INPLASY PROTOCOL

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None declared.

Efficacy and safety of modified Ermiao decoction in the treatment of gouty arthritis: A protocol for systematic review and meta-analysis

Qu, PD[1]; Huang, J[2]; Wang, SQ[3]; Li, S[4]; Hu, Q[5]; Wang, W[6]; Tang, XH[7].

Review question / Objective: **The purpose of this study is to comprehensively evaluate the efficacy and safety of modified Ermiao decoction in the treatment of gouty arthritis.**
Information sources: **We will conduct searches of Web of Science, PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform (Wanfang), Weipu Chinese Science and Technology Journal Full-text Database (VIP), and Chinese Biomedical Literature Database (CBM) from their inception to July 2022. In addition, trial registration platforms will also be searched for ongoing or unpublished trials, including International Clinical Trials Registry Platform and Chinese Clinical Trial Registry Centre. The languages of included studies will be restricted in English and Chinese. Medical Subject Headings and free words terms will be used during the retrieval process. The main search terms include "gouty arthritis", "modified Ermiao", and "randomized controlled trial." A draft of the PubMed search strategy is included in Table 1. Similar retrieval strategies will be applied to the other databases mentioned above. We will also search for relevant systematic reviews of using MED for GA and reference lists of eligible studies to improve recall ratio.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2022 and was last updated on 12 July 2022 (registration number INPLASY202270063).

INTRODUCTION

Review question / Objective: **The purpose of this study is to comprehensively evaluate the efficacy and safety of modified Ermiao decoction in the treatment of gouty arthritis.**

Condition being studied: **Gouty arthritis (GA), the most common form of**

inflammatory arthritis worldwide, is an inflammatory disease caused by the deposition of monosodium urate (MSU) crystals in joints and other connective tissues. It generally manifests as recurrent severe pain, active inflammation symptoms, swollen joints, and dysfunction of the affected joints. The prevalence of GA, with the improvement of living standards and the change of dietary structure and habits, increases worldwide reaching 0.9% of French adults, 1.4% of British and German adults, 3.9% of American adults, and 9.7% of Australian adults. In China, the prevalence of GA has reached 1.1%. GA flares lead to reduced quality of life, decreased physical function, increased healthcare costs, and lost economic productivity. The total annual healthcare cost of refractory GA in the United States is at least $10 222. GA patients will have not only joint deformities but also disabilities with the development of the disease. Furthermore, GA is strongly associated with the metabolic syndrome, and may contribute to myocardial infarction, type 2 diabetes mellitus, chronic kidney disease, and premature mortality.

In the GA treatment guidelines issued by American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR), the drugs for treating GA include allopurinol, febuxostat, benzbromarone, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), etc. Although the above drugs show good short-term efficacy, long-term use of these may lead to some bothersome adverse effects. For example, the incidence of allopurinol hypersensitivity in China is 2.7%. The use of benzbromarone may not only cause explosive liver necrosis, but also significantly increase the concentration of urinary acid and increase the risk of urinary acid kidney stone formation. Using NSAIDs may cause renal ischemia, and induce or aggravate renal insufficiency. Repeated use of glucocorticoids may increase the incidence of gout stones. Consequently, we now urgently need to find a safe and effective treatment method to better treat GA based on the problems of the above-mentioned drugs.

Ermiao decoction, derived from the monograph Chengfang Biandu in Qing Dynasty of China, is composed of Atractylodis Rhizoma and Phellodendri Cortex. To cope with the intricate pathologic states of GA in different stages, modified Ermiao decoction (MED), based on Ermiao decoction, have been developed according to different syndromes and traditional Chinese medicine theory. MED have been widely used in China to treat various joint diseases for thousands of years, such as rheumatoid arthritis, GA, and osteoarthritis. Many studies have proved the therapeutic effect of MED on GA from network pharmacology, plasma metabolomics, and experiment in vitro or in vivo. For example, the potential mechanism of MED in treating GA may be achieved by regulating immune and inflammatory reactions, improving metabolism and endocrine, and MED can decrease serum uric acid and xanthine oxidase levels in hyperuricemic-gout mice. MED could invert the pathological process of hyperuricemia to varying degrees through in part regulating the perturbed lipid metabolic pathway of disturbed rats. Pretreatment with MED ameliorated MSU-induced acute GA in mice with increased PI3K/Akt activation and M2 macrophage polarization in the joint tissues; in vitro, MED treatment significantly inhibited MSU-triggered inflammatory response, increased p-Akt and Arg-1 expression in macrophages, and promoted M2 macrophage polarization. In addition, accumulating clinical evidence has indicated that MED can significantly alleviate the clinical symptoms of GA and improve the pathological changes of joints in GA patients. Therefore, MED is considered as an important alternative choice for the clinical treatment of GA.

