The Effectiveness of Acupuncture and Moxibustion for Rheumatoid Arthritis: A Protocol of an Overview of Systematic Reviews and Meta-analysis

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Protocol

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Abstract

**Background:** Rheumatoid Arthritis (RA) is a common chronic disease with an annual incidence of 25 per 10,000 of the population, which will result in severe joint damage, disability and death. It is strongly supported by systematic reviews (SRs) as part of the treatment of these patients. However, the evidence has not been methodically integrated. This overview aims to describe, synthesize, evaluate the reliability of evidence come from current systematic reviews of acupuncture and moxibustion therapy for RA.

**Methods:** We will search for SRs and meta-analyses from Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PubMed, MEDLINE, Wan-Fang Databases, China National Knowledge Infrastructure (CNKI), Citation Information by National Institute of Informatics, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP Database). Additionally, we will search for the ongoing, unpublished, or recently completed SRs on the PROSPERO database. Two reviewers will assess those SRs, select data independently. Any disagreement will be resolved through discussion or arbitrated by the third author if necessary. The overview of SRs and meta-analysis will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.

**Results:** The results in this study will be published in a peer-reviewed journal.

**Conclusion:** The conclusion of our study expects to provide extensive evidence from multiple meta-analysis and systematic reviews for patients with RA.

**INPLASY registration number:** INPLAS202080031.

1. Background

1.1. Description of the condition

Rheumatoid arthritis (RA) is the most prevalent inflammatory arthritis, and a significant cause of severe joint damage, disability and death. RA is well-characterized by a circadian rhythm of clinical manifestation exacerbate symptoms in the early morning, while alleviated to a correlatively stable condition in the afternoon [1–3]. The incidence of RA is varying between 0.5% and 1% depending on the population studied [4]. In China, RA has an incidence of 0.32% to 0.38% [5]. The global annualized incidence for self-reported disability is approximately 2.5%, and the Social Security disability about 1.9% [6]. A persistent inflammation of joint swelling, bone destruction, morning stiffness and increased risk of pulmonary, nervous, cardiovascular and other complication affect people in every way, prompting treatment for RA is essential [7][8].

Currently, the treatments of RA are mainly focus on early aggressive therapy and treat to target such as anti-inflammatory, biologic therapy reduce inflammation, prevent damage, and change the course of rheumatoid arthritis to limit late complications [9]. However, these treatment options may cause the increasing number of side effects, such as gastrointestinal toxicity effects and cartilage damage [10][11].
Meanwhile, acupuncture and moxibustion is an unique therapy which can relieve pain, improve the blood circulation, protects neurons in immune system diseases such as RA\[^{12}\]. Previous Some clinical trials have reported that acupuncture and moxibustion are effective and safe and may have some strengths over routine drug therapy. Besides, it has the benfits of convenience, reliability, and minimal adverse reactions. However, the evidence has not been methodically integrated. In this overview, we aim to describe, synthesize, evaluate the reliability of evidence generated from current SRs of acupuncture and moxibustion therapy for RA.

### 1.2 Description of the intervention

Acupuncture is an ancient therapy that is defined by the insertion of needles into specific acupoints or surface parts of the body for thousands of years \[^{13}\][\(^{14}\)] . It is a well-tolerated therapy, and used to treat kinds of symptoms and disease processes. It has been specifically advantageous due to the low risk of adverse events compared to common conventional treatments. It is believed that acupuncture is widely used in RA patients to relieves symptoms such as joint pain, inflammatory biomarkers joint swelling, stiffness joints, morning stiffness time, the index of dysfunction\[^{15}\]. The mechanism by which acupuncture leads to physiological or clinical changes is still unclear, but traditional Chinese medicine (TCM) believe that acupuncture works through stimulating the meridians and motivating energy to regulate the zang-fu organs\[^{16}\].

A traditional Chinese therapy of moxibustion is based on traditional Chinese medicine (TCM), which use the heat generated by burning herbal preparations containing mugwort (Artemisia vulgaris) to stimulate acupoint. The significant effects of moxibustion on pain in patients with RA have been reported in various conclusions, but the effects on inflammatory factors in RA were unclear. Moxibustion enhanced the analgesic effects and anti-inflammatory of traditional and can enhance the effect of traditional medicine, reduce HIF-1\(^\alpha\)/VEGF contents to inhibit angiogenesis\[^{18}\].

