of gout rats, and effectively improve various pathological conditions, such as synovial hyperplasia and hyperemia and joint structural disorder. Yang et al. demonstrated that the development of AGA is closely related to the NLRP3/ASC/caspase-1 pathway [49]. When the macrophages in the synovium of the ankle recognize the danger signal, which is the deposition of MSU in the joint cavity, through pattern recognition receptors (PRRs), the expression of NLRP3 inflammatory bodies is upregulated and posttranscriptional modification is carried out [50]. At this point, NLRP3 is activated, leading to the further recruitment of apoptosis-associated spot-like proteins (ASC), which then combines with caspase-aspartate protease (caspase-1) to form the NLRP3 inflammatory complex, cleaving the inactive caspase-1 into active cle-caspase-1 [51]. Cle-caspase-1 triggers the downstream inflammatory response, that is, the activation and release of interleukin-1 family proteins (e.g., IL-1) [52], followed by the production of several proinflammatory factors. These

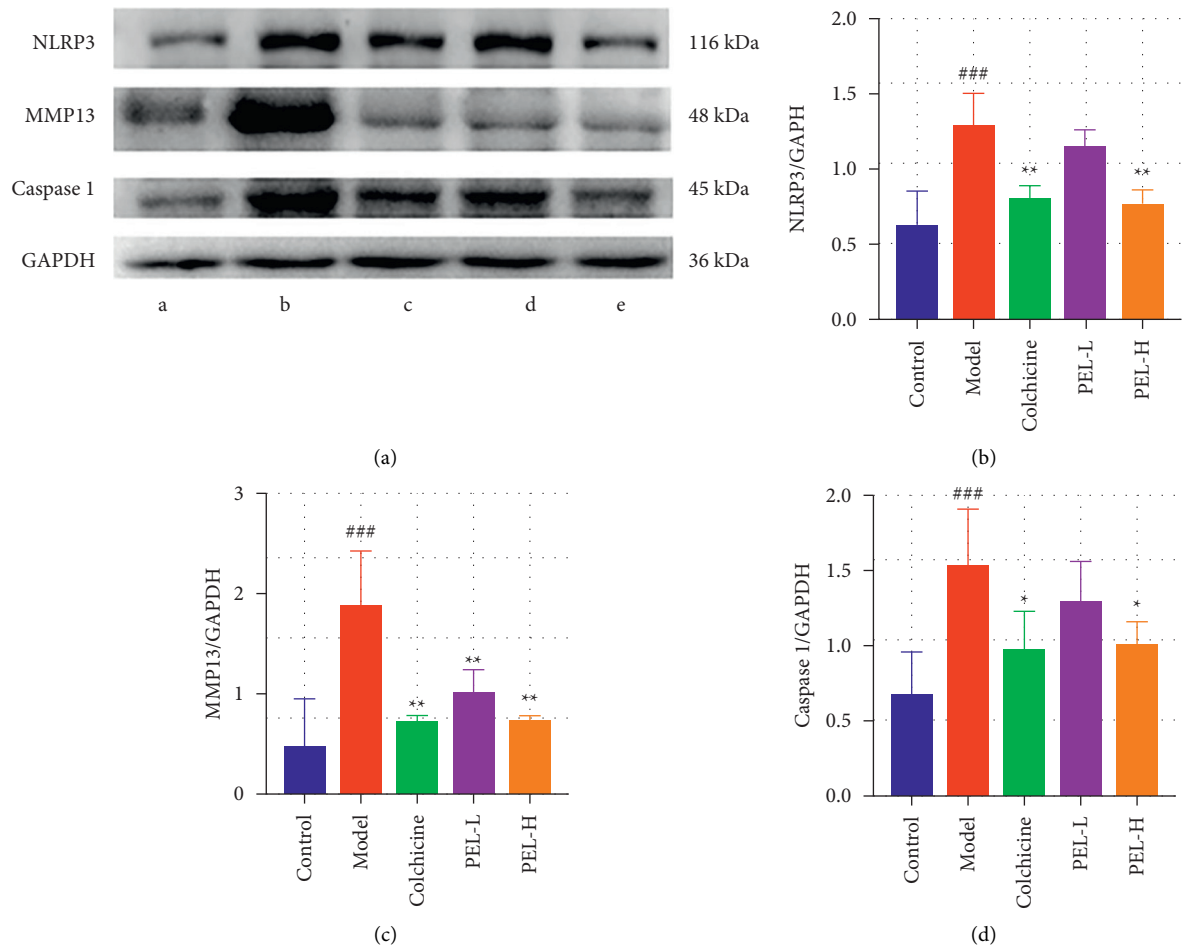


Figure 11: Changes in synovial protein and related factors in ankle joints of rats in each group after treatment. (a) The related factors in ankle joints of rats in each group, including a for Control group, b for Model group, c for Colchicine group, d for PEL-L group, and e for PEL-H group. The relative expression values of NLRP3 (b), MMP13 (c), and caspase-1 (d) in synovium of rat ankle joints were determined. Compared with the blank group, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$; compared with the model group, $^{*}P < 0.05$, $^{**}P < 0.01$.

factors include TNF-α, IL-1β, chemokine monocyte chemoattractant protein-1, and macrophage inflammatory protein-1α produced by M1 macrophages to promote inflammation [53–55]. The results of the current study showed that the ethanol extract of PEL could significantly inhibit the expression of NLRP3 and caspase-1 and downregulate the expression of the proinflammatory cytokine IL-1β. This shows that PEL can be used for the treatment of AGA because it inhibits the activation and assembly of the NLRP3 inflammasome and regulates the production of downstream inflammatory factors. In the maintenance stage of inflammation, polarized M2 macrophages can secrete anti-inflammatory cytokines including TGF-β and IL-10, which may relieve gout inflammation [56]; however, the mechanism underlying spontaneous resolution has not been clearly elucidated. The alcohol extract of PEL could increase the level of IL-10 in gout rats, although there was no significant difference.

In addition, although the general process of NLRP3-mediated AGA is well understood, little is known about the upstream pathway that connects MSU crystals and NLRP3 activation. The two prerequisite steps for NLRP3 to mediate AGA are initiation and activation [57]. Activation occurs through the activation of nuclear factor NF-κB by PRRs. The activation signal of NLRP3 is generated following the recognition of MSU by PRRs (mainly TLR4) [58, 59]. However, the exact pathway by which MSU activates NLRP3 is still unclear. It is suggested that the release of oxidative mitochondrial DNA, mitochondrial reactive oxygen species (ROS), and cardiolipin caused by K^+-dependent or non-K^+-dependent pathways is the main factor for the activation of the NLRP3 inflammasome [38]. Notably, the antioxidant activity of PEL is as significant as its anti-inflammatory activity. Nambiar et al. confirmed that PEL fruit extract has satisfactory antioxidant capacity through DPPH-free radical scavenging experiments [60], and Zhang et al. confirmed that PEL exerts a protective effect against H_2O_2-induced cellular injury [61]. We speculate that the ethanol extract of PEL may inhibit the activation of NLRP3 by scavenging ROS. It is believed that more experimental studies on the capacity of PEL for scavenging mitochondrial ROS in vivo in the future will not only reveal the internal relationships among different pharmacological activities of PEL but also enable an improved understanding of the pathogenesis of gout.

For patients with gout, osteoarthritis is a type of degenerative disease usually accompanied by inflammation, which eventually causes substantial damage to the articular cartilage. MMP13 is considered the key enzyme of cartilage degradation in osteoarthritis [62]. Compared with other proteins of the MMP family, the expression of MMP13 is markedly limited to connective tissue and has strong activity to degrade type II collagen in the cartilage [63]. It can degrade not only type II collagen in the cartilage but also proteoglycan, type IV collagen, and osteonectin [64], resulting in the destruction of the collagen network and the exposure of chondrocytes to inflammatory factors. Finally, under the action of the mechanical load and inflammatory factors, the apoptosis of chondrocytes occurs, which further aggravates the tissue injury of patients with gout. In view of the biological activity of MMP13, it has become an attractive target for the treatment of osteoarthritis, cancer, and cardiovascular diseases. However, safety and clinical efficacy are still two important problems to be solved for the clinical use of specific MMP13 inhibitors. The experiment described in the present study confirmed that the alcohol extract of PEL could effectively inhibit the expression of MMP13 in the synovium of the ankle joints of AGA rats. As a substance that can be used as both medicine and food, the safety of PEL is also relatively high [9]. Chaphalkar et al. found that PEL did not show any significant change in body weight and behavioral pattern in acute toxicity study [65]. Chaiyasut et al. also reported the safety of consuming Lactobacillus sp. mediated fermented PEL [66]. The resulting safer consumption of the PEE may be attributed to the presence of antioxidant and hepatoprotective activities [8]. This may provide novel insights into the treatment of osteoarthritis.

5. Conclusions

In this study, we confirmed that PEL extract can be used to treat gout as it reduces serum uric acid levels, inhibits inflammation, and protects ankle cartilage. PEL can reduce uric acid levels by inhibiting XOD activity, suppress the inflammatory response by inhibiting the NLRP3/caspase-1/IL-1 inflammatory axis, and protect ankle cartilage by inhibiting MMP13 expression. However, its mechanism of action and clinical dosage need to be further explored.

Abbreviations

ASC: Apoptosis-associated spot-like proteins
AGA: Acute gouty arthritis
BP: Biological processes
CC: Cellular components
Colchicine: Colchicine group
Control: Control group
CTP: Component-target-pathway
DL: Drug-like
HE: Hematoxylin and eosin
MCODE: Molecular complex detection
MF: Molecular functions
Model: Model group
MSU: Monosodium urate
OB: Oral bioavailability
PEL: *Phyllanthus emblica* L.
PEL-L: Low-dose PEL-treated group
PEL-H: High-dose PEL-treated group
PPI: Protein-protein interaction
PRR: Pattern recognition receptors
ROS: Reactive oxygen species
SD: Sprague Dawley
XOD: Xanthine oxidase
UA: Uric acid
SPF: Specific-pathogen-free
HUA: Hyperuricemia.

Data Availability

The data that support the findings of this study are openly available.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

The graphical abstract is provided to clarify the main strategies of the research. (*Supplementary Materials*)

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Research Article

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

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Background. Acute gouty arthritis (AGA) is a common arthritis disease, with the characteristics of acute onset, severe condition, and poor prognosis. The conventional treatments have shown certain curative effects but are accompanied with many adverse reactions. The combination of orally taken Qinpi Tongfeng Formula (QPTFF) and bloodletting therapy could effectively alleviate arthralgia and joint swelling in AGA patients. However, there is a lack of high-quality randomized controlled trials (RCTs) to evaluate the clinical efficacy and safety of the combined therapy against AGA. *Methods*. This is a prospective, randomized, parallel controlled trial conducted in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine to explore the efficacy and safety of QPTFF combined with bloodletting therapy in the treatment of AGA. Eighty-six AGA patients meeting the inclusion and exclusion criteria will be randomly divided into the treatment group and control group in a 1 : 1 ratio using a randomization table. The investigators and the patients will not be blinded, while the outcome assessors and statisticians will be blinded to the allocation. Patients in the treatment group will take QPTFF and bloodletting therapy simultaneously, while patients in the control group will be instructed to orally take colchicine tablets. The primary outcome is the total effective rate, and the secondary outcomes are the pain changes after the first treatment, pain scores, complete pain relief time, joint symptom scores, TCM syndrome score, and laboratory test. SPSS22.0 will be used for statistical analysis. *Discussion*. This study will evaluate the clinical efficacy and safety of QPTFF combined with bloodletting therapy in the treatment of AGA, and the results of this study will provide reliable clinical evidence for the clinical use of QPTFF combined with bloodletting in the treatment of AGA. The trial is registered with ChiCTR2100048836.

1. Introduction

Gout, a crystal-induced arthritis, is caused by monosodium urate deposition because of purine metabolic disorder and/or reduced uric acid excretion [1]. Due to the disorder of purine metabolism or renal excretion, serum uric acid level increases abnormally, and finally, urate crystal deposition and acute persistent inflammatory reaction appear in the joints [2, 3]. Gout can be caused by both genetic factors and environmental factors. With the improvement of people's living standards and the change of diet structure and habits, the prevalence of gout increases largely, and the onset age of gout becomes younger and younger [4, 5]. According to the statistics of the World Health Organization (WHO), about 3.9% of people in the world are suffering from gout [6], with the ratio of male to female as 3 : 1 to 4 : 1 [7]. Gout patients are often accompanied by obesity, hypertension, nephropathy, hyperlipidemia, and other diseases, which have a serious burden on the health and economy of patients [8].

Acute gout arthritis (AGA) is the acute manifestation of gout, characterized by sudden and severe arthralgia with heat, redness, swelling, and restricted movement. At present, nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are recommended as the first-line clinical treatments of AGA [9]. These medicines usually have good short-term efficacy, but long-term use may lead to gastrointestinal reactions, rashes, and even liver and kidney function injury [9, 10]. Hence, a multimodality therapy with fewer side effects to improve arthralgia and swelling of AGA is urgently needed, especially for some patients allergic to NSAIDs and colchicine.

Gout belongs to the paralysis syndrome (bi zheng) in traditional Chinese medicine (TCM), which is caused by dampness-heat accumulation and qi-blood stasis in the channels [11]. In China, the TCM treatment of gout has a long history. It was first discussed separately in Ge Zhi Yu Lun as early as 1347 AD. It has been reported that TCM formula combined with external treatment can alleviate the symptoms of gout quickly and delay the development of gout [12]. Qinpi Tongfeng Formula (QPTFF) is a derived compound prescription from Sheng Ji Zong Lu in 1117 AD according to the modern clinical application. The formula is composed of Cortex Fraxini (Qin Pi), Rhizoma Coptidis (Huang Lian), Radix Saposhnikoviae (Fang Feng), Semen Plantaginis (Che Qian Zi), Rhizoma Smilacis Glabrae (Tu Fu Ling), Rhizome Dioscoreae Hypoglaucae (Bi Xie), Radix Clematidis (Wei Ling Xian), and Herba Siegesbeckiae (Xi Xian Cao). QPTFF has shown the function of clearing dampness-heat, reducing swelling, and relieving pain [13]. A previous clinical study indicated that QPTFF had the same effect on alleviating arthralgia and joint swelling in AGA patients with an analgesic. Moreover, during the clinical trial, serious adverse reactions such as liver and kidney function damage and allergic dermatitis were not found [14]. Bloodletting therapy, one of the traditional external treatment methods, is the withdrawal of blood from a patient to prevent or cure illness and disease. During the process of bloodletting therapy, the operator uses a needle to prick into the skin at specific acupoints and suck a little blood through cupping to dredge the meridians, promote blood circulation, and relieve pain [15]. Clinical studies have found that bloodletting therapy can improve the local microcirculation and promote inflammatory absorption to relieve arthralgia [16]. However, there is still a lack of high-quality clinical study to verify the clinical efficacy of the combination of the two therapies in the treatment of AGA. Hence, in this study, we try to conduct a randomized, controlled trial to analyze the efficacy and safety of QPTFF combined with bloodletting therapy in the treatment of AGA.

2. Materials and Methods

2.1. Study Design. This trial is designed as an open-label, prospective, randomized, controlled, and parallel-group study. It will be conducted in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine from August 1, 2021 to October 30, 2021. Figure 1 shows the research flow chart, and the details of patient follow-up are summarized in Figure 2. The research follows the latest Consolidated Standards of Reporting Trials (CONSORT 2017) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (the SPIRIT checklist is provided in Table S1).

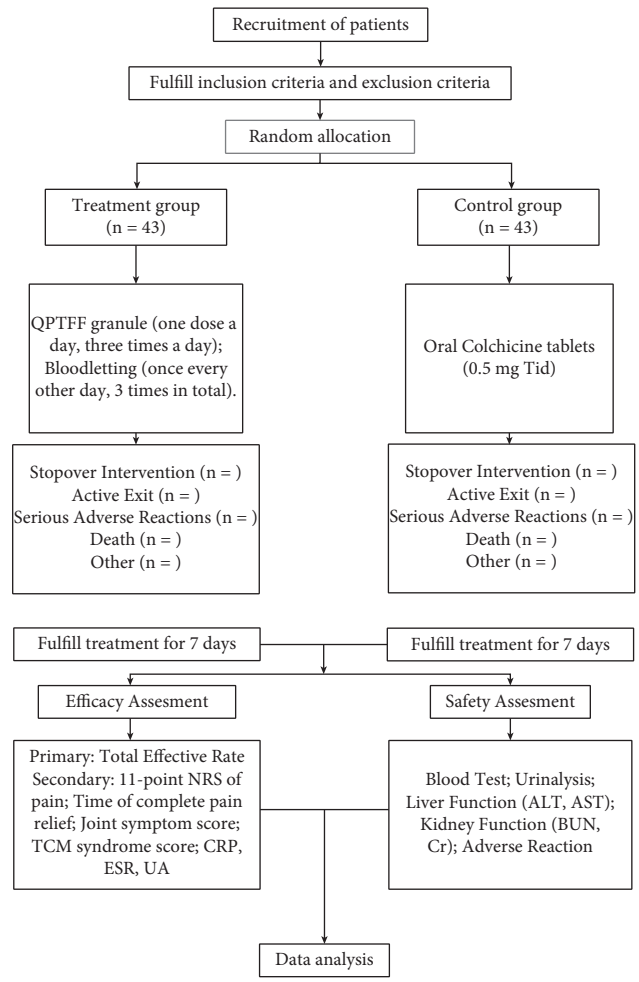

Figure 1: The flow chart of this study.

