Effectiveness and Safety of Duantengyimu-tang for Rheumatoid Arthritis: A Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Background: Per-oral pharmacological medication is a representative treatment for rheumatoid arthritis (RA), and has improved over several guidelines. However, limitations of long-term use of these medications including adverse events, led to the introduction and utilization of complementary and alternative treatments for RA. Several herbal medicine decoctions have been reported to be effective and safe; a recent study introduced Duantengyimu-tang (DTYMT). Regardless of the pharmacological effects of the DTYMT components, there are concerns about its safety. Therefore, this systematic review (SR) will focus on the effectiveness and safety of DTYMT treatment for RA.

Methods: Searches for randomized controlled trials using DTYMT treatment for RA will be performed using multiple electronic databases, manual searches, and emails (if necessary). A summary will be written using data on outcome measurements of the study participants, interventions, adverse events, and risk of bias in the studies. The primary outcomes will be disease activity scores including effective rate, tender joints, swollen joints, and morning stiffness. The secondary outcomes will include adverse events and blood tests for RA (erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factors). This SR will use Review Manager software to perform a meta-analysis, the Cochrane Collaboration “risk of bias” tool, and determine the quality of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation method.

Results: This SR will investigate the clinical effectiveness and safety of DTYMT treatment in patients with RA.

Conclusion: This SR aims to be informative for patients and clinicians in clinical practice, researchers, and policymakers in managing RA.

Trial Registration Number: INPLASY, INPLASY202340100.

Keywords: Duantengyimu-tang, meta-analysis, randomized controlled trials, rheumatoid arthritis, systematic review

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Introduction

Severe symptoms of rheumatoid arthritis (RA) interfere with patients’ daily lives, and several clinical practice treatment guidelines have been developed [1]. The representative pharmacological treatments for RA are disease-modifying antirheumatic drugs (DMARDs); the use of these medications is well established, with guidelines for their use in various clinical situations [2,3]. However, these Western medications have various limitations including side effects, and interest in alternative treatments has grown [4,5].

Herbal decoctions are commonly used as complementary alternative treatments for RA. Representative decoctions include Guizhishaoyaozhimu-tang and Duhuojisheng-tang, and their effects as treatment for RA have been reviewed systematically covering experimental studies, and expert consensus [6-8]. Wutou-tang and Simiaoxiaobi-tang decoctions have also been studied using the systematic reviews (SR) protocol [9,10].

Duantengyimu-tang (DTYMT) was recently reported as a potential treatment for RA. It has three main components (Phlomis umbrosa, Leonurine herba, and Tripterygium hypoglaucum Hutch) [11-13]. Several experimental studies have reported the pharmacological effects of these herbs on osteoarthritis, and it has been suggested that they may be effective in treating RA [11-13]. However, there are also questions regarding the safety of DTYMT, especially the Tripterygium hypoglaucum Hutch component, which has been reported to be potentially toxic [14].

Several randomized controlled trials (RCTs) have been conducted and have reported the effectiveness and safety
of DTYMT [15]. However, it is necessary to evaluate the effectiveness and safety of DTYMT for RA by conducting an SR.

**Materials and Methods**

1. **Study registration and design**

   The protocol has been registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (registration no.: INPLASY202340100). This SR was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2020 Statement [16].

2. **Ethics**

   Ethical approval was not required as there would be no collection of personal information or patient recruitment.

3. **Inclusion criteria**

   **3.1. Participants**

   Patients diagnosed with RA will be included. There will be no age or sex restrictions according to the criteria for RA; however, patients diagnosed with other types of arthritis including osteoarthritis, will be excluded.

   **3.2. Type of intervention**

   This SR will include RCTs that mainly use DTYMT as an intervention. The use of combination therapy with DTYMT in the experimental and control groups should be consistent. Studies comparing different doses, treatment periods, and dose types would be excluded.

   **3.3. Type of comparator**

   The comparator would be conservative RA treatment including injections, physiotherapy, and oral medications such as nonsteroidal anti-inflammatory drugs, DMARDs, and glucocorticoid steroids.

   **3.4. Type of study**

   This SR will only include RCTs that have investigated the effects of DTYMT treatment for RA. Non-RCTs or uncontrolled clinical trials including observational, cross-sectional, pilot, case reports, and SRs will be excluded. RCTs that did not provide a “randomization” word or performed incorrect randomization will be excluded. There will be no restrictions on the language or the journals.