### 1.3 Description of the Objectives

The objectives of this study are as follows:

1. Comprehensively explore the methodological, evidence quality reporting quality of available using the Assessment of Multiple systematic Reviews-2 (AMSTAR-2) \[^{19}\] and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) \[^{20}\].

2. To summarize the significant evidence for the effectiveness and safety of acupuncture and moxibustion for RA and provide reliable recommendations for clinical practitioners and researchers.

- To analyze how our studies can provide reliable recommendations for clinical practitioners and researchers and be used to guide clinical medicine.

## 2. Methods
2.1. Study registration

This protocol is registered on the International Prospective Register of Systematic Reviews in INPLASY, registration number: INPLASY202080031 [https://inplasy.com/inplasy-2020-8-0031/] on 08 August 2020. The study will be conducted based on the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA) statement guidelines[21].

2.2. Study design

2.2.1. Type of studies

For this overview, we will include SRs and meta-analysis of randomized controlled trials (RCTs) for acupuncture and moxibustion in patient with RA.

2.2.2. Type of participants

We will include patients with RA, regardless of sex, age, ethnicity, course, disease severity restrictions or disease duration.

2.2.3. Type of interventions

Acupuncture and moxibustion is used as a major intervention will be included. There is no limitation of the type of moxibustion therapy such as natural moxibustion, direct moxibustion, moxa-burner moxibustion, etc. Literatures in which acupuncture and moxibustion is not used as a major intervention will be excluded.

2.2.4. Type of outcome measures

2.2.4.1. Primary outcomes

Main outcome indicators:

(1) Pain visual analog scale (VAS) score;

(2) The score of joint functional activity or other validated scales.

2.2.4.2. Secondary outcomes

(1) Safety outcome: adverse effects;

(2) Quality of life;

(3) Total effective rate.

2.3. Search methods
A electronically search literature will be regulated by GHT, SYZ, and ZYZ in the following databases of PubMed, EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wan-Fang Databases, Citation Information by National Institute of Informatics, Chinese Scientific Journal Database (VIP Database) from their inception to October 2020. No language restrictions will be set.

In the process of literature retrieval, we will combine the advice of evidence-based medicine experts based on the actual situation to develop a search strategy and make corresponding records to find the most appropriate retrieval strategy, the intent is to ensure the comprehensiveness and accuracy of the literature retrieval. The reference lists and the citation lists of studies meeting the inclusion criteria and relevant systematic reviews will also be searched to identify further studies for inclusion. Before this review completed, two reviewers (ZZY and SYZ) will manage the searching strategy once again to ensure the studies that met the inclusive criteria could be included. The search is no restriction on any national languages. The primary selection search strategy for PubMed will is shown in Table 1.

2.4. Studies selection

The results of the searching will be identified using NoteExpress 3.2. After initial duplicate removal, two authors (LBL and JC) will be independently screen titles and abstracts from the searches. Full-text articles of the potentially relevant titles will be retrieved includable SRs or SR protocols. If articles contain incomplete information that has been decided to eligibility, XCZ will try to communicate with authors of the original studies to get further details. When two reviewers have any disagreements, the situation will be resolved discussion or consensus with another reviewer (HG). Study selection will be performed according to the PRISMA flowchart (Figure 1). If any unpublished or ongoing study is identified, we will contact with the corresponding author for the necessary information about whether any preliminary data may be included in our study.

2.5. Data extraction

The following literature types of information will be extracted based on the exclusion and inclusion criteria, including the following several aspects:

(1) Study characteristics: author, date of publication, number of participants, follow-up time; study setting;

(2) Patient characteristics: sex, age, type of RA;

(3) Intervention: intervention measures in the experimental group, intervention measures in the control group;

(4) The outcome of the study: Two researchers (LBL and JC) will independently cross-examined the outcome of extraction of the included review. Any differences should be resolved through discussion.

2.6. Evaluation of the quality of the included studies
2.6.1. Assessment of methodological quality of the included studies

For each systematic review that met the inclusion criteria, two authors (HG and GHT) will use the Assessment of Multiple Systematic Reviews-2 (AMSTAR-2) Measurement Tool to evaluate the methodological quality\[22\]. The AMSTAR-2 tool contains 16 items, 7 of which are critical areas. According to evaluation criteria, each study will be segmented into “high confidence” (if there is no critical weakness and no or only one non-critical weakness); “moderate confidence” (if there is more than 1 non-critical weakness with no critical weakness); “low confidence” (if there is one critical weakness with or without non-critical weaknesses); and “critically low confidence” (if there is more than one critical weakness with or without non-critical weaknesses). Disagreements will be resolved through discussion between them. The results of the methodological quality assessment of the included studies will be recorded in an additional Table 2.