2.2. Ethics and Registration. This study protocol will be conducted in accordance with the *Declaration of Helsinki* and the *Ethical Guidelines for Clinical Research*. This study has been approved by the ethics committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Ethics number: TYLL2021 [Z] 014), and it has been registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2100048836).

2.3. Participants. Participants will be recruited from outpatients in the rheumatology department of the First Teaching Hospital in Tianjin University of Traditional Chinese Medicine via posters and WeChat. Recruitment members in the rheumatology department will be in charge of the recruitment and registration of the participants meeting the inclusion and exclusion criteria. Written informed consent will be obtained from participants or their legal representatives, and the personal information will be kept with utmost secrecy.

Project \ Period	Screening Period	Treatment Period							Follow -up
	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
	Day 0								
Eligibility screen	√								
Informed consent	√								
Randomization	√								
Treatment	√		√	√	√	√	√	√	√
Combined medication record		√	√	√	√	√	√	√	√
Efficacy Observation									
NRS change after the first treatment	√	√							
NRS	√								√
Complete pain relief time									√
Joint symptom score	√								√
TCM syndrome score	√								√
Laboratory Indexes	√								√
Safety Evaluation									
Blood Test and urinalysis	√								√
Liver and kidney function	√								√
Adverse event		√	√	√	√	√	√	√	√

Figure 2: Patient follow-up process.

2.4. Diagnostic Basis. The diagnosis of AGA is according to the diagnostic criteria of the American College of Rheumatology in 2015 [17]. The syndrome diagnosis of dampness-heat accumulation syndrome in TCM is according to the guidelines for the combined diagnosis and treatment of gout and hyperuricemia issued by the Chinese Society of TCM in 2020 [18], with two primary symptoms or one primary symptom plus two secondary symptoms in combination with the tongue and pulse. The primary symptoms include redness, swelling, heat, and pain in the joint and

sudden onset of arthralgia, and the secondary symptoms include poor joint movement, fever, and dysphoria. The tongue should be red, with yellow, greasy or thick coating, and the pulse should be slippery.

2.5. Recruitment Criteria. The inclusion criteria are as follows:

(1) Meeting the diagnostic criteria of AGA of the American Society of Rheumatology in 2015
(2) Meeting the TCM diagnostic criteria of gout with dampness-heat accumulation syndrome
(3) 72 hours within the onset of AGA
(4) With moderate, severe, or extreme arthralgia and the score of the numerical rating scale (NRS) ≥4
(5) Without taking any other medicines for AGA 72 hours before the enrollment
(6) Without taking any uric acid-lowering medicines during the last 2 weeks
(7) Age of 18–70 years
(8) With signed informed consent form

2.6. Exclusion Criteria. The exclusion criteria are as follows:

(1) Secondary gouty arthritis caused by other factors (e.g., renal failure, chemotherapy or radiotherapy, and drugs)
(2) With rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, knee osteoarthritis, and other arthritis
(3) With multiple joints involved (>4 joints)
(4) Alanine aminotransferase (ALT), alanine aminotransferase (AST), or creatinine (Cr) 1.5 times higher than the upper limit of normal [19]
(5) History of allergy to any ingredients of the medicines in both groups
(6) Women in pregnancy or lactation
(7) With peptic ulcer and bleeding
(8) Having participated in other clinical trials in the past month
(9) With serious mental illness, unable to express accurately or take medicine on time, and unable to cooperate

2.7. Termination Criteria

(1) Participants experiencing adverse events (e.g., cardiovascular embolism, gastrointestinal reaction, and severe liver and kidney dysfunction) or other complications that the investigators consider it necessary to terminate trial treatment
(2) Participants could not benefit or even get worse from the trial treatment that the investigators deem necessary to terminate trial treatment
(3) Participants stop or discontinue the medication or take other drugs at will without authorization
(4) Participants are unwilling or impossible to continue the trial and request to withdraw and terminate the trial

2.8. Sample Size. PASS15.0 is used to calculate the sample size. The study is suitable for the noninferiority test. According to our preliminary study, the total effective rate of QPTFF combined with bloodletting is 95%, and the total effective rate of colchicine is 90% [20]. Taking $\alpha = 0.05$, $\beta = 0.2$, a ratio of 1 : 1, and the boundary value = −0.1, the sample size of the two groups is 78 cases. Considering a loss to follow-up of 10%, 86 cases are finally needed, with 43 cases in each group.

2.9. Randomization and Allocation Concealment. Participants will be randomly divided into the treatment group and control group in a 1 : 1 ratio using a randomization table. The randomization sequence will be generated by an independent statistician with Excel 2013 software. The random numbers will be placed in opaque, sealed envelopes and kept in a safe place until the study is completed. Chunliu Liu will be responsible for the enrollment and assignment of the participants.

2.10. Blinding. Due to the limitation of the intervention program, the blinding of bloodletting therapy is quite difficult to achieve. The investigators and the patients will not be blinded, while the outcome assessors and statisticians will be blinded to the allocation.

2.11. Intervention. In the treatment group, patients will take QPTFF and bloodletting therapy simultaneously. The QPTFF will be provided as granules, composed of Cortex Fraxini (Qin Pi) 30g, Rhizoma Coptidis (Huang Lian) 10g, Semen Plantaginis (Che Qian Zi) 20g, Rhizoma Smilacis Glabrae (Tu Fu Ling) 80g, Radix Clematidis (Wei Ling Xian) 30g, Herba Siegesbeckiae (Xi Xian Cao) 30g, and Radix Saposhnikoviae (Fang Feng) 10g, prepared by Sichuan New Green Pharmaceutical Technology Development Co., Ltd. The patients will be instructed to orally take the granules one dose a day by dissolving them in 50 mL warm water, three times a day, for 1 week. The bloodletting therapy will be performed by qualified members who have more than 3-year experience in bloodletting therapy after being retrained for standard management for the study. The main acupoints are Ashi points (affected side), SP10 (Xuehai) (bilateral), SP9 (Yinlingquan) (bilateral), ST36 (Zusanli) (bilateral0), BL40 (Weizhong) (bilateral), BL20 (Pishu) (bilateral), and SP6 (Sanyinjiao) (bilateral). At the same time, local points will be selected. For the first metatarsophalangeal joint, SP3 and LR3 will be added; for medial malleolus, KI7 will be added; for the lateral ankle, BL57 will be added. During the bloodletting operation, the patient will take the prone position. The operator disinfects the acupoints with 75% alcohol, pricks the acupoints with the sterilized lancet, place a

fire cup on the point for 5 min to suck the blood, and then disinfects the skin with 75% alcohol. The bloodletting therapy will be performed once every other day, 3 times in total.

In the control group, patients will be instructed to orally take colchicine tablets (Guangdong BIDI Pharmaceutical Co., Ltd., China, H20113208), 0.5 mg once, 3 times a day, for 1 week.

If the pain in the two groups is severe and unbearable during the treatment, etocoxib (Hangzhou MSD Pharmaceutical Co., Ltd., China, J20180059) 120 mg, once a day, will be used. The patients will be asked to record the dosage and administration of the medicine.

2.12. Outcome Measures. The primary outcome is the total effective rate according to the *Guiding Principles for Clinical Research of New Traditional Chinese Medicine*, as divided into clinical cured, remarkably effective, effective, and ineffective [21, 22]. Clinical cured means that the clinical symptoms and signs disappear or basically disappear, and the curative effect index decreases more than 95% (included). Remarkably effective means that the clinical symptoms and signs are significantly improved, and the curative effect index is reduced more than 60% (included) but less than 95%. Effective means improvement of clinical symptoms and signs, and a reduction of curative effect index of more than 30% (included) but less than 60%. Ineffective means that the clinical symptoms and signs are not improved or even aggravated, and the curative effect index is reduced less than 30%. Total effective rate = (clinical cured number + remarkably effective number + effective number)/total × 100%. The total effective rate of the treatment of patients will be evaluated after the treatment by Fangfang Lin.

The secondary outcomes are the pain changes after the first treatment, pain scores, complete pain relief time, joint symptom scores, TCM syndrome score, and laboratory test, as measured by Wenliang Lv and Danna Yang.

(1) The pain changes after the first treatment will be evaluated by the 11-point Numerical Rating Scale (NRS) [23]. The scale includes 0–10 points to represent the different degrees of pain, and the grading standards of pain degree are 0 for painless, 1–3 for mild pain, 4–6 for moderate pain, and 7–10 for severe pain. In the treatment group, the patients will be instructed to take QPTFF once at the first visit and then to accept bloodletting therapy. After the bloodletting therapy, the changes of NRS scores at 0.5 h, 1 h, 1.5 h, and 2 h will be recorded to evaluate the immediate efficacy of TCM therapy. In the control group, after taking colchicine for the first time, the NRS scores of patients will be recorded at 0.5 h, 1h, 1.5 h, and 2h.

(2) Pain scores will be measured by the NRS on day 0 and day 8 (follow-up).

(2) Complete pain relief time is defined as the number of days required from the initial treatment to the complete pain relief measured by the NRS at the end of the study.

(3) Joint symptom score is used to evaluate the tenderness, redness, swelling, and mobility of joints. The higher the score, the heavier the symptom is. The scores will be recorded on day 0 and day 8 (follow-up).

(4) TCM syndrome score, according to the *Guiding Principles for Clinical Research of New Traditional Chinese Medicine* [22], includes TCM syndromes such as joint swelling, skin temperature, thirst, and yellow urine. The higher the score, the more serious the condition is. The scores will be recorded on day 0 and day 8 (follow-up).

(5) Laboratory tests include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and uric acid (UA). The results will be recorded on day 0 and day 8 (follow-up).

2.13. Safety Evaluation. Blood test, urinalysis, liver function, and renal function (urea nitrogen and serum creatinine) will be measured on day 0 and day 8 to evaluate the safety of treatment. At the same time, patients are required to record any adverse reactions during the study and report to the investigator at any time. Details of all adverse events will be recorded in case report dorms (CRFs), including time, degree and duration, suspected causes, measures, and results. After the treatment, the adverse reactions of the two groups will be counted.

2.14. Data Management and Quality Control. Any modification or change of the protocol will be approved through the formal procedures of the ethics committee of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine. Independent clinical research assistants will regularly review the study progress. CRFs will be used in data collection to record demographics, assessment, and reasons for drop-out. All CRFs will be stored in an independent storage room to protect confidentiality. Without the written permission of the supervisor, the participant's information will not be disclosed and shared. At the end of the study, the investigator will submit the CRFs to the data management committee, and the investigators cannot modify the data.

2.15. Statistical Analysis. Efficacy evaluation will be determined by full analysis set (FAS) and per-protocol set (PPS), and safety evaluation will be based on safety set (SS). The statistical evaluation of FAS will follow the intent-to-treat (ITT) principle. The last observation carried forward (LOCF) method will be used to estimate the missing values of main variables. The collected data will be statistically analyzed by using the SPSS22.0 software (International Business Machines Corporation, New York, USA). For continuous data, they will be represented as mean ± standard deviation and frequency or percentage for categorical data. For the primary outcome, the

chi-square test will be used. For secondary outcomes, independent samples T test or Mann–Whitney U test for intergroup comparison will be used for pain scores, complete pain relief time, joint symptom scores, TCM syndrome score, and laboratory test and generalized linear models or repeated measures analysis of variance for the pain changes after the first treatment after considering the normality and homogeneity. Statistical testing is two-sided, and $P < 0.05$ is considered statistically significant.

3. Discussion

The main TCM syndrome of AGA is dampness-heat accumulation syndrome [24], which is characterized by arthralgia, swelling, redness, and fever, accompanied by dysphoria, thirst, and yellow urine [21]. Based on the theory of TCM, the treatment of AGA with dampness-heat accumulation syndrome should follow the principle of clearing dampness-heat and dredging meridians. The mechanism is to inhibit inflammatory factors in the joint fluid, reduce serum uric acid, promote uric acid excretion, regulate immune function, and block peripheral nerve pain [12].

Traditional Chinese medical formula has the characteristics of multicomponent, multitarget, and multilevel in the treatment of AGA [24]. Modern pharmacological studies have found that aescin, the effective component of the main herb Cortex Fraxini (Qin Pi) in QPTFF, can inhibit the overexpression of inflammatory factors and catabolic genes, promote the upregulation of cartilage-specific genes and scavenge reactive oxygen species (ROS), to show anti-inflammatory, antioxidant, and protective effects on chondrocytes [26, 27]. Rhizoma Smilacis Glabrae (Tu Fu Ling) can inhibit uric acid production and promote uric acid excretion, reduce capillary permeability, improve microcirculation, and improve joint swelling [28]. Its effective component, resveratrol, can inhibit IL-1β secretion and downregulation of NF-κB p65 expression and reduce the production of inflammatory factors and chemokines and inflammatory cell infiltration [29]. Herba Siegesbeckiae (Xi Xian Cao) has anti-inflammatory and analgesic effects. It can regulate joint inflammation and pain by controlling inflammatory factors in joints and reducing immune response [30]. Rhizome Dioscoreae Hypoglaucae (Bi Xie) can regulate the expression of inflammatory factors, reduce uric acid in the blood, and protect renal function [31]. In a word, a variety of effective components in QPTFF could play therapeutic roles against AGA.

In China, bloodletting therapy is often used to treat AGA with dampness-heat accumulation syndrome. Clinical studies have found that bloodletting therapy can upregulate the local anti-inflammatory factors IL-4 and IL-10, mediate TLR4/IL-1 signal pathway, regulate immune response, reduce inflammatory cell infiltration [15], and relieve pain. Stimulating BL40 can promote uric acid excretion and improve microcirculation [32], and stimulating SP6 and SP9 can inhibit the synthesis of inflammatory cytokines and reduce TNF-α in serum to play anti-inflammatory and detumescence roles [33]. ST36 could effectively function in reducing inflammation in many studies [34, 35], and SP6 can reduce the production and secretion of pain-causing factors and monoamine transmitters in AGA rats to relieve pain [33, 36].

The combination of QPTFF and bloodletting therapy has positive and safe effects on AGA patients, but there is still a lack of high-quality clinical study. The previous reported RCTs of TCM in the treatment of AGA showed many limitations. For example, the treatment in the control group was not a classic control such as NASID or colchicine [37]. In addition, those RCTs did not observe the immediate efficacy of TCM treatment [38]. In our study, we try to observe the pain changes within 2 hours right after the patients take the combined therapy, which is helpful to analyze the immediate effect of TCM therapy. Therefore, this study intends to explore the efficacy of QPTFF combined with bloodletting therapy through a high-quality RCT. We take the changes of patients' clinical symptoms and signs as the main outcome indicators, including joint symptoms and TCM syndromes. In addition, we use laboratory indexes to evaluate the efficacy of TCM therapy objectively and liver and kidney function, blood test, and urinalysis to evaluate the safety of the treatment.

Still, there are also some limitations in this study. Due to the characteristics of bloodletting therapy, the operator and the patients cannot be blinded, which may impact the research results. Due to the lifestyle and diet habits of the population in Tianjin, the similar baseline information of the body mass index (BMI), history of gout, and uric acid level in both groups may lead to a single sample and regionalization. Because we just observed the short-term curative effect on AGA, it was difficult to observe the long-term efficacy in two groups after the trial.

Abbreviations

NSAIDs:	Nonsteroidal anti-inflammatory drugs
CONSORT:	Consolidated Standards of Reporting Trials
RCT:	Randomized controlled trial
QPTFF:	Qinpi Tongfeng Formula
ROS:	Reactive oxygen species
ALT:	Alanine aminotransferase
AST:	Alanine aminotransferase
Cr:	Creatinine
CRP:	C-reactive protein
ESR:	Erythrocyte sedimentation rate
UA:	Uric acid
NRS:	Numerical rating scale
CRF:	Case report form
FAS:	Full analysis set
PPS:	Per-protocol set
SS:	Safety set
ITT:	Intent-to-treat
LOCF:	Last observation carried forward.

Data Availability

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

data will be available in the "Chinese Clinical Trial Registry" (http://www.chictr.org.cn). The registration number is ChiCTR2100048836.

Ethical Approval

This study has been approved by the ethics committee of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (TYLL2021 [Z] 014).

Consent

All the patients participating in the study will sign an informed consent form. Patient privacy and research data will be kept confidential in accordance with clinical trial requirements. The data used for statistical analysis and paper writing will also be anonymously performed with the consent of the patient. The results of this study will be published in the form of a paper.

Disclosure

Hang Lu, Wei Liu, and Yihua Fan are co-first authors. The funding body had no role in the study design or the decision to submit the manuscript for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Hang Lu and Yihua Fan conceived the study and developed the first trial protocol. Hang Lu, Wei Liu, and Yihua Fan designed the study and drafted the manuscript. Wenliang Lv and Danna Yang guided the research program. Chunliu Liu Fangfang Lin, and Qingxiang Gu revised the manuscript. Hang Lu, Wei Liu, and Yihua Fan contributed equally to this work.

