INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Comparative efficacy and safety of Chinese herbal medicine for knee osteoarthritis: A protocol for systematic review and network meta-analysis

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Review question / Objective: **Knee osteoarthritis (OA) is a major public health concern causing chronic disability as well as a substantial burden on healthcare and the economy. However, effective treatments for knee OA were still not available. Numerous clinical studies have suggested that Chinese herbal medicine (CHM) seems to be clinically effective in treating knee OA. Thus, this study aims to evaluate the efficacy and safety of CHM in the treatment of knee OA through a systematic review and network meta-analysis.**
Information sources: **PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang Database, Chinese Biomedical Database (CBM), and clinical trials registries (Clinicaltrials.gov, Chinese Clinical Trial Registry, and International Clinical Trials Registry Platform).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2021 and was last updated on 27 June 2021 (registration number INPLASY202160060).

INTRODUCTION

Review question / Objective: **Knee osteoarthritis (OA) is a major public health concern causing chronic disability as well as a substantial burden on healthcare and the economy. However, effective treatments for knee OA were still not available. Numerous clinical studies have suggested that Chinese herbal medicine (CHM) seems to be clinically effective in treating knee OA. Thus, this study aims to**

evaluate the efficacy and safety of CHM in the treatment of knee OA through a systematic review and network meta-analysis.

Condition being studied: Knee OA is a prevalent degenerative osteoarticular disease characterized by progressive destruction of articular cartilage, which lead to impaired physical function and decreased quality of life . Although there are symptomatic treatments for knee OA patients, currently there is no effective approaches to prevent or cure knee OA . Owing to this unsatisfactory status quo, complementary and alternative medicines have recently received increasing attention from researchers . CHM is the main method of complementary and alternative medicines, and the recent studies based on the effects of CHM have generally highlighted its effectiveness . However, most studies focus on the effectiveness of single CHM therapy. A direct comparison between the CHM therapy is lacking and it remains uncertain which CHM therapy are the most effective and safest for the management of knee OA.

METHODS

Participant or population: Participants (18 years or older) were diagnosed with knee OA based on radiographic evidence and clinical criteria.

Intervention: Any form of CHM will be included, including Chinese patent medicine, TCM decoction, pills, etc. Considering that clinicians may combine CHM with conventional pharmacotherapy (western medicine), those studies will also be included.

Comparator: Conventional pharmacotherapy (western medicine) or placebo.

Study designs to be included: Randomized control trials (RCTs).

Eligibility criteria: Types of studies: RCTs that assessed the efficacy and safety of CHM for knee OA will be included. Languages will be restricted to English and Chinese. Descriptive studies, reviews, letters, conference abstracts, retrospective clinical studies, case reports, case series, protocols, animal studies, reports with incomplete data, studies unrelated to CHM and knee OA will be excluded. For duplicate studies, the most informative and complete report will be selected. Types of participants: Participants (18 years or older) were diagnosed with knee OA based on radiographic evidence and clinical criteria. Type of interventions and comparisons: In the experimental group, any form of CHM will be included, including Chinese patent medicine, TCM decoction, pills, etc. Considering that clinicians may combine CHM with conventional pharmacotherapy (western medicine), those studies will also be included. Patients in the control group were treated with conventional pharmacotherapy (western medicine) or placebo. In addition, we will exclude studies involving combination treatment of multiple CHM. Types of outcomes: The primary outcomes will include visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and total effective rate. The adverse events will be selected as a secondary outcome.

Information sources: PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang Database, Chinese Biomedical Database (CBM), and clinical trials registries (Clinicaltrials.gov, Chinese Clinical Trial Registry, and International Clinical Trials Registry Platform).

Main outcome(s): Visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and total effective rate.

Additional outcome(s): Adverse events.

Quality assessment / Risk of bias analysis: For each included study, methodological quality will be assessed independently by two reviewers using the Cochrane Collaboration's tool for assessing risk of bias in RCTs. This risk-of-bias tool consists of six major domains of bias: selection

bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each domain will be categorized as low risk, high risk, and unclear risk. Also, a third reviewer will be available to resolve any disagreement.

Strategy of data synthesis: We will perform the pairwise meta-analysis with STATA 15.0. For dichotomous variables, outcomes will be expressed as odds ratio (OR) with 95% confidence intervals (CI), while for continuous variables, mean difference (MD) or standard mean difference (SMD) with 95% CI will be calculated. Heterogeneity between the studies will be assessed with the I-square (I2) statistic. A fixed-effect model will be selected when I250%. We will perform the NMA with Addis1.16.8, WinBUGS 1.4.3, and STATA 15.0. A random effects model will be employed because of anticipated heterogeneity. The outcomes of dichotomous variables or continuous variables will be estimated by OR, MD, and SMD with their 95% CI respectively. The Brooks-Gelman-Rubin method will be used to assess the convergence of iterations. Convergence will be calculated using the Potential Scale Reduction Factor (PSRF), with PSRF closed to 1 indicating a better convergence. Besides, the surface under the cumulative ranking curve (SUCRA) will be applied to rank the size effect of treatments.

Subgroup analysis: If the heterogeneity or inconsistency among the included studies is detected, a subgroup analysis will be performed. Subgroup analysis will be conducted according to samplesize, types of conventional pharmacotherapy (western medicine), treatment duration, length follow-up, and other relevant parameters.

Sensitivity analysis: If feasible, we will perform a sensitivity analysis to explore the stability of the results. The influence of each study on the overall effect will be analyzed by removing one study at a time.

Country(ies) involved: China.

Keywords: Chinese herbal medicine; knee osteoarthritis; network meta-analysis.

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