

# INPLASY PROTOCOL

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**Corresponding author:**  
Wenhai Zhao

6177252@163.com

**Author Affiliation:**  
Affiliated Hospital of  
Changchun University of  
Chinese Medicine.

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None declared.

## Evaluation of the effectiveness and safety of icariin in the treatment of knee osteoarthritis A protocol for a systematic review and meta-analysis

Liu, L<sup>1</sup>; Zhao, CW<sup>2</sup>; Zhao, S<sup>3</sup>; Xu, HX<sup>4</sup>; Peng, ZY<sup>5</sup>; Zhang, BH<sup>6</sup>; Cai, WJ<sup>7</sup>; Mo, YF<sup>8</sup>; Zhao, WH<sup>9</sup>.

**Review question / Objective:** The purpose of this study was to explore the efficacy of icariin in the treatment of Knee osteoarthritis and to provide clinicians and patients with new treatment strategies.

**Information sources:** This protocol describes a systematic review and meta-analysis of previously published studies, so ethical approval is not required. This study was designed in strict accordance with the 2015 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P). We will search 4 foreign language electronic databases, including PubMed, Embase, Web of Science, and Cochrane Library, and 3 Chinese literature databases, including the China National Knowledge Infrastructure Database (CNKI), Wanfang Database, and China Biomedical Database (CBM). Two researchers will screen randomized controlled trials (RCTs) examining the use of icariin in the treatment of KOA, and the main search terms will be "icariin" and "KOA".

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 November 2021 and was last updated on 04 November 2021 (registration number INPLASY2021110015).

### INTRODUCTION

**Review question / Objective:** The purpose of this study was to explore the efficacy of icariin in the treatment of Knee osteoarthritis and to provide clinicians and patients with new treatment strategies.

**Condition being studied:** Knee Osteoarthritis(KOA) is the most common chronic progressive disease in the world and one of the main causes of physical disabilities.[1, 2] The knee is the joint with the highest incidence of osteoarthritis, and the degeneration of this joint can seriously

affect people's daily lives.[3, 4] An epidemiological survey found that the global prevalence of KOA is 16% among people over 15 years old and 22.9% among people over 40 years old. As of 2020, there were approximately 654.1 million people suffering from KOA worldwide. The incidence of KOA varies greatly between different countries and increases with age. [5] Although the incidence of KOA is increasing year by year, its pathogenesis is still not completely clear.[6] Recent studies have reported additional factors leading to the development of KOA, such as external mechanical load (including obesity), joint trauma, metabolism and genetics.[7, 8] The current treatments for KOA include drug therapy, physical therapy, exercise, intra-articular injection therapy, cognitive behavioral therapy, cell therapy and even surgery.[9, 10] Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs for KOA and can effectively relieve pain. However, for elderly and frail patients with osteoarthritis, long-term use of oral NSAIDs can affect the gastric mucosa and cause adverse reactions such as gastric ulcers and gastric bleeding.[11] Therefore, it is important to find a drug that can replace oral NSAIDs in the treatment of KOA. In recent years, an increasing number of scientific researchers have turned their attention toward examining the efficacy and mechanism of using Chinese herbal extracts to treat KOA. [12] Icariin is a flavonoid compound isolated from the traditional Chinese medicine Epimedium. It is the main biologically active ingredient in Epimedium. It has a long history of clinical treatment of bone and joint diseases in China.[13] Many in vitro and animal studies have found that icariin has a positive effect in the treatment of KOA, which can inhibit bone resorption while inducing bone formation.[14] Animal experiments have confirmed that icariin can promote the differentiation of Sprague–Dawley rats (6 months old) bone marrow mesenchymal stem cells (BMSCs) into osteoblasts. [15] In summary, an increasing number of studies have reported the potential value of icariin in the treatment of KOA, but its effectiveness and safety need more clinical

evidence for verification. Therefore, this study proposes a systematic review of icariin for the treatment of patients with KOA.

## METHODS

**Participant or population:** The participants will be patients who have been diagnosed with KOA according to the criteria established by the American College of Rheumatology (ACR) without restrictions based on sex, age, race, time of onset, and course of disease.

**Intervention:** The experimental group will comprise individuals who used icariin as an intervention in RCTs. There will be no restriction regarding the method of administration, time, dosage or cycle during intervention.