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Supplementary Materials

Table S1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents. (*Supplementary Materials*)

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Research Article

Efficacy and Safety of Acupuncture Combined with Herbal Medicine in Treating Gouty Arthritis: Meta-Analysis of Randomized Controlled Trials

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Background. Gouty arthritis is a common metabolic disease caused by long-term purine metabolism and elevated serum uric acid. In recent years, the incidence of gouty arthritis has been increasing year by year. As an effective method for treating gouty arthritis, acupuncture combined with herbal medicine has been widely used in clinical practice. However, the evidence for the treatment needs to be evaluated through systematic review and meta-analysis. Methods. The Cochrane Library, PubMed, Web of Science, EMBASE, China CBM database, Clinical Trials, CNKI, China Wanfang database, and VIP information database were searched from the establishment of each database to March 2021. Randomized controlled trials (RCTs) were included in the study, and the therapeutic effects of acupuncture combined with herbal medicine *versus* conventional therapy, or acupuncture combined with herbal medicine *versus* anti-inflammatory drugs, or acupuncture combined with herbal medicine *versus* acupuncture/herbal medicine alone were compared in the subjects with gouty arthritis. Two authors screened all references, assessed the risk of bias, and independently extracted the data. The binary outcome was summarized using 95% confidence intervals (CIs) and risk ratios (RRs). The overall quality of the evidence was assessed with hierarchy, and meta-analysis was performed with a random-effects model. *Results*. A total of 14 randomized controlled trials (1,065 participants, 540 treatment groups, and 525 control groups) with treatment courses of 5 to 21 days were included. Acupuncture combined with herbal medicine and acupuncture was compared in three trials, acupuncture combined with herbal medicine and conventional therapy was compared in 14 of them, and acupuncture combined with herbal medicine and anti-inflammatory drugs was compared in 8 of them. The clinical efficacy (clinical symptoms, serological tests, and visual analogue scale (VAS) results) was significantly improved in the acupuncture combined with herbal medicine treatment group ($P = 0.0005$, 95% CI 0.03 to 0.13; 687 participants; 8 trials), and the efficacy in reducing uric acid was also better ($P < 0.00001$; 95% CI −102.89, −68.37; 100 participants; 2 trials; evidence with moderate quality). The effect of acupuncture combined with herbal medicine was better than that of acupuncture alone (RR 1.22, 95%CI 1.06 to 1.41; 139 participants; 3 trials), the effect of acupuncture combined with herbal medicine was better than that of herbal medicine alone (RR 1.31 95%CI 1.08 to 1.57, 100 participants, 2 trials, evidence with moderate quality), and the effect of acupuncture combined with herbal medicine was better than that of colchicine ($P = 0.02$, RR 1.14 95%CI 1.02 to 1.27, 2 trials, evidence with moderate quality). The incidence of adverse events was considerably different between the two groups, and the acupuncture combined with herbal medicine group was significantly superior to the control group in terms of adverse events ($P < 0.00001$; 95% CI (0.08 to 0.32)). *Conclusions*. The efficacy of acupuncture combined with herbal medicine was better than conventional drug therapy in treating gouty arthritis. The study results must be interpreted with caution due to the high or unclear risk of bias of the trials included in the study. PROSPERO registration number: CRD42020202544. INPLASY registration number: 202090006.

1. Introduction

Gouty arthritis is one of the most common clinical conditions, which account for 5% of all arthritis [1–3]. It is mainly caused by purine disorders and tissue damage induced by elevated serum uric acid [4]. It can have serious adverse effects on the physical and mental health of subjects and their normal life. Therefore, it is necessary to explore the best way to treat gouty arthritis [5]. The clinical trials have shown that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids can significantly improve clinical symptoms [6–8].

Nevertheless, long-term use of this approach [9] can probably lead to an increase in drug resistance and a decrease in treatment efficacy [10–14]. Although there are no evidence-based guidelines, many patients with gouty arthritis seek acupuncture and herbal remedies, which have been used with safety and efficacy for quite a long time [15–17]. Acupuncture is a treatment method that stimulates specific acupoints on the body surface. It has been used for the prevention and treatment of disease in other eastern countries and China for thousands of years [18].

In ancient traditional Chinese medicine, acupuncture and herbal medicine were believed to work by stimulating acupoints and maintaining a balance between Yin and Yang to mediate the circulation of Qi and blood [19]. In Western medicine, traditional Chinese medicine treatment mechanisms have not yet been well established [20]. Human and animal studies have shown that acupuncture and herbal medicine may play a positive role in reducing blood uric acid, reducing the expression of inflammatory factors, relieving pain, and improving clinical symptoms [21–25].

There has been more and more research on acupuncture and herbal medicine for gouty arthritis in recent years. Several studies reported that acupuncture combined with herbal medicine can promote the dissolution of blood uric acid, increase the clearance of blood uric acid from the kidney [26], and improve treatment efficacy [27–30]. An exploratory systematic review and meta-analysis of acupuncture for the treatment of gouty arthritis published in 2016 found that acupuncture is associated with decreased serum uric acid concentration ($P < 0.05$) [31]. Nevertheless, it is not vital to recommend the methodology because its quality in these reviews is not good enough [32].

Therefore, the purpose of this systematic review was to evaluate the safety and efficacy of acupuncture combined with herbal medicine in the treatment of gouty arthritis and to compare acupuncture combined with herbal medicine and conventional therapy or herbal medicine/acupuncture therapy alone to guide clinical treatment. To ensure the accuracy of these systematic review and meta-analysis, the results of this study needed to be as consistent as possible with the reporting project stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33].

1.1. Search Methods. The Cochrane Library, PubMed, Web of Science, EMBASE, China CBM database, Clinical Trials, CNKI, China Wanfang database, and VIP information database were searched (as of March 2021). The therapeutic effect of acupuncture combined with herbal medicine was compared (e.g., acupuncture included electroacupuncture, three-edged needle bloodletting, and auricular acupuncture, and herbal medicine included Chinese patent medicine and traditional Chinese medicine). Search terms related to acupuncture, traditional Chinese medicine, gouty arthritis, and randomized controlled trials were set, and the searched literature was limited to clinical studies published in Chinese and English.

1.2. Eligibility Criteria

(1) Study type: only randomized controlled studies were included.

(2) Subject type: the subjects diagnosed with gouty arthritis were included according to clear diagnostic criteria or references, with no restrictions on course of the disease, gender, age, or ethnicity.

(3) Type of intervention: the intervention method was composed of acupuncture combined with herbal medicine. The original literature needed to have a specific description of the application process of acupuncture and herbal medicine, such as sterilization, acupuncture manipulation, post-treatment, dosage form, medication method, dosage, and a specific course of treatment.

(4) Type of control: the controlled measures should be standard drugs, and the medication method, treatment course, and dosage should be clearly described.

(5) Types of observed outcome indicators: clinical efficacies (improvement of clinical symptoms and serological test results) were mainly observed, and adverse effects were concerned with secondary outcome indicators.

In this review, clinical studies of acupuncture combined with Western medicine or needle knife combined with herbal medicine were excluded. Reviews, case reports, retrospective studies, or clinical studies without predetermined results were excluded. For duplicate studies, the author of the study was contacted to resolve any ambiguity. If the author of the study cannot be contacted, the first published study was assumed to be original. If the control group did not implement the regular treatment for gouty arthritis, it was not included in the study. Two reviewers (H Liang and FS Huang) independently selected the randomized controlled trials to be included in the study, and a flow chart to choose the included studies was designed according to the requirements of PRISMA. Much effort was made for this review to find out the ethical approval numbers of the included studies, but unfortunately, no information on ethical approval numbers was available. Considering that this review was a meta-analysis, which pertained

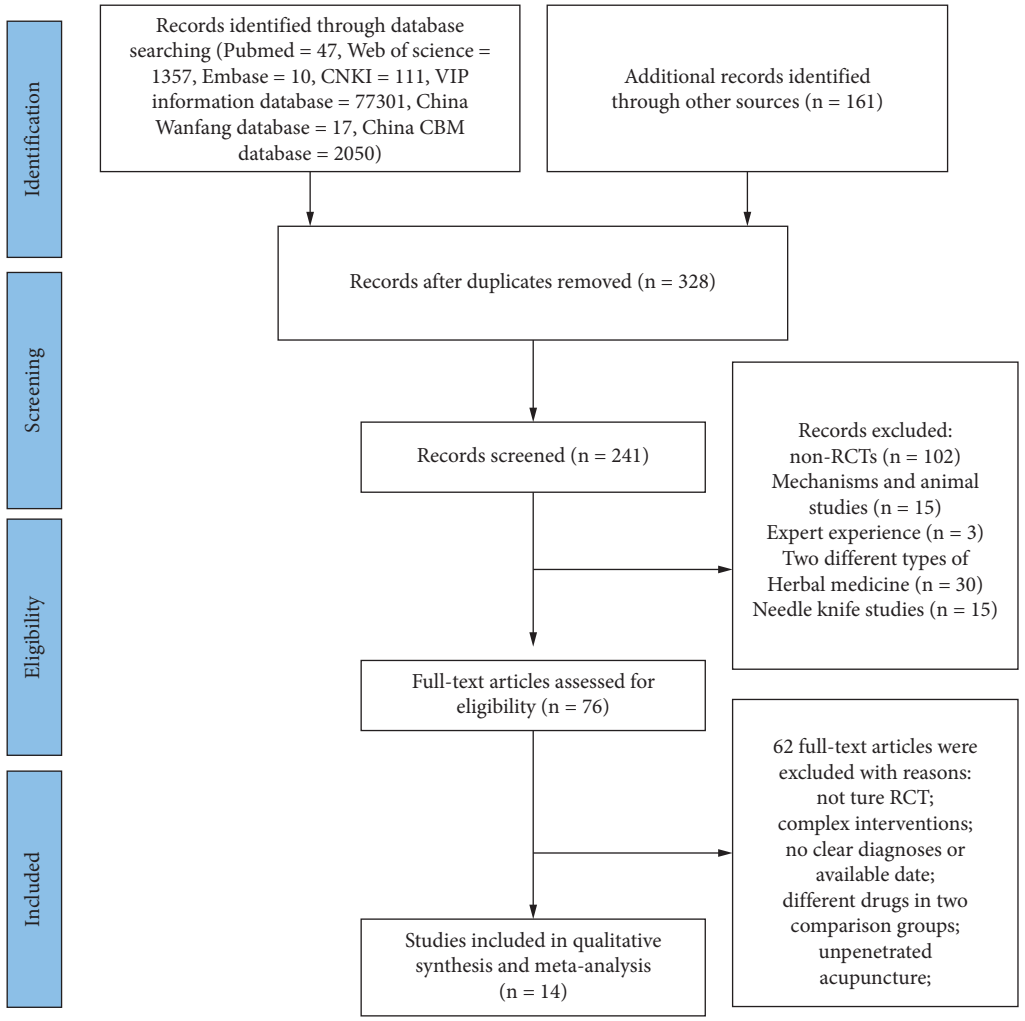


Figure 1: Flow chart for the selection of trials. Flow diagram following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.

to a secondary study, the ethical requirements were not applicable. However, the lack of clear ethical criteria in clinical studies was a factor of bias.

1.3. Data Extraction and Management. The literature data were extracted into Microsoft Excel 2013, and the information collected was as follows:

(1) The basic information of the included literature studies: ID (year of publication, initial of the first author, and year), sample size, language, course of treatment, control measures, and intervention measures; (2) basic information of the subjects: gender, age, severity of the disease, course of the disease, and stage of disease; (3) outcome measurement: primary observed outcomes: clinical efficacy and inflammatory serological factors; observed secondary outcomes: adverse effects.

The authors of this review (P Deng and JL Han) independently used the Cochrane-risk-of-bias assessment tool to determine the risk of bias of each included study [34]. If there were any discrepancies, a third review author (H Liang) was consulted to address the problem. The following items were assessed according to "unclear," "low," or "high" risk: random sequence generation, blinded outcome assessment, blinded subject and personnel, allocation concealment, selective reporting, incomplete outcome data, and other biases.

1.4. Data Synthesis and Analysis. Review Manager Meta 5.3 analysis software was used for data analysis. For clinical efficacy, adverse events, and serological measures, they were shown with the data with 95% confidence intervals (CIs) of risk ratio (RR) (postintervention values used to calculate the efficacy estimates). Statistical analysis was performed according to the latest Cochrane Handbook for Systematic Reviews of Interventions [31]. The meta-analysis would be achieved if the trials were well homogeneous in terms of participants, study design, intervention, control, and outcome. Statistical heterogeneity was calculated using the Higgins I^2 statistic. If there was any significant heterogeneity among studies (I^2>75%), the meta-analysis would not be performed, and the source of the heterogeneity would be assessed. If more than 10 randomized controlled trials tested

the same results in a single meta-analysis, a trim-and-fill analysis was used to intuitively assess and publish the bias. The overall quality of the included research evidence was assessed with hierarchy [35]. The subgroup analysis was performed for different types of controls.

2. Results

2.1. Study Description. A total of 569 pieces of literature were searched, and 76 remained after filtering the titles and abstracts. The full texts of the 76 pieces were read, 62 were excluded, and finally, 14 were obtained [36–49]. The filtering process is shown in Figure 1. Basic information of included trials was as follows: 14 randomized controlled trials were included (1,065 participants, 540 treatment groups, and 525 control groups), all the trials were conducted in China, including 13 studies written in Chinese and 1 study reported in English, 8 of them compared acupuncture combined with herbal medicine and anti-inflammatory drugs [39, 40, 41, 43, 44, 45, 47, 49], and 14 compared acupuncture combined with herbal medicine and conventional therapies [36–49]. Three treatment groups were divided into the other 2 trials [48, 49]. The course of treatment was 6–7 days. The participants aged from 18 to 80 years old. The disease course was 3 days to 22 years. There were 729 men and 336 women. The characteristics of the participants included in the trials are shown in Table 1. The details of intervention in acupuncture groups and control groups are shown in Table 2.

2.2. Risk of Bias in Included Trials. A total of six studies reported that the participants were randomized with the random number table and block randomization. These six trials were considered to have a low risk of bias [38, 41, 43, 44, 48, 49]. Only one study used the card approach and sufficient allocation concealment [49]. Therefore, it was supposed to have a low risk of bias. None of them reported whether the assessments of subjects and outcomes were blinded, which were considered as undefined risk of biases. In terms of other biases, 6 showed that if the whole trial was completed by one author, the risk of bias would be greater [36, 38, 42, 44, 47, 49]. Details of the risk assessment deviations of the included studies are shown in Figure 2. In addition, the dot plot was used to describe the risk of bias for each study combined with the forest plot.

2.3. Primary Outcomes

2.3.1. Clinical Effect. The criteria for clinical effect referred to the consensus on the diagnosis and treatment of gouty arthritis [51]. Clinical symptoms and serological examination were used as criteria for efficacy evaluation. Clinical outcomes were reported in all included studies.

2.3.2. Acupuncture Combined with Herb versus Conventional Medicine. The treatment efficacy of acupuncture combined with herbal medicine and conventional therapy was compared in 14 trials (involving 1,065 subjects) [36–49]. The duration of the trials ranged from 5 to 21 days. The treatment efficacy of acupuncture combined with herbal medicine was 1.11 times that of conventional therapy (RR 1.11) (Figure 3). There was statistical heterogeneity among studies, and the clinical treatment efficacy of acupuncture combined with the herbal medicine group was better than that of conventional therapy ($P < 0.00001$; 95%CI 1.06, 1.15).

2.3.3. Acupuncture Combined with Herbal Medicine versus Acupuncture. The treatment efficacy of acupuncture combined with herbal medicine and acupuncture was compared in three trials (involving 170 subjects) [37, 48, 49]. The number of participants ranged from 60 to 90, and the duration of the trials ranged from 5 to 7 days. As shown in Figure 4, there was no statistical heterogeneity between studies. The clinical treatment efficacy of acupuncture combined with herbal medicine was better than that of acupuncture alone ($P = 0.007$, RR 1.22, 95%CI 1.06 to 1.41).

2.3.4. Acupuncture Combined with Herbal Medicine versus Herbal Medicine. The treatment efficacy of acupuncture combined with herbal medicine and herbal medicine alone was compared in two trials (involving 83 subjects) [46, 48]. The number of participants ranged from 60 to 70, and the duration of the trials was 7 days on average. As shown in Figure 5, there was no statistical heterogeneity between studies. The clinical efficacy of acupuncture combined with herbal medicine was 1.31 times that of herbal medicine alone (RR 1.31), and the performance of acupuncture combined with herbal medicine group was better than the herbal medicine alone group in the aspect of the clinical efficacy improvement ($P = 0.005$, RR 1.31, 95%CI 1.08 to 1.57).

2.3.5. Acupuncture Combined with Herbal Medicine versus Anti-Inflammatory Medications. The treatment efficacy of acupuncture combined with herbal medicine and anti-inflammatory drugs was compared in eight trials (involving 549 subjects) [39, 40, 41, 43, 44, 45, 47, 49]. The number of participants ranged from 48 to 156, and the duration of the trials ranged from 3 to 21 days. As shown in Figure 6, there was statistical heterogeneity between studies, so the fixed-effects model was used. The clinical treatment efficacy of acupuncture combined with herbal medicine was better than that of anti-inflammatory drugs ($P = 0.0005$, 95%CI 0.03 to 0.13).