2.6.2. Report quality of the included reviews

The studies will assess the report quality of the included reviews according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist\[23\]. PRISMA contains 27 items, and each checklist item will be evaluated as yes, no, or partially yes to indicate compliance.

2.7. Evaluation of the evidence quality of the included studies

The strength of the evidence in the included reviews will be evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system\[24\]. Two authors (XCZ and ZYZ) will put forward the preliminary recommendations about the following contains: the weights of weaknesses and strengths, the quality of the evidence, and the patient’s preferences and values. The evidence quality will be ranged from "strong no recommendation", "weak no recommendation", "weak recommendation", "unclear recommendation", "strong recommendation". The purpose of this is to reach a better agreement.

2.8. Dealing with lost data

Data from unspecified or insufficient outcomes of SRs, we will contact for the necessary information. If the data from the original study has not been extracted, it will be considered as “no evidence”.

2.9. Synthesis of data

Two reviewers (GHT and JC) will separately use the bias risk tool from the guidelines of Cochrane Reviewer’s Handbook 5.0.24 to evaluate the quality of the literature\[25\]. This recommended tool in included studies will be evaluated according to the following domains: sequence generation, selective result reporting, allocation concealment, incomplete outcome data, blinding of results evaluation, blinding of participants and personnel, and other biases. Each of them will be classified into “low,” “unclear,” or “high” judgments for each study. The result will be separately assessed by 2 reviews and differentials.
will be discussed with a third reviewer(HG). The statistical analyses will be conducted using RevMan5.4 software.

Continuous outcomes will be represented by relative 95% confidence intervals(CI) and its relative risk (RR). Measurement data will be represented by meandifference (MD) and its 95%CI. Heterogeneity among all included studies will be detected by $X^2$ test. When statistical homogeneity was found among the results ($P > 0.1, I^2 < 50\%$), we will choose the fixed effects model for meta-analysis of the results. If statistical heterogeneity exists among the results ($P < 0.1, I^2 > 50\%$), the source of heterogeneity needs to look for the possible causes. When the results are too much substantial heterogeneity or considerable heterogeneity, statistical methods such as subgroup analysis, descriptive analysis or subgroup analysis can be used to treat the heterogeneity.

3. Discussion

Our study will be a comprehensive synthesis of the existing SR literature describing the effectiveness of acupuncture and moxibustion for rheumatoid arthritis. This overview will facilitate the treatment of SP by clinicians, as well as for teaching and educating patients.

Up to now, we have found some limitations of this study: (1) Most of SRs and meta-analysis included in the study are in China; (2) The small number of included studies also caused publication bias to some extent. (3) The differences of acupuncture and moxibustion operation methods between different countries should be cautions.

This study has the following Contributions: (1) To the best of our knowledge, it will be the first such study to assess acupuncture and moxibustion medical treatment for patients with RA; (2) Our study will provide sufficient data for doctors and policymakers, which will help them make decisions the optimal method of treating RA. (3) This study is helpful to choice the correct operation method of acupuncture and moxibustion for treating RA and the relationship between the therapeutic effect, the total amount of acupuncture and moxibustion, the time of acupuncture and moxibustion, improving the effective and safety of RA with acupuncture and moxibustion.

Abbreviations

RA= rheumatoid arthritis, SRs= systematic reviews, TCM= traditional chinese medicine, AMSTAR-2= Assessment of Multiple Systematic Reviews-2, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs= randomized controlled trials, VAS= visual analog scale, CI= confidence intervals, RR= relative risk, CENTRAL= Cochrane Central Register of Controlled Trials, GRADE= Grading of Recommendations, Assessment, Development, and Evaluation, CNKI= China National Knowledge Infrastructure, VIP Database= Chinese Scientific Journal Database, CBM= Chinese Biomedical Literature Database.
Declarations

Ethical Approval and Consent to participate

This study will not contain any individual data and will not prejudice individual rights, so ethics approval is not required. The study will be subject to rigorous peer review and may be published in a peer-reviewed journal.

Consent for publication

Results will be disseminated on peer-reviewed publication and conference presentations.

Availability of data and materials

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

Additional information

Additional file 1. Table1. Flowchart of literature selection

Additional file 2. Table2. Methodological quality assessment of included reviews using AMSTAR-2

Additional file 3. Figure1. Search strategy for PubMed

Additional file 4. PRISMA-P Checklist.

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