**Comparator:** The control group will comprise individuals who were treated with placebo or other alternative drugs.

**Study designs to be included:** Randomized controlled trials.

**Eligibility criteria:** Only RCTs using icariin in the treatment of KOA will be included. Non-RCTs, review papers, qualitative studies, and documents with incomplete data will be excluded. The participants will be patients who have been diagnosed with KOA according to the criteria established by the American College of Rheumatology (ACR) without restrictions based on sex, age, race, time of onset, and course of disease. The experimental group will comprise individuals who used icariin as an intervention in RCTs. There will be no restriction regarding the method of administration, time, dosage or cycle during intervention. The control group will comprise individuals who were treated with placebo or other alternative drugs.

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**Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).**[16] We will search 4 foreign language electronic databases, including PubMed, Embase, Web of Science, and Cochrane Library, and 3 Chinese literature databases, including the China National Knowledge Infrastructure Database (CNKI), Wanfang Database, and China Biomedical Database (CBM). Two researchers will screen randomized controlled trials (RCTs) examining the use of icariin in the treatment of KOA, and the main search terms will be "icariin" and "KOA".

**Main outcome(s):** The primary outcome measures will be the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS) and total effective rate.

**Additional outcome(s):** The secondary outcome measures will be the Short-Form 36 (SF-36) and adverse reactions.

**Quality assessment / Risk of bias analysis:** We will use the risk of bias assessment tool recommended by Cochrane System Reviewer Manual 5.1.0 to evaluate the quality of the included RCTs. Two researchers (BZ and ZP) will perform the analysis, and then, their evaluations will be cross-checked. We will evaluate the following aspects: random sequence generation, allocation concealment, participants, personnel, blinding of result evaluation, completeness of result data, selective reporting and other deviations. The assessment results will be divided into three levels: low risk, high risk, and uncertain risk. Disagreements in the evaluation of the quality of the literature will be resolved by discussion or judgement from an expert (WZ).

**Strategy of data synthesis:** Meta-analysis of the main outcome measures will be performed using RevMan 5.3 software. In this study, odds ratios (ORs) will be used as effect measures for binary variables. For measurement data with the same unit and measurement method, the mean difference (MD) will be used along with the 95%

confidence interval (CI).  $P < 0.05$  will indicate significant differences. The  $I^2$  test will be used to examine heterogeneity. If  $P > 0.05$  and  $I^2 \leq 50\%$ , then a fixed effects model will be used for meta-analysis; otherwise, a random effects model will be used for meta-analysis. Obvious clinical heterogeneity will be addressed by subgroup analysis, sensitivity analysis or descriptive analysis.

**Subgroup analysis:** If the heterogeneity between the studies is substantial large, subgroup analysis will be carried out. Subgroup analysis can be performed according to the patient's age, race, intervention, type of treatment and duration.

**Sensitivity analysis:** Sensitivity analysis is used to assess the stability and reliability of meta-analysis results. We will perform sensitivity analysis or descriptive analysis by eliminating studies one at a time to assess the stability of the results.

**Country(ies) involved:** China.

**Other relevant information:** References: [1]Wiggers TG,Winters M, Van den Boom NA, et al. Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials. *Br J Sports Med* 2021;55(20):1161-1169. [2]Li X, Xu Y, Li H, et al. Verification of pain-related neuromodulation mechanisms of icariin in knee osteoarthritis. *Biomedicine & Pharmacotherapy* 2021;144:112259. [3]Betzler BK, Chee YJ, Bin Abd Razak HR. Intraosseous Injections Are Safe And Effective in Knee Osteoarthritis: A Systematic Review. *Arthrosc Sports Med Rehabil* 2021;3(5):e1557-e1567. [4]Hawker G A. Osteoarthritis is a serious disease. *Clin Exp Rheumatol* 2019;120(5):3-6. [5]Cui A, Li H, Wang D, et al. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *E Clinical Medicine* 2020;29-30:100587. [6]Primorac D, Molnar V, Rod E, et al. Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic

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**Contributions of each author:**

Author 1 - Lang Liu - Writing—original draft.  
Email: 920352049@qq.com  
Author 2 - Changwei Zhao - Project administration.  
Email: zcw\_1980@126.com  
Author 3 - Shuang Zhao - Data curation.  
Email: 2267112045@qq.com  
Author 4 - Hanxun Xu - Investigation.  
Email: 123746214@qq.com  
Author 5 - Zeyu Peng - Data curation.  
Email: 550193768@qq.com  
Author 6 - Binghua Zhang - Methodology.  
Email: 842208281@qq.com  
Author 7 - Wenjun Cai - Investigation.  
Author 8 - Yifang Mo - Methodology.  
Email: 1275540938@qq.com  
Author 9 - Wenhai Zhao - Supervision; Writing—review & editing.  
Email: 6177252@163.com