2.3.6. Acupuncture Combined with Herbal Medicine versus Colchicine. The efficacy of acupuncture combined with herbal medicine and colchicine was compared in two trials (111 patients) [39, 47]. The number of participants ranged from 59 to 60, and the duration of the trials ranged from 14 to 21 days. As shown in Figure 7, there was no statistical heterogeneity between studies, so the random-effects model was applied. The clinical treatment efficacy of the acupuncture combined with herbal medicine was better than that of colchicine ($P = 0.02$, RR 1.1495%CI 1.02 to 1.27).

Table 1: Characteristics of included randomized trials of acupuncture combined with herbal medicine for gouty arthritis.

Study ID	Year	Gender male/female	Sample size	Age (mean or range, yrs)	Course of disease (mean or range)	Course of treatment, days	Intervention vs. control	Outcomes	Control measures
JinRT 2011	2011	I:29/1 C: 28/2	I:30 C: 30	I:47.50 ± 10.29 C:43.37 ± 11.34	I:17.62 ± 44.24 C:17.92 ± 35.0	10	Acupuncture plus herbal medicine vs. benzbromarone	Clinical effect, UA, VAS	Benzbromarone: 1 time/day, 50 mg/time
liuF 2011	2011	NR	I:34 C: 36	I:40~60(52) C: 40–60(52)	I:2 month-4 years C:2 month-4 years	5	Acupuncture plus herbal medicine vs. acupuncture	Clinical effect	Acupuncture: 1 time/day
liYM 2019	2019	I:21/9 C: 23/7	I:30 C: 30	I:37~72 C: 35~70	I:3d-10 years C: 7d-12 years	10	Acupuncture plus herbal medicine vs. benzbromarone	Clinical effect	Benzbromarone: 1 time/day, 50 mg/time
ZhongYH 2021	2021	I:28/2 C: 29/1	I:30 C: 30	I:18–80 (42.33 ± 14.36) C:18–80 (39.30 ± 12.99)	NR	14	Acupuncture plus herbal medicine vs. febuxostat and colchicine	Clinical effect, UA, Scr, BUN, 24 hour urine protein, CRP, TCM score, AEs	Febuxostat: 1 time/day, 40 mg/time; colchicine: 3 times/day, 0.5 mg/time
FengPD 2017	2017	I:22/9 C: 12/3	I:31 C: 18	I:22–71 C: 31–73	NR	14	Acupuncture plus herbal medicine vs. dafen capsules	Clinical effect	Dafen capsules: 1 time/day, 75 mg/time
ZhangSJ 2010	2010	I:34/0 C: 33/0	I:34 C: 33	32–71 48	7 day-14 years	3–7 days	Acupuncture plus herbal medicine vs. diclofenac sodium enteric-coated tablets	Therapeutic effects	Diclofenac sodium enteric-coated tablets: 3 times/day, 25 mg/time
LiuZY 2014	2014	NR	I:87 C: 87	I:44.1 C:43.4	NR	14	Acupuncture plus herbal medicine vs. benzbromarone tablets	Clinicaleffect, CRP, BUA, ESR, VAS, AEs	Benzbromarone: 1 time/day, 50 mg/time
GuanFY 2014	2014	I:28/2 C: 29/1	I:30 C: 30	I:31–72 (45.3 ± 6.17) C: 28–70 (44.7 ± 6.40) C: 1–10 (5.76 ± 3.77) years	I:0.5–11 (5.71 ± 3.72) years	7	Acupuncture plus herbal medicine vs. meloxicam and sodium bicarbonate tablets	Clinical effect, UA, VAS,	Meloxicam tablets: 1 time/day, 15 mg/time; sodium bicarbonate tablets: 3 times/day, 1 g/time
XieYF 2015	2015	I:41/4 C: 42/2	I:45 C: 44	I:40–73 C: 42–72	I:1d-14 years C: 2d-13 years	7	Fire acupuncture plus herbal medicine vs. diclofenac sodium enteric solution tablet and allopurinol tablet	Clinical effect, VAS,	Diclofenac sodium enteric-coated tablets: 1 time/day, 75–25 mg/time; allopurinol: 1 time/day, 50 mg/time
ChenKW 2016	2016	I:47/31 C:48/30	I:78 C: 78	I:(54.1 ± 7.7) C: 53.9 ± 8.1	I:(4.1 ± 1.3) years C: (3.9 ± 1.4) years	7	Acupuncture plus herbal medicine vs. diclofenac sodium sustained-release tablets and allopurinol tablets	Clinical effect, adverse triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, and AEs	Diclofenac sodium sustained-release tablets: 1 time/day, 75 mg/time; allopurinol: 3 times/day, 100 mg/time

Table 1: Continued.

Study ID	Year	Gender male/ female	Sample size	Age (mean or range, yrs)	Course of disease (mean or range)	Course of treatment, days	Intervention vs. control	Outcomes	Control measures
JinZ 2012	2012	I:29/1 C: 27/3	I:30 C: 30	I:23–67 C: 25–66	NR	7	Acupuncture plus herbal medicine vs. gout tablets	Clinical effect, VAS, UA, AES	Gout tablets (Chinese patent medicine): 3 times/day, 0.12 g/time
liJY 2013	2013	I:28/3 C: 28/31	I:31 C: 29	I:49.67 ± 9.33 C:46.53 ± 10.29	I:4–11(7.1 ± 3.9) d C: 2–10(6.7 ± 3.2)d	21	Acupuncture plus herbal medicine vs. colchicine vs. diclofenac sodium sustained-release tablets	Clinical effect, UA, AEs	Colchicine: 1 time/day, 0.5 g/ time; diclofenac sodium sustained-release tablets: 1 times/ day, 100 mg/time
WangMJ 2015	2015	Male: 35 Female: 25	I:20 C1: 20 C2: 20	NR	2–13 years	7	Acupuncture plus herbal medicine vs. Acupuncture vs. herbal medicine	Clinical effect, UA	Acupuncture: 1 time/day, herbal medicine 2 times/day
ZhuC 2011	2011	I:30 C1: 30 C2: 30	I:30 C1: 30 C2: 30	I:48.12 ± 11.21 C1: 47.44 ± 11.29 C2: 50.36 ± 11.07	I:25.52 ± 9.87 C1:24.16 ± 10.07 C2:26.04 ± 10.03	6	Acupuncture plus herbal medicine vs. indomethacin vs. acupuncture	Clinical effect, UA, ESR,	Indomethacin: 3 times/day, 25 mg/ time; herbal medicine: 3 time/day

Note: NR: not reported; I: intervention; C: comparison; Y: yes; N: no; AEs: adverse effects; UA: uric acid; VAS: visual analogue scale; Scr: serum creatinine concentration; BUN: blood urea nitrogen; CRP: C-reactive protein; TCM: traditional Chinese medicine; BUA: blood uric acid; ESR: erythrocyte sedimentation rate; Yrs: years; vs: versus.

Table 2: Details of intervention in acupuncture groups and control groups.

Study ID	Acupuncture point [50]	Acupuncture on one or both sides of the body	Duration of each treatment	Frequency	With or without conventional medicine
JinRT 2011	Yinlingquan(SP9), Sanyinjiao(SP6), Zusanli(ST36), Quchi(LI11)	On both sides	30 min	1 time/day;	Y
liuF 2011	Quchi(LI11), Hegu(LI4), Yinbai(SP1), Dadu(SP2), Sanyinjiao(SP6), Yinlingquan(SP9)	NR	30 min	1 time/day;	N
liYM 2019	Taibai(Sp3), Taichong (Liv3), Xingjian(Liv2), Neiting (S44), Xiangu(S43), Qiuxu(G40), intense redness, swelling, and pain areas (usually the location of gouty tophus deposits)	NR	NR	1 time every other day;	Y
ZhongYH 2021	Local joint with recurrent gout	On one side	NR	Acupuncture:1 time;	Y
FengPD 2017	The local tenderness point of the joint lesion and the surface of the distended and bruising vein	On one side	3–5 min	2 times/week	Y
ZhangSJ 2010	Local joint with recurrent gout	NR	2–5 min	3 times/day	Y
LiuZY 2014	Xuehai(SP10), Zusanli(ST36), Sanyinjiao (SP6), Fenglong(S40), Yinlingquan(SP9), Quchi(LI11), Hegu(LI4), Taichong (Liv3), Dadu(SP2), Local ashi point	NR	30 min	1 time/day	Y
GuanFY 2014	Taichong (Liv3), Sanyinjiao(SP6), Zusanli(ST36), Fenglong(S40), Yinlingquan(SP9), Yanglingquan(GB34)	NR	20 min	1 time/day	Y
XieYF 2015	Ashi point	NR	NR	1 time/day	Y
ChenKW 2016	Ashi point(Pain point), Zusanli(ST36), Sanyinjiao(SP6)	NR	15 min	1 time/day	Y

Table 2: Continued.

Study ID	Acupuncture point [50]	Acupuncture on one or both sides of the body	Duration of each treatment	Frequency	With or without conventional medicine
JinZ 2012	Xuanzhong(G39), Sanyinjiao(SP6), Shangqiu(Sp5), Zhaohai(K6), Yanglingquan(GB34), Yinlingquan(SP9), Liangqiu(ST34), Xuehai(SP10), Quchi(LI11), Shaohai (H3), Shousanli(LI10), Chize(L15)	NR	NR	1 time/day	N
liJY 2013	Zusanli(ST36), Sanyinjiao(SP6), Yinlingquan(SP9), Fenglong(S40), Xuehai(SP10), Quchi(LI11), Hegu(LI4), Taichong (Liv3), ashi point	NR	30 min	1 time/day	Y
WangMJ 2015	Zusanli(ST36), Sanyinjiao (SP6), Yinlingquan(SP9), Yanglingquan(GB34), Fenglong(S40), gongsun (SP 4) (both sides), Ashi point	On both sides	30 min	NR	N
ZhuC 2011	Yinbai(SP1), Taichong(Liv3), Sanyinjiao(SP6), Fenglong(S40), Zusanli(ST36), Yinlingquan(SP9), Yanglingquan(GB34), Taibai(Sp3), Hegu(LI4), ashi point	NR	30	1 time every other day;	Y
	Yinlingquan(SP9), Sanyinjiao(SP6), Zusanli(ST36), Quchi(LI11)	On both sides			

Note: NR: not reported; Y: yes; N: no.

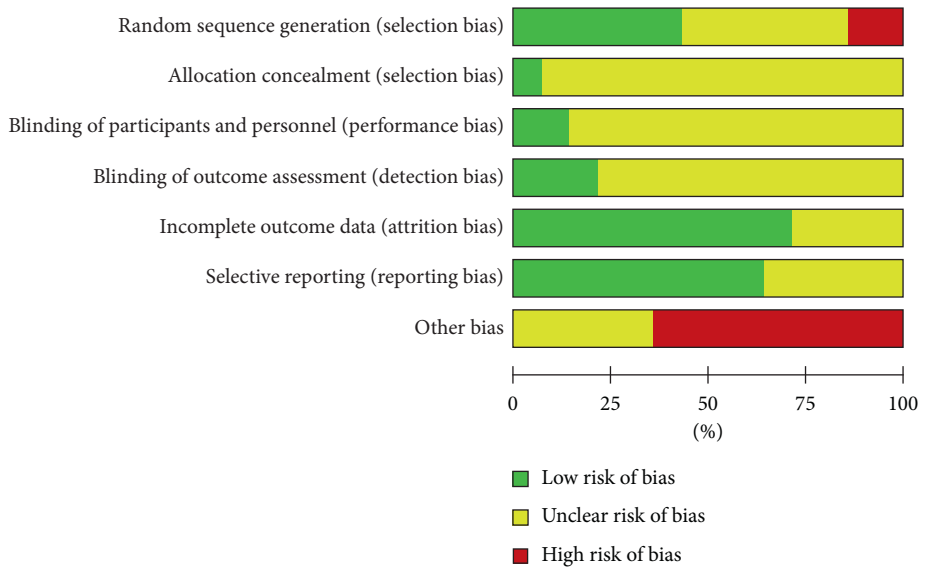
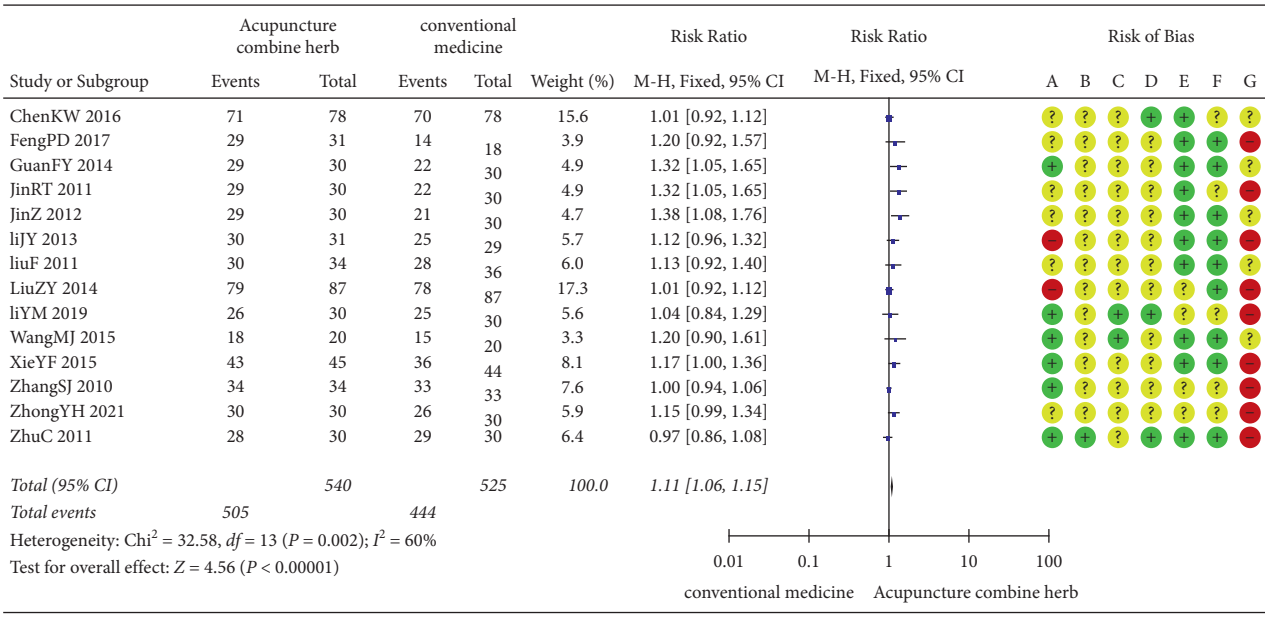


Figure 2: Risk of bias of randomized clinical trials of acupuncture combined with herbal medicine for gouty arthritis. Note: A: Selection bias; B: selection bias C; performance bias of participants and personnel; D: detection bias; E: attrition bias; F: reporting bias; and G: other biases.

2.3.7. Uric Acid (UA)

(1) Acupuncture combined with herbal medicine versus acupuncture. The efficacy of acupuncture combined with herbal medicine and acupuncture in reducing uric acid was compared in two trials (involving 100 subjects) [48, 49]. The number of participants ranged from 40 to 60, and the duration of the trials ranged from 6 to 7 days. As shown in Figure 8, there was no statistical heterogeneity between studies, so the random-effects model was applied. The clinical treatment efficacy of acupuncture combined with herbal medicine was better than that of the acupuncture ($P < 0.00001$; 95% CI (102.89, 68.37)).