Although many clinical research trials show that MED is widely used in the treatment of GA, there is still a lack of systematic reviews and meta-analysis on the efficacy and safety of MED in the treatment of GA.

METHODS

Participant or population: Patients who are diagnosed as GA, regardless of age, sex, country, or disease stage, will be included

as long as they meet internationally recognized diagnostic criteria for GA, such as the diagnostic criteria for GA of ACR or EULAR.

Intervention: Eligible interventions must be MED, that is, include at least both Atractylodis Rhizoma and Phellodendri Cortex. MED combined with any Western medicine will also be included, such as febuxostat, allopurinol, and colchicine.

Comparator: The control group using Western medicine only will be included, such as NSAIDs, febuxostat, allopurinol, or colchicine.

Study designs to be included: We will only consider clinical randomized controlled trials (RCTs) of MED in the treatment of GA regardless of region and publication status. Non-RCTs, animal experimental studies, retrospective studies, case reports, conference articles, expert experience, and reviews will be excluded.

Eligibility criteria: (1) Types of study subjects and interventions that do not meet inclusion criteria will be excluded.(2) Non-RCTs reviews, case reports, observational studies, animal studies, expert experience, and conference articles on GA will be excluded.(3) Articles with missing data that cannot be obtained and duplicate publications will be excluded.(4) Treatment groups with any other type of traditional Chinese medicine intervention will be excluded, such as external application of herb, acupuncture, and moxibustion.

Information sources: We will conduct searches of Web of Science, PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform (Wanfang), Weipu Chinese Science and Technology Journal Full-text Database (VIP), and Chinese Biomedical Literature Database (CBM) from their inception to July 2022. In addition, trial registration platforms will also be searched for ongoing or unpublished trials, including International Clinical Trials Registry Platform and Chinese Clinical Trial Registry Centre. The languages of included studies will be restricted in English and Chinese. Medical Subject Headings and free words terms will be used during the retrieval process. The main search terms include "gouty arthritis", "modified Ermiao", and "randomized controlled trial." A draft of the PubMed search strategy is included in Table 1. Similar retrieval strategies will be applied to the other databases mentioned above. We will also search for relevant systematic reviews of using MED for GA and reference lists of eligible studies to improve recall ratio.

Main outcome(s): Primary outcomes include clinical efficacy, serum uric acid (SUA), adverse events (AEs), and visual analogue scale (VAS).

Additional outcome(s): Secondary outcomes include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC).

Data management: A predesigned, standardized data extraction sheet will be used by 2 reviewers (PQ and JH) to independently extract the following data from included studies:

(1) Basic information: first author, title, journal, publication year, and country.

(2) Participant's characteristics: age, sex, race, country, and sample size.

(3) Methodological characteristics: interventions, comparisons, risk of bias assessment, method of randomization, and blinding method.

(4) Outcomes, follow-up, and adverse events.

The 2 reviewers will discuss any disagreement during the data extraction process. The third reviewer (XT) will be consulted to resolve the differences when no consensus is reached.

Quality assessment / Risk of bias analysis: The risk of bias of included studies will be assessed using the Cochrane Collaboration risk-of-bias tool. The Risk of bias includes 7 aspects: random sequence generation, allocation concealment, blinding participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting, and other bias. The risk assessment will be divided into 3 levels: low risk, high risk, and unclear risk. Two reviewers (PQ and YJ) will independently evaluate the above content, and any differences will be resolved through discussion with the third reviewer (XT).

Strategy of data synthesis: Meta-analyses will use Review Manager (RevMan) 5.3 software for data synthesis. We will use relative risk with 95% CI for dichotomous variables and use MD or standard mean difference with 95% CI for continuous variable. The fixed-effects model will be used for data synthesis when there is no significant heterogeneity; otherwise, the random effects model will be used. Furthermore, sensitivity or subgroup analyses will be generated when heterogeneity is considered significant. The review will only represent and summarize the evidence under the circumstance of the data are insufficient for quantitative analysis.

Subgroup analysis: Subgroup analysis will be conducted according to the severity of GA, the course of treatment, sex, etc., when there is significant heterogeneity in the included studies.

Sensitivity analysis: Sensitivity analysis will be conducted when the inclusion study is still heterogeneous after subgroup analysis. The analysis will assess the source of heterogeneity and check the stability of the results based on methodological quality, sample size, and the impact of missing data. In addition, the meta-analysis will be re-performed after excluding studies of low methodological quality.

Language: The languages of included studies will be restricted in English and Chinese.

Country(ies) involved: This study is being carried out in China.

Keywords: gouty arthritis, traditional Chinese medicine, modified Ermiao decoction, meta-analysis, protocol.

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