   **3.5. Measurement of results**

   Based on previous SRs for RA, disease activity scores including the effective rate, tender joints, swollen joints, and morning stiffness, will be the main outcomes. The secondary outcomes will be the blood tests used in the RA diagnosis (erythrocyte sedimentation rate, C-reactive protein, and rheumatoid factors) and adverse events.

4. **Information sources and search strategies**

   The following electronic databases will be searched: MEDLINE, Cochrane Library, China National Knowledge Infrastructure, CiNii, J-STAGE, KoreaMed, Korean Medical Database, Korean Studies Information Service System, National Digital Science Library, Korea Institute of Science and Technology Information, and Oriental Medicine Advanced Searching Integrated System. Studies published from initiation to August 2023 will be retrieved and search terms for RA (e.g., rheumatoid arthritis) and Duantengyimu-tang, Duantengyimu-decoction (DTYMT) will be used. The search will be performed according to the language in each database. Further research will be performed manually, including a search of textbooks and references list from the included studies. In addition, we will attempt to contact the authors if necessary (Table 1).

5. **Study selection**

   Two researchers (JHM and GEP) will conduct an eligibility review. Studies will be identified by title, abstract, and full text (if possible) during the screening procedure. After excluding duplicate and unrelated studies, an eligibility assessment will be conducted using the original text. Disagreements will be resolved by discussion or by consultation with a 3rd reviewer (WSS).

6. **Data extraction and management**

   The reviewers (JHM and GEP) will extract information, including the 1st author, year of publication, patient characteristics, interventions for each group (dose and duration), outcome measurements, results, and research quality. Disagreements will be resolved through discussions or other reviewers (WSS and EJK) decisions. If necessary, the author will be contacted to obtain incomplete data. If there is no response, the SR will contain this omission. Study management will be conducted using EndNote X20 (Clarivate, Philadelphia, PA, USA).

7. **Data synthesis and analysis**

   This SR will use Review Manager software (version 5.3; Copenhagen, Denmark; The Nordic Cochrane Center, The Cochrane Collaboration, 2014) for the meta-analysis. The change from baseline to completion of intervention will be used to calculate the mean difference and 95% confidence interval for the same outcome measurement, and the
standardized mean difference and 95% confidence interval for different outcome measurements. Heterogeneity will be determined using chi-square and I-squared tests. The interpretation of heterogeneity will be performed using I-squared where 0-40% indicates unimportant heterogeneity; 30-60% moderate heterogeneity; 50-90% substantial heterogeneity; and 75-100% considerable heterogeneity [17]. If subgroup analysis is possible, it will be based on the main intervention and the control group. If a quantitative synthesis is impossible, a descriptive synthesis will be performed using the available data. A funnel plot will be used to evaluate publication bias (for more than 10 studies). Grades of Recommendation, Assessment, Development, and Evaluation methods will also be used to determine the quality of evidence [18].

8. Risk of bias assessment

The reviewer will independently evaluate the risk of bias using the Cochrane Collaboration “Risk of bias” tool [19]. There are seven domains (sequence generation, allocation concealment, participant and investigator blinding, outcome assessment blinding, incomplete outcome data, selective outcome reporting, and other biases). Disagreements will be resolved by discussion or by intervention from a 3rd reviewer.

Discussion

Due to the increasing prevalence of RA and the economic burden of this disease, active treatment for RA is recommended. Although existing treatments including medication have been developed and are recommended, they are hindered by known limitations and adverse events. For this reason, several alternative complementary treatments have been introduced for RA. Traditional Chinese medicine treatments, including acupuncture, pharmacopuncture [20], and herbal medicine [9,10], have been introduced as a new option for patients with RA. Among them, acupuncture and pharmacopuncture might have disadvantages due to the limited treatment points and types of stimulation. However, in terms of treatment with herbal medicine, it has the advantage of various combinations of herbs. DTYMT may be a potential therapeutic herbal medicine option, and recent reports support its use in RA [9,10]. However, there is a need to perform a SR to determine its efficacy and safety. This SR will aim to provide useful resources to patients, clinicians, and researchers.

Author Contributions

Conceptualization: WSS. Investigation: GEP and JHM. Methodology: WSS. Project administration: EJK and WSS. Supervision: WSS. Writing—original draft: GEP and JHM. Writing—review & editing: EJK and WSS.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Ethical Statement

This study is not related to any human or animal experiments.

Data Availability

All relevant data are included in this manuscript.

References