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

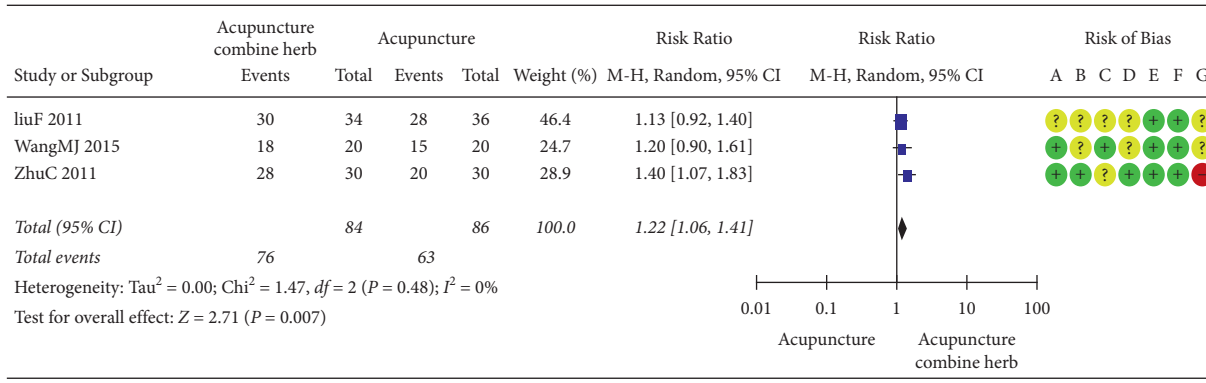
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 3: Clinical effect of acupuncture combined with herbal medicine versus conventional medicine.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

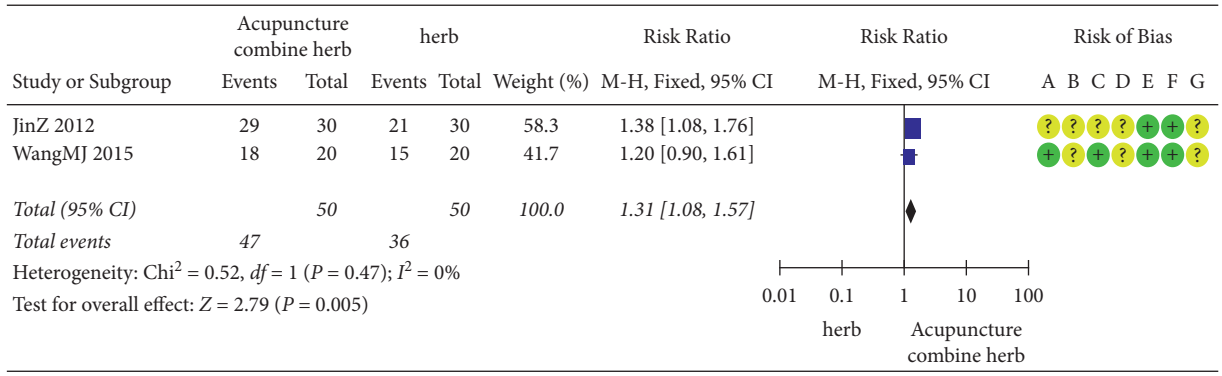
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4: Clinical effect of acupuncture combined with herbal medicine versus acupuncture alone.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

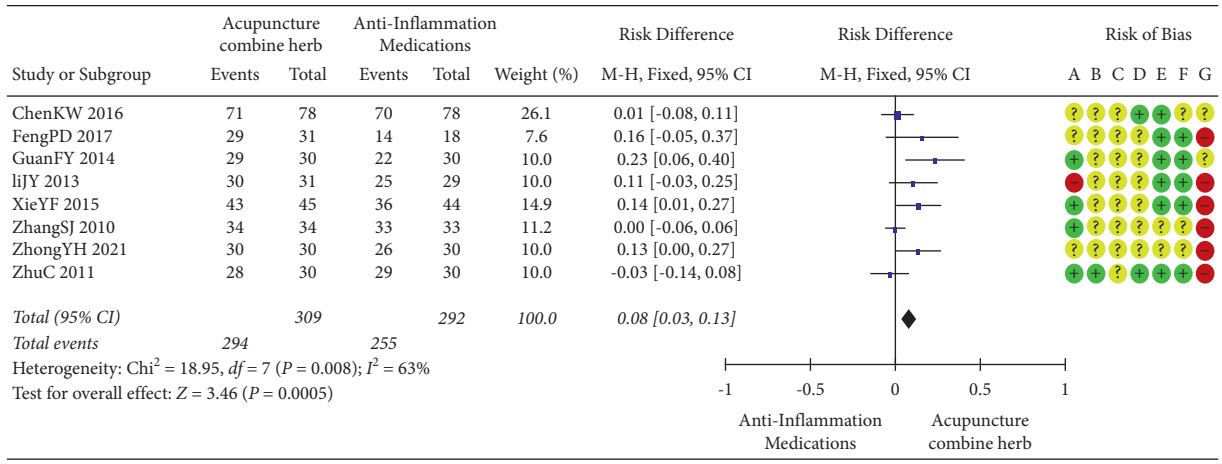
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 5: Clinical effect of acupuncture combined with herbal medicine versus herb alone.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

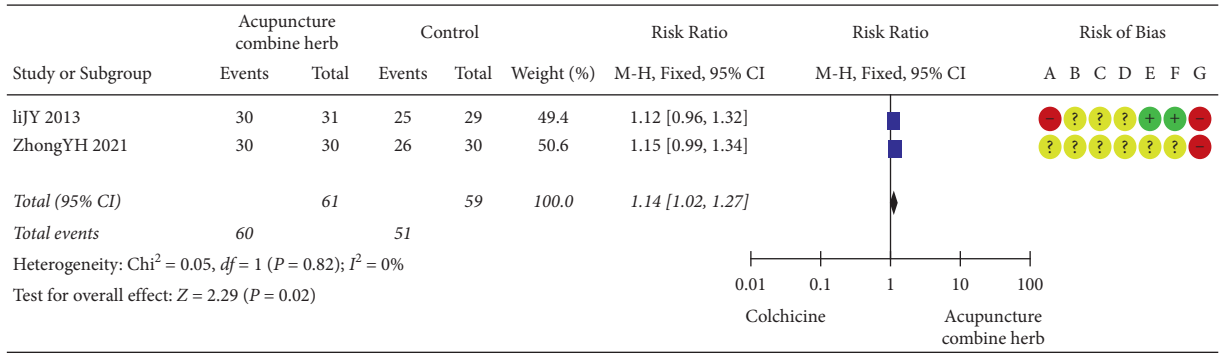
(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6: Clinical effect of acupuncture combined with herbal medicine versus anti-inflammatory medications.

2.3.8. Visual Analogue Scale (VAS)

(1) Acupuncture combined with herbal medicine versus anti-inflammatory medications. VAS (involving 149 subjects) was measured in 2 trials [43, 44]. The number of participants ranged from 60 to 89, and the duration of the trials was 7 days on average. As shown in Figure 9, there was no statistical heterogeneity between the studies. Acupuncture combined with herbal medicine was better than the anti-inflammatory drugs for the reduction in VAS score ($P < 0.00001$, mean difference = −0.78; 95% CI (1.12, 0.45)).



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

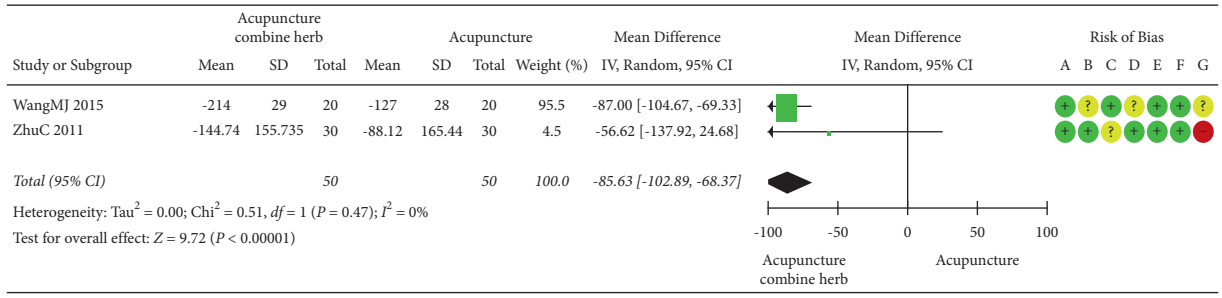
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7: Clinical effect of acupuncture combined with herbal medicine versus colchicine.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 8: Uric acid of acupuncture combined with herbal medicine versus acupuncture alone.

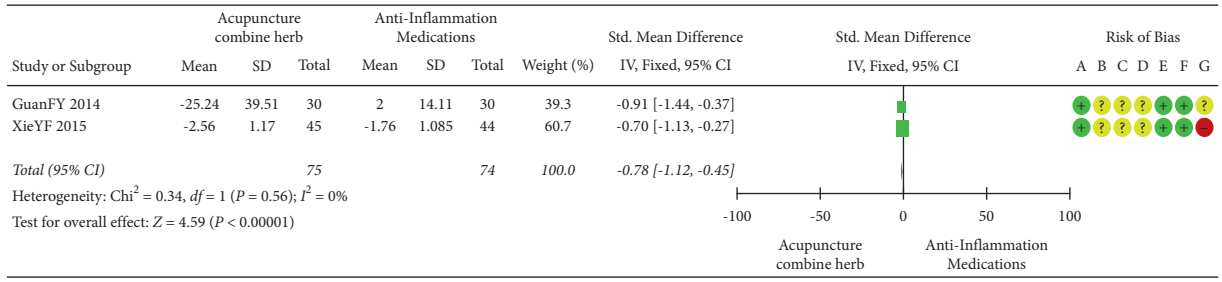
2.4. Secondary Outcomes

2.4.1. Adverse Events. In the 14 included randomized controlled trials, 5 of them reported adverse events [39, 42, 45–47]. The difference of adverse events between the acupuncture group and the control group is shown in Figure 10. The acupuncture group performed better than the control group in the aspect of the adverse events ($P < 0.00001$; OR = 0.16; 95% CI (0.08 to 0.32)).

2.4.2. Publication Bias. The 14 included studies involved 8 types of comparison and contrast. More than 10 trials compared the treatment efficacy of acupuncture combined with herbal medicine and conventional therapy to treat gouty arthritis, and it could be manifested through trim-and-fill analysis. The publication bias no longer existed when the results were saturated after 5 iterations ($P > 0.05$). Therefore, as shown in Figure 11, this result also indicates that more high-quality studies are needed to verify the conclusions of this review in the future.

3. Discussion

Currently, Chinese medicine therapies have attracted increasing attention in the treatment of gouty arthritis, and acupuncture and Chinese herbal medicine are the commonly used therapies in clinical practice. In recent years, there had been a corresponding increase in the study on the treatment of gouty arthritis with acupuncture or herbal therapy [52–54]. Acupuncture is an ancient and effective



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

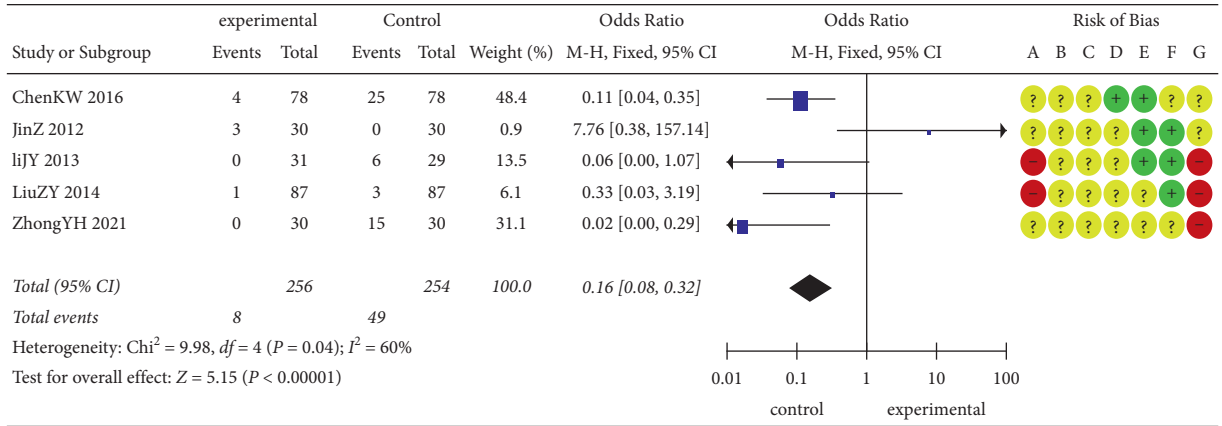
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 9: VAS of acupuncture combined with herbal medicine versus anti-inflammatory medications.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 10: Adverse events of acupuncture combined with herbal medicine compared to conventional medicine.

Chinese medicine treatment method. Modern studies suggest that acupuncture can reduce the release of inflammatory and pain-causing substances, improve the microcirculation in the focal area, and mobilize the immune function of the body, thus stimulating the defense mechanisms of the body [55]. Traditional Chinese medicine treatment plays an essential role in treating gouty arthritis. Some studies included in the review showed that oral or external application of formulas with the main functions of clearing away heat and dampness, promoting blood circulation, and removing blood stasis could effectively relieve the pain of the patients with gouty arthritis and decrease the degree of redness, swelling, heat, and pain of target joints, and traditional Chinese medicine had the advantages of high safety, low incidence of adverse reactions, and individualized treatment [25, 56, 57]. Therefore, acupuncture and traditional Chinese medicine had good clinical application prospects and research value in treating gouty arthritis. There were many studies researched on acupuncture combined with traditional Chinese medicine in treating gouty arthritis, but most of the studies had fewer clinical cases and were single-center studies. Besides, the control groups had several types of treatment, such as acupuncture alone, Chinese medicine alone, and Western medicine alone. No other scholars to date used the method of meta-analysis for system analysis to compare the efficacy of acupuncture combined with Chinese

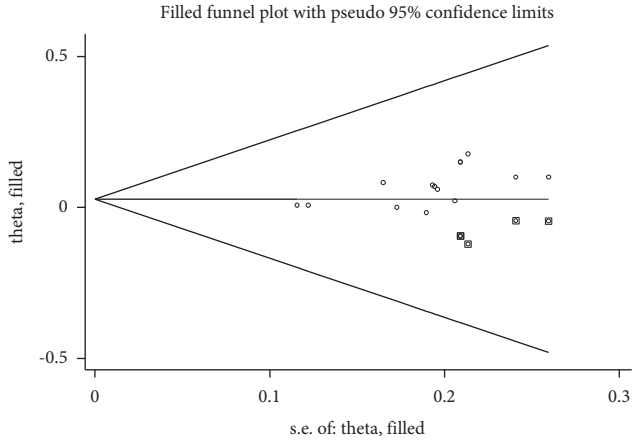


Figure 11: Trim-and-fill analysis for the comparison of clinical treatment efficacy between acupuncture combined with herbal medicine and conventional therapy.

herbal medicine versus Western medicine for gouty arthritis from the perspective of evidence-based medicine. The randomized controlled trials with the intervention group treated by acupuncture combined with herbal medicine were included in this study, the meta-analysis method was used, and 4 treatment options including Chinese herbal medicine alone, acupuncture alone, Western medicine alone, and acupuncture combined with Chinese herbal medicine were involved, which might provide some reference for clinical decision-making in treating gouty arthritis.

A systematic search and a rigorous assessment of the original studies were conducted in this systematic evaluation, with more stringent intervention procedures than other similar studies. This study included 14 RCTs involving 1,065 patients, which aimed to examine the clinical efficacy of acupuncture combined with herbal medicine in treating gouty arthritis. Unlike previous meta-analyses, this study was the first one to include all types of meta-analyses and systematic evaluations on acupuncture combined with herbal medicine for gouty arthritis, which followed the criteria and guidelines of the QUOROM systematic review and meta-analysis [33] with no language restrictions, and multiple literature databases were searched through a comprehensive search strategy. In addition, more trials were added after previous reviews. Thus, this present systematic review differed from previous reviews. This review analyzed clinical efficacy, uric acid, VAS, and adverse effects. Based on the subgroup analysis of the 14 included studies, it was found that acupuncture combined with herbal medicine therapy significantly improved the clinical outcomes of patients compared with acupuncture and herbal medicine therapy alone. Subgroup analysis depicted that acupuncture combined with herbal treatment was superior to conventional treatment, acupuncture alone, herbal therapy alone, anti-inflammatory drugs, and colchicine therapy for improving overall efficiency, relieving pain, and improving signs and symptoms. In terms of improving blood uric acid and VAS scores, acupuncture combined with herbal medicine was much better than acupuncture or anti-inflammatory drug therapy alone. The results of this review were consistent with those of Han et al.'s study in terms of urine acid [58]. These results suggest that acupuncture combined with Chinese herbs can treat gout and reduce the incidence of gouty arthritis. From the point of view of the occurrence of adverse reactions, patients were more likely to have adverse drug reactions in the process of treating gout with Western medicine treatment, which would affect the daily life of patients during the whole treatment process; gouty arthritis patients treated with acupuncture combined with traditional Chinese medicine had fewer adverse reactions, which were mostly caused by the inadaptability of the body to herbal medicine or acupuncture and would gradually disappear during the treatment process. Besides, this review compared acupuncture combined with herbal medicine versus conventional therapy versus Western treatment in a subgroup analysis rather than acupuncture combined with Western medicine therapy versus Western medicine as other meta-analyses did. Therefore, this review could directly compare the efficacy of acupuncture combined with herbal medicine versus Western medicine versus conventional treatment. Blood pricking was the most used acupuncture therapy in the literature included in this study, and a total of 12 studies used this method, accounting for 30% of all acupuncture therapies. The main tools used in blood pricking therapy include three-edged needles and injection needles combined with cupping. The site selection for bloodletting was based on the ashi points and the target joint with recurrent pain, and the volume of blood pricked was about 10–50 ml. This review summarized the clinical effect of acupuncture combined with herbal medicine in treating gouty arthritis and put forward new treatment options.

However, this study has several limitations. First, most included studies presented an unclear risk of bias regarding random sequence generation and allocation concealment. Some of these studies were also at unclear risk of bias in selective reporting and incomplete outcome data. Among the included 14 RCTs, only 6 studies described specific randomization methods, and the remaining studies only mentioned randomization in the articles without a specific description of the randomization method. None of them mentioned allocation concealment and blinding, making it impossible to truly judge their risk of bias. Second, 13 of the 14 were published in Chinese, and 1 was written in English, which reduced the accessibility to other researchers and restricted further research based on these findings. Third, the interventions were not completely consistent among the included studies in this review, such as selected acupuncture points, the formulation and dosage of herbal medicine, and the type of Western medicine. Treating acupuncture combined with herbal treatment and Western medicine treatment as the same intervention method during meta-analysis might cause the bias of the analysis results.

In the subgroup analysis of acupuncture combined with herbal medicine versus conventional treatment, the heterogeneity was higher ($I^2 = 63\%$) (Figure 3). It is suggested that differences in the type, dose, and duration of therapy of Western drugs in conventional treatment may be responsible for the heterogeneity. After analyzing the publication

bias through the trim-and-fill method, it was found that bias no longer existed if the results were saturated after five iterations ($P > 0.05$). This result also indicated that although this study showed that acupuncture combined with herbal medicine was more effective than conventional therapy in treating GA, few studies had high-quality, large-sample, multicenter RCTs. More high-quality studies are needed to verify the findings of this review in the future.

4. Conclusions

Based on the evidence in this systematic review, it was found that acupuncture combined with herbal medicine performed better than acupuncture or herbal medicine alone and conventional therapy in terms of improving clinical efficacy, lowering uric acid, and improving VAS score. Due to the generally poor methodological quality of the included trials (based on hierarchical evidence analysis results), the included clinical trials were limited. Hence, the safety and efficacy of acupuncture combined with herbal medicine for the treatment of GA needed to be further validated with high-quality randomized trials. Good trials are the prerequisite for reliable results. To improve the evidence of evidence-based medicine, RCTs should be strictly designed and carried out in the future. Clear and specific randomization methods, allocation concealment, and blinding method should be effectively implemented to control bias. A large sample size is also required. At the same time, in order to improve the reliability of the results to a certain extent, it is recommended to include clinical follow-up to observe the long-term efficacy, report the long-term effectiveness of acupuncture combined with Chinese medicine, and evaluate the quality of life of the patient.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Advances in Experimental and Clinical Research of the Gouty Arthritis Treatment with Traditional Chinese Medicine

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Gouty arthritis (GA) is a multifactorial disease whose pathogenesis is utterly complex, and the current clinical treatment methods cannot wholly prevent GA development. Western medicine is the primary treatment strategy for gouty arthritis, but it owns an unfavorable prognosis. Therefore, the prevention and treatment of GA are essential. In China, traditional Chinese medicine (TCM) has been adopted for GA prevention and treatment for thousands of years. Gout patients are usually treated with TCM according to their different conditions, and long-term results can be achieved by improving their physical condition. And TCM has been proved to be an effective method to treat gout in modern China. Nevertheless, the pharmacological mechanism of TCM for gout is still unclear, which limits its spread. The theory of prevention and treatment of gout with TCM is more well acknowledged in China than in abroad. In this article, Chinese herbs and ancient formula for gout were summarized first. A total of more than 570 studies published from 2004 to June 2021 in PubMed, Medline, CNKI, VIP, Web of Science databases and Chinese Pharmacopoeia and traditional Chinese books were searched; the current status of TCM in the treatment of GA was summarized from the following aspects: articular chondrocyte apoptosis inhibition, antioxidative stress response, inflammatory cytokine levels regulation, uric acid excretion promotion, immune function regulation, uric acid reduction, and intestinal flora improvement in subjects with gout. The literature review concluded that TCM has a specific curative effect on the prevention and treatment of GA, particularly when combined with modern medical approaches. However, lacking a uniform definition of GA syndrome differentiation and the support of evidence-based medicine in clinical practice have provoked considerable concern in previous studies, which needs to be addressed in future research.

1. Introduction

Gout is a crystal-related disease aroused by the sedimentation of monosodium urate (MSU), directly related to hyperuricemia caused by decreased uric acid excretion or purine metabolic disorders [1]. Gout incidence rate and prevalence have risen steadily over the past few decades due to lifestyle changes, westernized diets, and an aging population [2]. Typical acute gouty arthritis is more common in middle-aged, older men, and obese postmenopausal women. It is usually manifested as redness, bright, and significant tenderness in the single affected joints, especially when the first metatarsophalangeal joint is involved [3]. A considerable part of the global population experiences gout every year [4]. According to World Health Organization (WHO) estimates, 3.9% of the people in the world suffer from gout [5]. Gout owns multiple risk factors such as obesity, coronary heart disease, hypertension, diabetes or glucose intolerance, and lipid metabolism disorders. Acute episodes of arthritis, chronic joint injury, and joint malformations can decrease the living quality and cause disablement in some severe cases [6, 7].

Western medicine is the primary treatment strategy for gout (such as uric acid-lowering drugs, pain relief, primary disease treatment, physical therapy, and surgical treatment). These drugs have certain adverse effects on liver, kidney, and

gastrointestinal tract, thus influence patients' treatment compliance [8]. However, the overall prognosis of gout is still not optimistic. TCM is considered a treasure trove of clinical practice for thousands of years and a significant contributor to global medical care. TCM originated in ancient China. Therefore, it has been applied to the prevention and treatment of gout for many centuries in China. Chinese medicine, with unique efficacy, has the long clinical practice and a lot of clinical experience in preventing and treating gout [9], No matter TCM is used alone or combined with other therapies, it is the most commonly used complementary and alternative medicine (CAM) in modern China and is beneficial to subjects with gout [10]. TCM contains rich culture and literature, which is mainly reflected in two parts: Chinese medicine itself and the theoretical system of TCM. "Disease prevention" is the principle of TCM for disease treatment. TCM has emphasized the prevention and treatment of diseases. For the prevention and treatment of gout disease, we can combine the theory of "treating pre-disease" and "the principle of a holistic view of TCM" according to the characteristics of the development of the disease.

As early as 2000 years ago, the authoritative work of TCM "Huangdi Neijing·Suwen" made a detailed discussion on the etiology, pathogenesis, syndrome classification, and prognosis of gout [11]. Etiology is the core of TCM theory, which studies gout syndrome based on holism. According to the theory of TCM, gout is associated with congenital deficiency and dysfunction of the spleen and kidney. Holism holds that the spleen is the root of after birth and the source of qi and blood, which transports the essence of water and grain to nourish the whole body. The kidney is often considered as the congenital foundation, which can store substances and regulate water metabolism [12]. TCM practitioners in China emphasize the intrinsic balance of the body. Consequently, TCM works not just by treating gouty arthritis itself but also by curing the patient as a whole in an indirect way [13].

For GA, it is proven that many effective fang-ji (formulations) can clinically delay gout's progress and prevent the occurrence of it. The fang-ji was designed according to the theory of spleen and kidney disorders and qi and blood in TCM [14]. In this review, the Chinese herbs and ancient formulas with remedial effects on GA were summed up first. Then, the current research situations of TCM in modern medicine were analyzed, coming up with existing issues in the development of TCM. Lastly, the future of TCM in the circumstance of integrated medicine and precision medicine was concluded. After the review was completed, it was convinced that TCM is a progressive GA therapy despite its development since ancient times; it has curative effects, although the controversy still exists. The theory of TCM also needs to be precisely analyzed and confirmed by systematic research methods.

2. History of TCM for GA Prevention and Treatment

Classical TCM formulas applied to prevent and treat gouty arthritis for thousands of years are the most popular utilization of TCM. Gout originated in the late Western Han Dynasty. In the ancient books about TCM, there is no clear concept of "gouty arthritis" as it is in the modern medicine. The symptoms and pathogenesis of "Li-Jie disease," "white tiger disease," and "gout" in TCM have many similarities with gouty arthritis. Gouty arthritis belongs to the category of "Bi syndrome" in TCM, and the TCM disease name "Bi syndrome" was observed for the first time in Huangdi's Internal Canon (Huang Di Nei Jing in Chinese) [15]. In TCM ancient literature, the scope of "Bi syndrome" is extensive, which includes many Western medicine diseases.

Following Huangdi's Internal Canon, Zhang Zhongjing of the Han Dynasty was the first to elaborate gout systematically. Zhang Zhongjing discussed gout treatment in "jin-gui-yao-lue" and proposed using "Ramulus Cinnamomi, Paeoniae and Anemarrhenae decoction" to treat gout syndrome of wind-damp associated with pathogenic heat. "Wu-tou decoction" treats gout syndrome of cold dampness. Since the Han Dynasty (over 2000 years ago), TCM physicians inherited and developed Zhongjing's doctrine and gained a deeper and more comprehensive understanding of the causes and mechanisms of Li-Jie disease, and the therapeutic methods and typical recipes were more abundant [16].

Cao Yuanfang of the Sui Dynasty emphasized the effects of deficient qi and blood and alcohol consumption on gout in his "General Treatise on the Cause and Symptoms of Diseases," stressing the deficiency in origin and excess in the superficiality of Bi's disease [17]. Wang Tao of the Tang Dynasty emphasized that the pathogenesis of gout was "dampness and heat, phlegm hinder the meridians" in his "Wai-tai-mi-yao," which is basically consistent with the view of the Huangdi's Internal Canon (Huang Di Nei Jing in Chinese) [18]. Zhu Danxi, one of the four schools of the Jin-yuan Dynasty, officially proposed the name of gout. In his book "Danxi's Mastery of Medicine·Gout," he pointed out that the pathogenesis of gout is "phlegm, wind-heat, wind-damp, blood-insufficiency, blood heat, and blood stasis, which are blocked in the meridians and collaterals [19].

The primary treatment is related to the specific pathogenesis of the patient. For people with blood-insufficiency symptoms, Chuanxiong Rhizoma (Chuan xiong) and *Angelicae Sinensis Radix* (Dang gui) are mostly used accompanied by Persicae Semen (Tao ren), Carthami Flos (Hong hua), and Radix Clematidis (Wei ling xian). In case of people with damp evil retention syndrome, consider adding *Atractylodes Lancea* (Cang zhu), *Atractylodes Macrocephala Koidz* (Bai zhu), and Bamboo Juice (Zhu li) based on Erchen decoction to invigorating the spleen and removing dampness. In the case of phlegm blockage, it is considered to add *Scutellariae Radix* (Huang qin), Notopterygii Rhizoma Et Radix (Qiang huo), and *Atractylodes Lancea* (Cang zhu) to Er Chen decoction to dissolve phlegm and clear the collaterals.

For patients with blood stasis symptoms, *Saposhnikoviae Radix* (Fang feng) and Notopterygii Rhizoma Et Radix (Qiang huo) are added to Siwu decoction to activate blood circulation and dissipate blood stasis. For patients with obvious blood stasis symptoms, add *Scutellariae Radix*

(Huang qin) and *Phellodendri Chinrnsis Cortex* (Huang bai) to Si Wu Tang to nourish the blood, promote blood circulation, clear heat, and dry dampness. During the Ming and Qing dynasties, Wang Kentang's classic work "zheng-zhi-zhun-sheng" attributed the cause of gout to wind-dampness invading the kidney meridian, causing stagnation in the blood vessels [20]. Zhang Jingyue pointed out in his "Jing-Yue-Quan-Shu" that the wandering arthritis syndrome in TCM is gout [21]. Wang Qingren of the Qing Dynasty proposed a Chinese medicine prescription to treat gout by invigorating Qi, promoting blood circulation, and creating a new way of thinking for clinical practice in his "Yilin Gaicuo" [22].

Zhu Liangchun, a modern physician, believes that the pathogenesis of gout is caused by the dysmetabolism of spleen and kidney metabolic disorders, which leads to turbid damp originating from interior blood stasis and obstruction of main and collateral channels [23]. In the acute attack phase, it is recommended to use Smilacis Glabrae Rhixoma (Tu fu ling) and Dioscoreae Septemlo Bae Rhizoma (Bixie) with a significant dose to clearing away heat, eliminating dampness, and discharging phlegm turbidity. For patients with apparent joint redness and swelling, it is recommended to use *Radix Rehmanniae* (Sheng Di), *Gypsum rubrum* (Han shui shi), *Anemarrhenae Rhizoma* (Zhi mu), and *Cape buffalo* (Shui niu jiao) to clear away heat and dredge collaterals.

For patients with obvious pain symptoms, add scorpion (Quan xie), centipede (Wu gong), and Corydalis Rhizoma (Yan hu suo) to disperse stasis and relieve pain. If the disease progresses in chronic or intermittent stage, *Raw Atractylodes Macrocephala Koidz* (Sheng bai zhu), *Poria cocos* (Fu ling), Fructus Ligustri Lucidi (Nv zhen zi), and *Polygoni Multiflori Radix* (He shou wu) can regulate the spleen and kidney. The ancient Chinese medical literature on preventing and treating gout is very plentiful and has provided valuable experience for later generations of physicians to study gouty arthritis (Figure 1). Based on the experience of our predecessors and modern medical methods, a more in-depth study of gouty arthritis can be conducted.

3. Therapeutic Effect Stimulated the Development of TCM for GA in Ancient China

3.1. Herbs for Prophylaxis and Treatment of GA. Herbal medicines include thousands of plants species. They are used for GA treatment, and many of them are widely used. Single Chinese medicine is mainly used to clear heat and promote dampness in treating gout. The following ten Chinese herbal medicines are the most commonly used ones *Coix Seed*(Yi ren), *Phellodendri Chinrnsis Cortex* (Huang bai), *Atractylodes Lancea* (Cangzhu), *Plantaginis Semen* (Che qian zi), *Alisma Orientale* (Ze xie), Chuanxiong Rhizoma (Chuan xiong), Achyranthis Bidentatae Radix (Niuxi), Polygoni Cuspidati Rhizoma Et Radix (Hu zhang), *Saposhnikoviae Radix* (Fang feng), and Radix Angelicae Biseratae (Du huo) influence jian-pi-li-shi, huo-xue-hua-yu, and qing-re-jie-du; the detailed information is shown in Table 1.

3.2. Herbal Formulas for the Prophylaxis and Treatment of GA. Herbal formulas are the most popular application of TCM, and some typical herbal formulas have significantly prophylactic and therapeutic effects on GA. TCM can benefit patients through treatment based on syndrome differentiation, which is the characteristic and advantage of Chinese medicine. TCM treats gouty arthritis with great emphasis on the causative factors of "dampness" and "heat [24]." Si-miao-tang and Dang-gui-nian-tong-fang are herbal formulas used for restraining gouty arthritis through invigorating the spleen and dispelling dampness. Invigorating the spleen is an essential principle for GA treatment, and Simiao decoction is a notable herbal formula for invigorating the spleen to remove dampness and for detoxification.

Straightly removing pathogenic elements is another vital principle to treat GA with herb-ju-zhi-zi-cha-fang. *Smilacis Glabrae Rhixoma* (Tu fu ling) and *Dioscoreae Septemlo Bae Rhizoma* (Bixie) are the classical herbal composition to treat GA by removing dampness and detoxification in addition to conditioning therapy, such as Si-huang-san and Ju-zhi-dihuang-wan. After analyzing the literature obtained through searching, it was found that the treatment principle with TCM prescriptions for the treatment of gouty arthritis mainly was invigorating the spleen and removing dampness, clearing away heat, and detoxifying; the prescriptions that appeared frequently were summarized and classified according to the mentioned treatment principle. Due to content limitations, Table 2 only lists the most common and classic prescriptions for the treatment of gouty arthritis. The details are illustrated in Table 2.

3.3. The Disadvantages of TCM Theory and Chinese Medicine. The theory of TCM is not broadly accepted, which is the main obstacle to the modernization of TCM. Practices of TCM depend on the integration of TCM theory and individual experiences of physicians. The pharmacological mechanism of Chinese medicine for treating gout is still unclear, and it still needs to be thoroughly explored and studied whether Chinese medicine has effective methods to promote the dissolution and removal of urea salt deposits. Therefore, molecular and cellular biology in modern medicine have offered valuable perspectives for the mechanisms of GA and provided anti-inflammatory strategies. Although Chinese medicine has been documented and demonstrated to be available for the treatment of GA [25–27], the critics still indicate that the toxicity of Chinese medicine (CHM) is indistinct [28]. Consequently, exploring the molecular signal transduction mechanism of CHM and removing toxic components may help to increase the acceptance of TCM in modern society [29].

4. Research Status and Application of Chinese Medicine for GA in Current Medicine

4.1. GA Treatment with Chinese Medicine. The curative rate of GA is not satisfactory. In China, TCM has been used to prevent and treat gouty arthritis for a long time and is regarded as an available disease-preventing method [30].

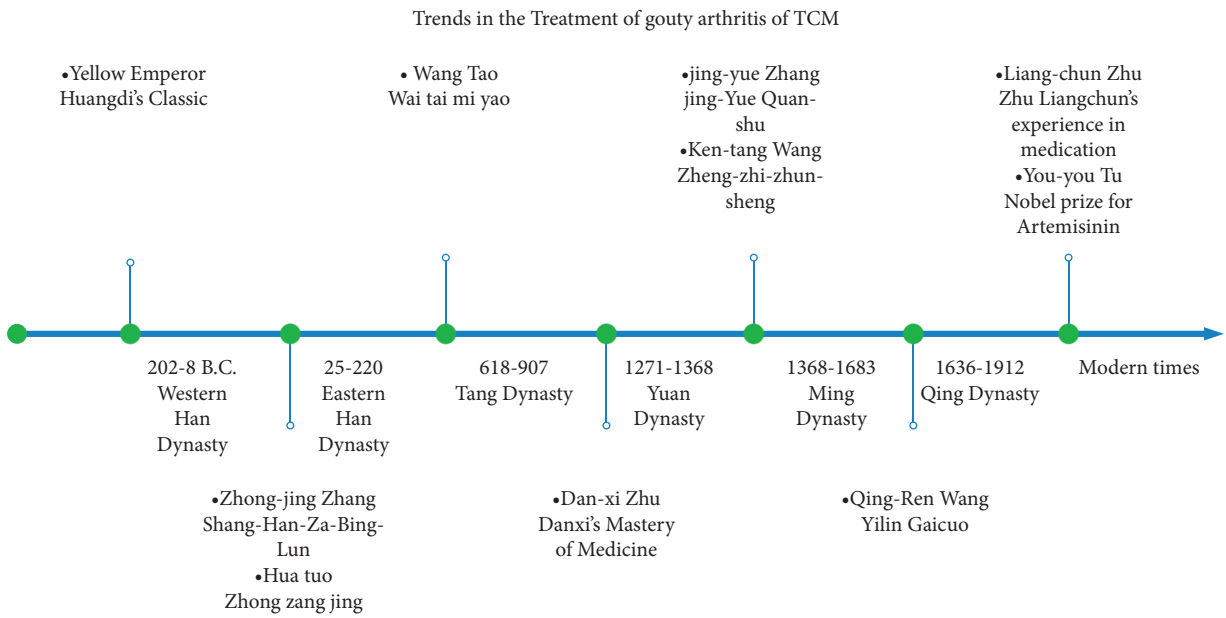

Figure 1: Trends in the treatment of gouty arthritis with TCM. TCM for the prevention and the treatment of gouty arthritis started in Western Han Dynasty and it developed and innovated in Tang Dynasty, Yuan Dynasty, Ming Dynasty, and Qing Dynasty, despite TCM had been doubted constantly. Throughout its history and even it is not valued in modern times, with special reference to the field of gouty arthritis treatment, it still plays a significant role in the treatment of acute and chronic diseases. A great honor and a huge breakthrough for TCM is You-you TU got the 2015 Nobel Prize in Physiology or medicine, and TCM received recognition of the world again. Abbreviations: TCM: traditional Chinese medicine.

Table 1: The herbal therapy for GA treatment.

TCM treatment principles	Herbs
Activating blood circulation and eliminating stasis	Chuanxiong Rhizoma (Chuanxiong), Achyranthis Bidentatae Radix (Niuxi), Radix Salviae (Danshen), Persicae Semen (Taoren), Carthami Flos (Honghua), Cortex Moutan (Danpi), Leonuri Herba (Yimucao)
Activating blood circulation and relieving pain	Pollen Typhae (Pohang), *Troopers Dung* (Willingham), myrrh (Moyao), Radix Paeoniae Rubra (Chishao), *Angelicae Sinensis Radix* (Danggui), Panax Notoginseng (Sanqi), *Siphonostegiae Herba* (liujinu)
Clearing away heat and removing dampness	*Phellodendri Chinrnsis Cortex* (Huangbai), *Poria cocos* (Fuling), *Scutellariae Radix* (Huangqin), *Plantaginis Semen* (Cheqianzi), Artemisiae Scopariae Herba (Yinchen), *Atractylodes Lancea* (Cangzhu), *Coicis Semen* (Yiren)
Expelling wind and activating meridians	*Radix Clematidis* (Weilingxian), Radix Angelicae Biseratae (Duhuo), Spatholobus Suberectus Dunn (Jixueteng), Fructuslipuidambaris (Lulutong), *Radix Puerariae* (Gegen), Trachelospermumjasminoides (luoshiteng), *Lumbricus* (Dilong), Ramulus Mori (Sangzhi), *Angelica dahurica* (Baizhi)

TCM treatment of gout has the effect of lowering uric acid and can effectively inhibit inflammation, relieves gout symptoms, avoids recurrence, and avoid the potential risk of low serum uric acid (SUA) controlling. One of the clinical trials showed that TCM formula named Skin-patch of Xin Huang Pian, which mainly consisted of *Panax Notoginseng* (San Qi), *Concha Margaritifera Usta* (Zhen Zhu Ceng Fen), Herba Sarcandrae (Zhong Jie Feng), *Urena lobata Linn* (Xiao Fan Tian Hua), and *calculus bovis artifactus* (Ren Gong Niu Huang) seemed to be efficacious and safe to alleviate joint symptoms of patients with acute gouty arthritis. The mechanism might be C-reactive protein and ESR decreasing [31]. RBXG formula stemmed from "Bixie Fenqing Yin" in "Medical Insights" have been demonstrated to reduce the risk of acute gouty arthritis recurrence. The classic decoction such as "Yellow-dragon Wonderful-seed Formula" and Simiao Pill is also efficacious for uric acid, erythrocyte sedimentation rate, and other inflammatory factors and have a clinical efficacy for gout patients [32, 33].

4.2. Anti-GA Therapy with Chinese Medicine. TCM is usually applied as an herbal formulation clinically based on TCM theory. Chinese medicine has unique advantages in preventing and treating gout due to its "multitarget" effect and has achieved good results in the treatment of gouty arthritis in recent years. Shi et al. reported 29 cases of gout patients

Table 2: The categories of herbal therapy for GA treatment.

Herbal formuls	Ingredients	TCM efficacy	Provenance	Author
Si-Miao-Wan	Phellodendri Chinensis Cortex (Huangbai), *Atractylodes Lancea* (Cangzhu), *Coix Seed* (Yiren), Achyranthes bidentata (Niuxi)	Clearing away heat and removing dampness	Cheng-fang-bian-du	Zhang bing cheng
Long-Dan-Xie-Gan-Tang	*Gentiana radix* (Longdancao), Glycyrrhiza uralensis (Gancao), *Scutellariae Radix* (Huangqin), *Gardeniae Fructus* (Zhizi), *Rehmannia glutinosa* (Shengdihuang), Radix Bupleuri (Chaihu), Caulis Akebiae (Mutong), *Angelicae Sinensis Radix* (Danggui), *Plantaginis Semen* (Cheqianzi), *Alisma Orientale* (Zexie)	Clearing away heat and dampness; detoxification	Tai-ping-hui-min-he-ji-ju-fang	Liu jing yuan
Bi-Xie-Shen-Shi-Tang	*Dioscoreae Septemlo Bae Rhizoma* (Bixie), *Coix Seed* (Yiren), *Red Poria Cocos* (Chifuling), *Phellodendri Chinrnsis Cortex* (Huangbai), Cortex Moutan (Danpi), *Alisma Orientale* (Zexie), *Talc* (Huashi), *Tetrapanacis Medulla* (Tongcao)	Clearing away heat and removing dampness	Yang-ke-xin-de-ji	Gao bing jun
Qing-re-Hua-Tan-Tang	*Ginseng Radix et Rhizoma* (Renshen), *Rhizoma Atratylodis Mac-rocephalae* (Baizhu), *Poria Poria Cocos* (Fuling), *Glycyrrhizae Radix et Rhizoma* (Gancao), *Red tangerine reel* (Juhong), *Pinellia* (Banxia), *Ophiopogon* (Maidong), *Grass-leaved sweetflag* (Shichangpu), *Fructus Aurantii Immaturus* (Zhishi), *Banksia rose* (Muxiang), *Caulis bambusae* (Zhuru), *Scutellariae Radix* (Huangqin), *Coptis chinensis* (Huanglian), *Arisaema wilsonii Engl* (Nanxing), *Succus bambusae* (Zhuli)	Clearing away heat and removing phlegm	Jing-lue-quan-shu	Zhang jing yue
Dang-gui-Nian-tong-Tang	Notopterygii Rhizoma Et Radix (Qianghuo), *Ginseng Radix et Rhizoma* (Renshen), Sophorae Flavescentis Radix (Kushen), Cimicifugae Rhizoma (Shengma), *Radix Puerariae* (Gegen), *Atractylodes Lancea* (Cangzhu), Glycyrrhiza uralensis (Gancao), *Scutellariae Radix* (Huangqin), Artemisiae Scopariae Herba (Yinchen), *Saposhnikoviae Radix* (Fangfeng), *Angelicae Sinensis Radix* (Danggui), *Anemarrhenae Rhizoma* (Zhimu), *Alisma Orientale* (Zexie), *Polyporus umbellatus* (Zhuling), *Atractylodes Macrocephala Koidz* (Baizhu)	Dispelling heat and dampness, dispelling wind and relieving pain	Dan-xi-xin-fa	Zhu dan xi
Yin-Chen-Wu-ling-San	Artemisiae Scopariae Herba (Yinchen), *Alisma Orientale* (Zexie), *Polyporus umbellatus* (Zhuling), *Atractylodes Macrocephala Koidz* (Baizhu), *Poria Cocos* (Fuling), Cinnamomi Ramulus (Guizhi)	Clearing away heat and removing dampness	Jin-gui-yao-lue	Zhang zhong jing
Ba-Zheng-San	Radix Rhei Et Rhizome (Dahuang), *Plantaginis Semen* (Cheqianzi), Dianthi Herba (Qumai), Polygoni Avicularis Herba (Bianxu), *Gardeniae Fructus* (Zhizi), Caulis Akebiae (Mutong), Glycyrrhiza uralensis (Gancao), *Talc* (Huashi)	Clearing away heat and purging fire, promoting urination	Wai-ke-zheng-zong	Chen shi gong
Wu-Wei Xiao-Du-Tang	*Lonicerae Japonicae Flos* (Jinyinhua), Chrysanthemi Flos (Juhua), *Dandelion* (Pugongying), *Violsse Herba* (Zihuadiding), *Begonia fimbristipula* (Zibeitiankui)	Clearing away heat and toxin, resolving carbuncle and node	Wai-ke-zheng-zong	Chen shi gong
Xuan-Bi-Tang	*Stephaniae Tetrandrae Radix* (Fangji), Amygdalus Communis Vas (Xingren), *Talc* (Huashi), *Forsythiae Fructus* (Lianqiao), *Gardeniae Fructus* (Zhizi), *Coicis Semen* (Yiren), Arum Ternatum Thunb (Banxia), *Silkworm excrement* (Cansha), Phaseoli Semen (Chixiaodou)	Clearing away heat and dampness, promoting channels and collaterals	Wen-bing-tiao-bian	Wu ju tong
Dang-Gui Shao-Yao-Tang	*Angelicae Sinensis Radix* (Danggui), *Paeoniae Radix Alba* (Baishao), *Poria Cocos(Schw),, Wolf* (Fuling), *Atractylodes Macrocephala Koidz* (Baizhu), *Alisma Orientale* (Zexixe), Chuanxiong Rhizoma (Chuanxiong)	Invigorating the spleen, nourishing the blood and regulating the liver	Jin-gui-yao-lue	Zhang zhong jing

with dampness heat turbid blood stasis syndrome who were treated with private (self-prescribed) herbal formula, and it showed that the levels of inflammatory factors such as Interleukin-1beta (IL)-1β, IL-6, Visual Analogue Scale (VAS) score, and Tumor necrosis factor (TNF)-α were significantly decreased [34]. Wang et al. found that the incidence of the adverse reaction of Chuanhu antigout mixture was lower than that of colchicine treating acute gouty arthritis. In addition, Chuanhu antigout mixture also had the function of protecting kidney and renal function [35]. Combined treatment is more familiar in clinic practice for GA patients. Ren et al. found that the allergic risk for acute gouty arthritis patients treated with external application of compound Qingbi granules combined with oral loxoprofen sodium was lower than that treated with Diclofenac Diethylamine Emulsion externally [36], and the adverse reactions were reduced and the curative effects were improved after Qinbi granules combined with Indomethacin [37], colchicine or Celecoxib [38] and allopurinol tablet [39].

4.3. Patients' Symptoms Improve with Chinese Medicine. The followings are the most common Chinese medicines used for swollen joint and higher skin temperature treatment: *Phellodendri Chinrnsis Cortex* (Huang bai), *Coicis semen* (Yi ren), *Anemarrhenae Rhizoma* (Zhi mu), Talc (Hua shi); the most commonly used Chinese medicines for arthritis pain: Aconiti Lateralis Radix Praeparata (Wu tou), Curcumaelongae Rhizoma (Jiang huang); and the most widely used Chinese medicines for gouty tophi: Radix Clematidis (Wei ling xian), Cinnamomi Ramulus (Gui zhi), and Lycopi Herba (Ze lan) [40]. Gouty tophi is also a common complication of advanced gouty arthritis. External application of compound Qingbi granules can effectively relieve pain and reduce synovium thickness caused by arthritis. Meanwhile, external application of Chinese herbal compounds can also avoid adverse effects, reducing GA patients' reliance on analgesic medicine [41]. External application of compound TCM to the affected area or acupuncture point can directly work on the affected area, reducing swelling and relieving pain and improving the clinical symptoms and signs of patients with acute gouty arthritis (AGA) significantly [42]. The clinical trial results showed that Chinese medicine combined with cupping therapy had satisfactory results in treating 34 patients with gouty arthritis. It was very effective in improving Budzyuski pain index, lowering blood uric acid, and lowering joint swelling index [43]. The meta-analysis of the compound TCM Simiao San treating gouty arthritis showed that Simiao San, as a traditional Chinese medicine decoction, can improve the clinical symptoms and signs of patients with AGA [44].

5. Research Status of Anti-GA Mechanisms in TCM

5.1. Various Herbal Formulas Are Generally Illustrated in the Theory of TCM. Herbal medicine has many active ingredients. Many herbal formulations and their active ingredients have significant effects on articular chondrocytes apoptosis inhibition, anti-inflammation, antioxidation stress reaction, inflammatory cytokine levels regulation, uric acid excretion promotion, immune function regulation (cellular immunity regulation), uric acid levels reduction and intestinal flora improvement for gout patients [45–48], body resistance enhancement [49], purine metabolism regulation [50], renal damage prevention for gout patients, etc. [51] (Figure 2).

5.2. Articular Chondrocyte Apoptosis Inhibition. Gouty arthritis is characterized by joint inflammation and uncontrolled articular chondrocytes apoptosis. Articular chondrocytes apoptosis inhibition is a new method for the treatment of gouty arthritis. Formulas such as Jiawei Simiao powder [52] and Guizhi Shaoyao Zhimu decoction [53] and herbs including *Phellodendri Chinrnsis Cortex* (Huang bai) [54] and *Rhizoma Atrac-tylodis Lanceae* (Cang zhu) [55] can significantly inhibit articular chondrocytes apoptosis and have an antigout effect. The compounds isolated from *Radix Rhei Et Rhizome* (Da huang) [56] and *Stephaniae Tetrandrae Radix* (Fang ji) [57] can inhibit the inflammatory reaction of cells and regulate the immunity and metabolism of the human body. Simiao pill can inhibit articular chondrocytes apoptosis and improve cartilage lesions by reducing IL-1β expression, upregulating B-cell lymphoma (Bcl)-2 gene expression, and downregulating Bax gene expression [58]. Compound TCM with the function of clearing away heat, promoting diuresis, and dredging collateral methods may treat acute gouty arthritis by promoting apoptosis, inhibiting cell proliferation, and blocking cell cycle of fibroblast-like synoviocytes (FLS) to alleviate the inflammatory reaction regionally [59].

5.3. Antioxidation Stress Reaction. Oxidative stress refers to the state of imbalance between oxidative and antioxidative effects in the body, which tends to be oxidized, resulting in the inactivation of antioxidant (superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), reduced glutathione, etc.) and aggravation of joint tissue damage [60]. Many kinds of Chinese medicine and effective ingredients have anti-inflammatory, antioxidant, and other pharmacological effects [61]. Tongfeng Kangning formula [62] and Zisheng Shenqi Pill can also relieve the oxidative stress state of the body and protect the joints from damage [63]. Quercetin [64] and papaya extract [65] can increase the activity of GSH-Px and superoxide dismutase (SOD) in GA animal model, reduce the level of malondialdehyde (MDA), and improve joint tissue damage through antioxidant effect. Resveratrol [66] is a polyphenol compound in Veratrum, which can regulate oxidative substances and reduce oxidative stress by activating Nrf2-mediated induction of heme oxygenase-1 (Nrf2/HO-1) signaling pathway. The ethanol extract of Chinese medicinal materials *Gentiana macrophylla* [67] can upregulate the expression of Sirtuin1 (SIRT1) and p53 protein acetylation (ac-p53) and downregulate the expression of p53 and MicroRNA 34a (miR-34a) protein in GA rats by regulating the SIRT1/p53 signaling pathway, so as

Figure 2: Chinese medicine herbal formulas include multiple ingredients for wholistic therapy. Herbal formulas consisted of many active ingredients that form the essential units of herbal function, such as the various mechanisms of anti-GA formulas.

to regulate antioxidants and reduce the oxidative damage to the body. Herba Ephedrae Sinicae (Mahuang) can remove reactive oxygen species (ROS) and has an obvious antioxidant effect [68].

5.4. Inflammatory Cytokine Levels Regulation. The inactivation of anti-inflammatory factors and the release of proinflammatory factors play an important role in the inflammatory response. Excessive release of inflammatory factors can induce a large number of neutrophils to infiltrate into the joint cavity and stimulate the activation of neutrophils, causing tissue inflammation [69]. The chemical components of TCM can regulate inflammatory cytokines. Berberine isolated from *Coptidis Rhizoma* (Huanglian) can inhibit the production of LPS (lipopolysaccharide)-mediated IL-1β and swelling of monosodium urate (MSU) mediated paw by blocking NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) signaling pathway [70]. The ethanol extract of Rhizoma Dioscoreae Nipponicae (Chuanshanlong) can act on MAPK/JNK pathway and inhibit the secretion of inflammatory factors in GA rats [71]. Emodin can reduce the release of inflammatory factors by inhibiting the activation of extracellular signal regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (MAPK) signaling pathways [72]. Gallic acid can inhibit the migration of MSU-induced macrophages and neutrophils to synovitis by inhibiting the activation of NLRP3 inflammasomes and apoptosis of nuclear factor erythroid-2 related factor 2 (Nrf2) signals [73]. Chinese Medicine Huzhen Tongfeng Formula(HZTF) can downregulate cyclooxygenase (COX) 1, COX-2, and 5-lipoxygenase, inhibit gouty arthritis cell infiltration significantly, improve the swelling of the affected joints, and increase pain threshold by inhibiting the inflammatory mediators and the arachidonic acid metabolism [74]. Simiao decoction has the effect of reducing blood uric acid levels, reducing myeloperoxidase (MPO), xanthine oxidase (XOD), adenosine deaminase (ADA) activity, and alleviating gout-related symptoms (such as foot swelling and pain). In addition, it can also reduce certain specific proinflammatory cytokines in serum, including IL-1β, IL-9, interferon (IFN) g, macrophage inflammatory protein (MIP) 1a, and MIP-1b [75].

5.5. Uric Acid Excretion Promotion. It has been reported that *Achyranthis Bidentatae Radix* (Niuxi) can promote the excretion of uric acid, improve cellular and humoral immunity, as well as nonspecific immune function [76]. Fucoidan can promote uric acid excretion and relieve symptoms of uric acid nephropathy (UAN) by upregulating the expression of protein kinase A (PKA) and organic cation

transporter 2 (OCT 2) in the kidney tissue surface [77]. Verbascoside is a phenylethanoid glycoside in *Plantago asiatica*, and it has been proved that it can inhibit XOD activity and decrease the expression of uric acid transporter 1 (URAT1) and glucose transporter (GLUT) 9 protein, reducing the production of uric acid and promoting the excretion of uric acid [78]. Eucommiae cortex alcohol extract [79] and anthocyanin [80] can enhance the expression of ATP-binding cassette subfamily G member 2 (ABCG2), OAT1, and organic anion transporter (OAT3) protein in hyperuricemia (HUA) and GA animal models and accelerate uric acid excretion by regulating the mechanism of renal reabsorption for uric acid. Gypenosides [81] and ethanol extracts of polygonum sibiricum [82] can lower the expression of URAT1 and GLUT9 protein, affect the mechanism of uric acid reabsorption, and thus regulate uric acid balance. Water extracts of Wudang Cherry can increase the expression of OCT1, OCT2, OCTN1, and OCTN2 protein in HUA animal models, mediate the absorption, reabsorption of various organic cations and carnitine transport, and participate in the excretion of uric acid [83]. *Liriodendron chinense*, commonly known as the Chinese tulip tree, and ethanol extract of the barks of *Liriodendron chinense* (EELC) can significantly increase the excretion of uric acid in hyperuricemic nephropathy (HN) mice, reduce the infiltration of inflammatory factors, and the accumulation of uric acid in the kidney. The progress of HN is reduced by upregulating organic anion transporter 1 (OAT1), OAT3, and ABCG2 protein [84]. Erding granule (EDG) is a kind of Chinese medicine that has the effect of reducing uricemia discovered in recent years. A study has found that 50% ethanol extract (EDG-50) has a significant effect on lowering blood uric acid, which may be related to the downregulation of expression of GLUT9 and URAT1 and upregulation of the expression of OAT1, thus reducing blood uric acid concentration [85]. Berberine can successfully reduce the serum uric acid level of rats with hyperuricemia by increasing the level of uric acid and the excretion fraction of urate in rats [86].

5.6. Immune Function Regulation. T cell subsets play an important role in the pathogenesis of gouty arthritis [87]. Isoglycyrrhizin can promote Treg cell induction in vitro and in vivo and inhibit inflammation by reducing IL-2 expression [88]. Simiao powder can improve T cell subsets, upregulate cluster of differentiation (CD3)+ and CD8+ levels, downregulate CD4+ and CD4/CD8 levels, inhibit inflammation, and improve immune resistance [89]. The activation of NLRP3 inflammasome is related to the tilted differentiation of Th subsets for a long time, and it is involved in the occurrence and development of the autoimmune attack. Doliroside A can inhibit both LPS-induced macrophage initiation and inflammatory body activation by inhibiting the caspase-1 dissociation and IL-1β secretion [90]. Icariin (ICA) can inhibit nuclear translocation of NF-κB pathway-associated protein and reduces the expression of NALP3 inflammasome in rats [91]. Total glucosides of herbaceous peony (TGPF) can reduce the weight of rats with hyperuricemia nephropathy, reduce serum uric acid (SUA), creatinine (Cr), blood urea nitrogen (BUN), xanthine oxidase (XOD), MCP-1, and TNF-α, downregulate kidney URAT1 and GLUT9, upregulate kidney OAT1, and reduce renal pathology associated with hyperuricemia [92]. Compound Shui Niu Jiao granules can significantly inhibit the protein expression of TNF-α and IL-8 by injecting sodium urate solution into the articular cavity of model rats with acute gouty arthritis (AGA), reducing inflammatory tissue [93]. Macroporous resin extract of *Dendrobium candidum* leaves is effective in uric acid production inhibition and anti-inflammation in rats with hyperuricemia, and it can inhibit the expression of nuclear factor (NF)-κB, Toll-like receptor (TLR) 4 protein and reduce inflammation [94]. The *Selaginella moellendorffii* prescription (SMP) can significantly reduce the level of uric acid in mice with hyperuricemia and reduce the levels of prostaglandin (PG)E-2, IL-8, nitric oxide (NO), and IL-1 in rats with gouty arthritis. This anti-inflammatory effect may be related to the inhibition of NF-κB p65 nuclear translocation and the expression of NLRP3 protein [95]. An extract of Tu-Teng-Cao (TTC) can inhibit the secretion of cytokines TNF-α and IL-6 in synovial fluid of rats, reduce ankle joint damage, and control uric acid and inflammation to treat gouty arthritis [96]. Berberine reduces monosodium urate crystals-induced inflammation by downregulating the expression of NLRP3 and IL-1. The regulation of berberine may be related to the inactivation of NLRP3 inflammasome [97]. Sanmiao wan (SMW) can partially regulate purine metabolism, arginine and proline metabolism, citric acid cycle, phenylpropanoid metabolism, and tryptophan metabolism, reversing the pathological process of hyperuricemia [98]. Modified-Simiaowan (MSW) can protect human umbilical vein endothelial cells (HUVECs) by reducing cell apoptosis and inhibiting the expression of intercellular cell adhesion molecule-1 (ICAM-1) [99]. The ethanolic extract of *Polygonum cuspidatum* can prevent and treat acute gouty arthritis in mice, and its mechanism may be related to the regulation of the expression of the NLRP3/ASC/caspase-1 axis in the gene and protein level [100].

5.7. Uric Acid Reduction. Elevated uric acid is the biochemical basis of gout. Uric acid is excreted mainly by filtration, reabsorption, secretion, and other processes involved in transport through the kidneys and intestines. In total, 10% of uric acid is excreted by glomerular filtration and finally discharged from the urine. Totally, 90% of uric acid is reabsorbed by the renal tubules and finally got into blood [101]. Hu et al. found that Simiao pill could promote uric acid excretion and protect the kidney by adjusting urate transporter protein in the kidney of rats with high uric acid [102]. Luteolin and luteolin-4-0-glucoside can act on hyperuricemia mice by lowering mouse urate transporter (mURA)-T1 levels and inhibiting XOD activity [103]. Paeonol is an effective component isolated from *Cortex Moutan*, which can inhibit the expression of proinflammatory cytokines and the activation of NF-κB, significantly decreasing the expression of TNF-α, IL-1β, and IL-6 in synovium of MSU-induced arthritis (MIA) rats and reducing the formation of uric acid [104]. Compound tufuling oral liquid can reduce gout-

induced recurrent joint swelling and pain, significantly reducing serum uric acid (SUA) levels. Besides, the incidence of leukopenia in the treatment group was lower than that in the control group [105]. Polydatin, the natural precursor of resveratrol, can reduce the levels of serum uric acid, creatinine, and urea nitrogen in hyperuricemia rats by interfering with the differential metabolites [106]. Chuanhu antigout mixture (CAGM) and its modified formulation can significantly improve potassium oxonate (PO) induced hyperuricemia in mice, which may be partly due to a decrease in liver XOD and kidney URAT1 levels [107]. Compound Tufuling granules (CTG) have a significant effect on lowering blood uric acid and protecting renal function, which may be related to CTG's ability to regulate the lymph node molecules against inflammation, lower uric acid levels, and protect kidneys [108]. Ethanol extract from *Polyrhachis vicina Roger* (EEPR) can reduce the serum uric acid level of model mice with hyperuricemia. Modified Simiao decoction (MSD) monotherapy is superior to anti-inflammatory drugs and/or uric acid-lowering drugs in treating gouty arthritis, and it can reduce uric acid (UA) and C-reactive protein (CRP) levels; regulate human metabolic disorders; and has no side effects [109–111]. Total flavonoids of *Humulus lupulus* (TFHL) can lower uric acid in hyperuricemia mice by inhibiting the activity of xanthine oxidase (XOD) [112]. Dampness-removing pill (Huashi pills) can inhibit the formation of calculus by regulating urine biochemical indicators and reducing the expression of osteopontin (OPN) in the kidney tissue of rats with kidney stones [113].

5.8. Improving Intestinal Flora of Gout Patients. Intestinal flora is associated with the development of many diseases, and intestinal microecology plays an important role in uric acid metabolism and inflammatory response. When the intestinal balance is imbalanced, the status of health will be disrupted, which leads to various diseases, such as gout [114]. After analyzing the diversity of intestinal flora in patients with primary gout and a healthy population, Shi et al. found that *E. faecalis* and xylose-degrading mimics were more abundant in the intestine of patients with gout, whereas *E. faecalis* and Bifidobacterium were absent [114]. Meng et al. found that the application of Chinese herbal medicine to strengthen the spleen and drain turbidity can significantly improve a series of symptoms such as joint redness and pain by reducing the activation of NLRP3 inflammasome in gout patients and regulating the intestinal microecology to increase uric acid excretion [115]. Lin et al. found that the traditional Chinese medicine (TCM) formula, Si-miao-tang, could reduce intestinal apoptosis by inhibiting the expression of NLRP3 inflammatory vesicles, regulating the expression of TNF-α, caspase 8, and AIFM1 proteins, and regulating the expression of APOB, LPL, and PPARα proteins to affect lipid metabolism and restore intestinal flora [116]. Gao et al. found that the TCM formula, CoTOL, could reduce body weight and uric acid in mice with hyperuricemia models by regulating intestinal flora [117]. The herbal chicory extract can reduce the activity of key enzymes of uric acid metabolism in hyperuricemic quail, which may be related to regulating intestinal flora and intestinal tight junction protein occludin, increasing the number of beneficial intestinal flora and reducing the number of pathogenic bacteria [118].

5.9. Shortcomings of TCM as GA Therapy

5.9.1. TCM Safety for GA Patients. CHM represents an enormous and remarkable treasure trove for new drug development, but the evaluation for the safety of CHM is also required. The oral Chinese medicine formulas have developed quickly and have their own diversity. The safety and efficacy of oral Chinese-patented medicines in treating GA have been confirmed in many clinical studies initiated by Chinese and Western medical researchers [119–124]. Besides, the clinical application of Chinese herbal medicine injection also has attracted attention [125, 126]. Nevertheless, due to the uncertainty of CHM composition, the safety of CHM is still questioned, and the toxic components in CHM have also been described [127]. With the widespread use of TCM worldwide, the safety problems/events of TCM have gradually raised [128]. Especially in recent years, it is reported that serious adverse reactions/events are caused by TCM or its ingredients, such as renal failure caused by Gentian and Liver Pill and liver damage caused by He Shou Wu, and these events have caused great concern both at home and abroad [129–131] and seriously affected the healthy and sustainable development and internationalization of TCM. Some researchers thought that long-term treatment with CHM is still risky, and Chinese medicine still requires massive clinical and basic trials to assess its safety [132, 133].

5.9.2. CHM's Efficacy in Anti-GA Is Still Being Questioned. Great progress has been made in the research of TCM on anti-GA, and some clinical studies have also achieved exciting results [134–138]. Nevertheless, some formulas have a good effect on gouty arthritis, but monotherapy or isolated components can weaken effects or even has no effect at all [139]. The components of CHM are very complicated, but many bioactive ingredients of CHM show only a strong antigouty arthritis effect in vitro, or the antigouty arthritis effect is lost or weakened after purification from the formula. In addition, deficiency of clinical research with high-level evidence seriously restricts CHM's development [140].

5.10. Molecular Network Integration for the TCM Modernization TCM in GA Treatment. The pathogenesis of gout is complex. Under the guidance of TCM theory, through long-term application practice, numerous Chinese medicines are effective, safe, cheap, and easily available for the treatment of gout. TCM formulas, consisted of many Chinese traditional herbs, have good efficacy and the least adverse reaction for GA prophylaxis and therapy. Although herbal formulas are widely used in TCM clinical practice, the integration principles based on the theory of TCM are very challenging to identify. In the international community, it is advocated molecular typing of pathogenic genes and the application of

precise targeted therapeutic drugs in gout treatment. However, its curative effect is limited, and a single target is not enough to change the prognosis of gout arthritis. Shifting the focal point of anti-GA treatment from accuracy to integration can benefit patients, and it is believed Chinese medicine has the intrinsic strengths for multiingredients strategy [141].

Traditional Chinese medicine has unique advantages in treating gout, but the composition of TCM is complex, and therapeutic targets are various and it is difficult to elucidate the therapeutic targets. Therefore, the specific therapeutic target is an important part of the pharmacodynamic evaluation [142]. Based on modern bioinformatics and network analysis technology, network pharmacology explores the relationship between medicines and gout from the aspects of multitarget and complex diseases, macroscopic and microscopic, fuzzy and visualization, and then clarifies its mechanism of action in treating gout. At the systematic level, network pharmacology promotes drug discovery in an accurate way, establishes a "drug-to-gene-to-target-to-disease subtype" network, and expounds the principle of herbal formula design guided by the theory of TCM, which provides a new way for the modernization of TCM in the future [143, 144].

As an emerging discipline, network pharmacology has made innovative breakthroughs in predicting the genes causing gout and identifying new targets of Chinese medicine. It also provides strong evidence for the development of new drugs, efficacy evaluation, safety evaluation, and quality evaluation of TCM. It will play an important role in all fields of TCM so as to promote the modernization of TCM.

6. Conclusions and Prospectives

TCM advocates the preventive treatment of diseases. Under the guidance of TCM theory, targeted rectification can reverse the condition of the disease as soon as possible and prevent the occurrence of diseases. The theory of TCM is often questioned due to its complexity, integrated concept, and symptomatic research. TCM holds that the human body is a complex and dynamic system, which pays more attention to the balance of the internal and external environment. Chinese medicine is a multicomponent, multitarget, and complex mixed system. There are many obstacles in the development of TCM under the background of modern medicine. The unidentified quality of TCM is a shortcoming for it; the necessity of accurate toxicological mechanisms and pharmacodynamic analysis impede the acceptance of TCM in modern times. Besides, antagonistic or synergistic effects of the components in TCM remain unknown. Only after resolving the above problems can TCM truly go abroad. TCM is an essential component of traditional Chinese culture. As Youyou Tu, the first Chinese woman who won the 2015 Nobel Prize in Physiology or Medicine, described, "TCM represents a great treasure house of China. We should make good use of it and create more valuable achievements, so as to bring benefit to human health."

Abbreviations

GA: Gouty arthritis
TCM: Traditional Chinese medicine
CHM: Chinese medicine
MSU: Monosodium urate
CAMs: Complementary and alternative medicines
WHO: World Health Organization
IL-6: Interleukin-6
VAS: Visual Analogue Scale
TNF-α: Tumornecrosis factor-α
AGA: acute gouty arthritis
Bcl-2: B-cell lymphoma
GSH-Px: Glutathione peroxidase
SOD: superoxide dismutase
B C: Before Christ
MDA: Malondialdehyde
Nrf2/HO-1: Nrf2-mediated induction of heme oxygenase-1 (HO-1)
SIRT1: Sirtuin1
miR-34a: MicroRNA 34a
ROS: Reactive Oxygen Species
LPS: Lipopolysaccharide
NLRP3: NOD-like receptor (NLR) family, pyrin domain-containing protein 3
ERK1/2: Extracellular signal regulate kinase 1/2
Nrf2: Nuclear factor erythroid-2 related factor 2
COX: Cyclooxygenase
MPO: Myeloperoxidase
XOD: Xanthine oxidase
ADA: Adenosine deaminase
IFN: Interferon
MIP-1a: Macrophage inflammatory protein-1a
PKA: Protein kinase A
OAT3: Organic anion transporter 3
HUA: Hyperuricemia
TLR 4: Toll like receptor 4
NO: Nitric oxide
(PG)E-2: Prostaglandin E-2
MIA: MSU-induced arthritis
SUA: Serum uric acid
UA: Uric acid
RBXG: Rebixiao granules
MSU: Monosodiumurate
GSH-Px: Glutathione peroxidase
GSH: Reduced glutathione.
UAN: Uric acid nephropathy.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Huan Liang and Pin Deng drafted the manuscript. CZJ designed and revised the manuscript. All authors read and approved the final manuscript. Huan Liang and Pin Deng contributed equally to this work.

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