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Effectiveness and safety of bee venom pharmacopuncture for rheumatoid arthritis: a systematic review protocol

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ABSTRACT

Introduction Rheumatoid arthritis (RA) is the common autoimmune disease with low quality of life. The representative treatment is medication and medication usage has improved through update of clinical guidelines, however, there are still limitations. Bee venom (BV) has been reported to have meaningful therapeutic effects and the possibility of alternative options for RA through several types of studies, but there is no well-organised and recent published systematic review (SR).

Methods We will search randomised controlled trials about the BV on RA from the inception to 31 May 2022 in various databases, manual research and contacting authors. Electronic databases will include MEDLINE, EMBASE, 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. With screening and reviewing process, we will identify the eligible studies and extract the needed data. The primary outcome will be the disease activity scores indicating the improvement of RA symptoms (American College of Rheumatology response criteria 20, 50, 70), functions (Health Assessment Questionnaire, Disease Activity Score of 28 joints), joint (Western Ontario and McMaster universities osteoarthritis index), pain (Visual Analogue Scale, Numerical Rating Scale) and effective rate. The secondary outcomes will be the RA-related blood test levels and adverse events. We will perform a meta-analysis by Review Manager software, the assessment of risk of bias by Cochrane Collaboration 'risk of bias' and the determination of quality of evidence by Grades of Recommendation, Assessment, Development and Evaluation.

Ethics and dissemination Our SR will suggest the clinical evidence of the use of BV for RA to patient, clinicians and policymakers. We will publish our results in a peer-review journal.

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Strengths and limitations of this study

► This study will evaluate the effectiveness and safety of bee venom on rheumatoid arthritis overcoming the limitations of existing studies.
► This study will assess more than 10 databases without language limitation.
► We will use credible assessments of bias and quality including risk of bias and Grades of Recommendation, Assessment, Development and Evaluation.
► Expected limitations include various outcomes and different quality of the identified studies.

the diagnosis by calculating the score in the section of joints, serology, symptom duration and acute phase reactants and RA is considered if there are definite swelling joints not explained by another disease, the presence of rheumatoid factor (RF), elevated level of C reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[2 3]

In the South Korea, the prevalence of RA increased yearly from 0.28% in 2009 to 0.32% in 2012 with the increasing incidence from 28.5 per 100 000 in 2010 to 42 per 100 000 in 2013.[4] Regarding worldwide, Tayar *et al* suggested that RA is the most common inflammatory polyarthritis with the prevalence of 1% and Safiri *et al* reported that the age-standardised prevalence increased by 7.4% and the incidence increased by 8.2% between 1990 and 2017, with the increasing economic loss between 2012 and 2017.[5 6]

The most recommendable treatment for RA is medication. Since the disease-modifying antirheumatic drugs (DMARDs) were introduced in 1970s,[7] recent clinical guideline has been updated including conventional synthetic, biologic, targeted synthetic DMARDs and glucocorticoid and provided the recommendable usage in the various clinical settings.[8] However, there are still adverse

INTRODUCTION

Rheumatoid arthritis (RA) is the autoimmune disease characterised by pain, swelling and joint destruction.[1] In the clinical practice, the criteria for RA have been used for

effects including rash, diarrhoea, chronic kidney disease, gastrointestinal distress and bone marrow suppression.[9]

Bee venom (BV) has been used in various diseases including pain, skin problem and cancer.[10] It contains various peptides and melittin, a major peptide component, is known to be have anti-inflammatory and anti-arthritis properties.[11] With other pharmaceutical properties including apamin, adolapin and various enzymes, several studies have reported its effect on RA through experiment, clinical trial and review.[12–14]

With diverse studies, there are two systematic reviews (SRs) about BV pharmacopuncture on RA, but there are some limitations.[15 16] One SR included only one randomised controlled trial (RCT) and publication year was old (2014). Another SR was published in 2020 and referred several studies but did not focus on RA. Therefore, the purpose of this SR was to evaluate the effectiveness and safety of BV by including recent published RCTs about RA.

METHODS
Study design
This SR was designed according to the Preferred Reporting Items for Systemic review and Meta-Analysis Protocols 2015 statement.[17]

Study registration
The protocol was registered in PROSPERO.

Eligibility criteria
Participants
Patients diagnosed as RA will be included in this SR. In the accordance with the criteria for RA, there is no limitation about age and gender, but we will exclude patients who were diagnosed as other arthritis including osteoarthritis.

Types of interventions
RCTs that used BV as intervention mainly will be included in this SR. The usage of combination treatment with BV in the experimental group should be consistent with control group. Regarding BV, studies comparing the different concentration, treatment duration, dosage and acupuncture points will be excluded.

Type of comparators
There is no limitation for comparators. Placebo, no treatment, conventional treatments for RA including medication, physical therapy will be eligible.

Type of studies
We will only include RCTs that investigated the effect of BV for RA. Non-RCTs or uncontrolled clinical trials including observational studies, cross-sectional studies, pilot studies, case reports and SR will be excluded. RCTs that did not provide the randomisation method or conducted an incorrect randomisation will be excluded. There will be no restriction about language or journal.

Table 1 Search strategy for the PubMed

No.	Search terms
#1	rheumatoid arthritis
#2	rheumatoid OR arthritis
#3	#1 and #2
#4	randomised controlled trial OR random* OR placebo
#5	controlled clinical trial OR trial
#6	bee venom
#7	bee venom pharmacopuncture OR bee venom acupuncture
#8	#6 OR #7
#9	#3 and (#4 OR #5) and #8

Outcome measures
Based on the previous SRs about RA,[18–20] disease activity indices that present the degree of RA symptoms will be the primary outcome measure. It includes the indicators about the RA improvement (American College of Rheumatology response criteria 20, 50, 70), function (Health Assessment Questionnaire, Disease Activity Score of 28 joints), joint (Western Ontario and McMaster universities osteoarthritis index), pain (Visual Analogue Scale, Numerical Rating Scale) and effective rate.[21] Blood test about RA including ESR, CRP, RF, anti-cyclic citrullinated peptides and adverse events will be included as secondary outcome measures.

Information sources and search strategy
We will use the following electronic databases: MEDLINE, EMBASE, Cochrane library, China National Knowledge Infrastructure, CiNii, J-STAGE (Japanese database), 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. Researchers will search the studies from the inception to 31 May 2022 and use search terms about RA (such as rheumatoid arthritis, rheumatoid) and BV (bee venom, bee venom acupuncture, bee venom pharmacopuncture). The search will be performed according to the language provided by each database (table 1). Regarding additional research, we will conduct manual searching including textbooks and reference lists on retrieved articles. We will also try to contact the corresponding authors if necessary.

Study selection
Two researchers will perform screening and reviewing for the eligibility. In the screening procedure, studies will be identified by the titles, abstracts and full-text (if possible). After excluding the duplicates and irrelevant studies, the reviewing procedure for eligibility will be performed by the full-texts (figure 1). Disagreement will be resolved by the discussion or the mediation by third reviewer.
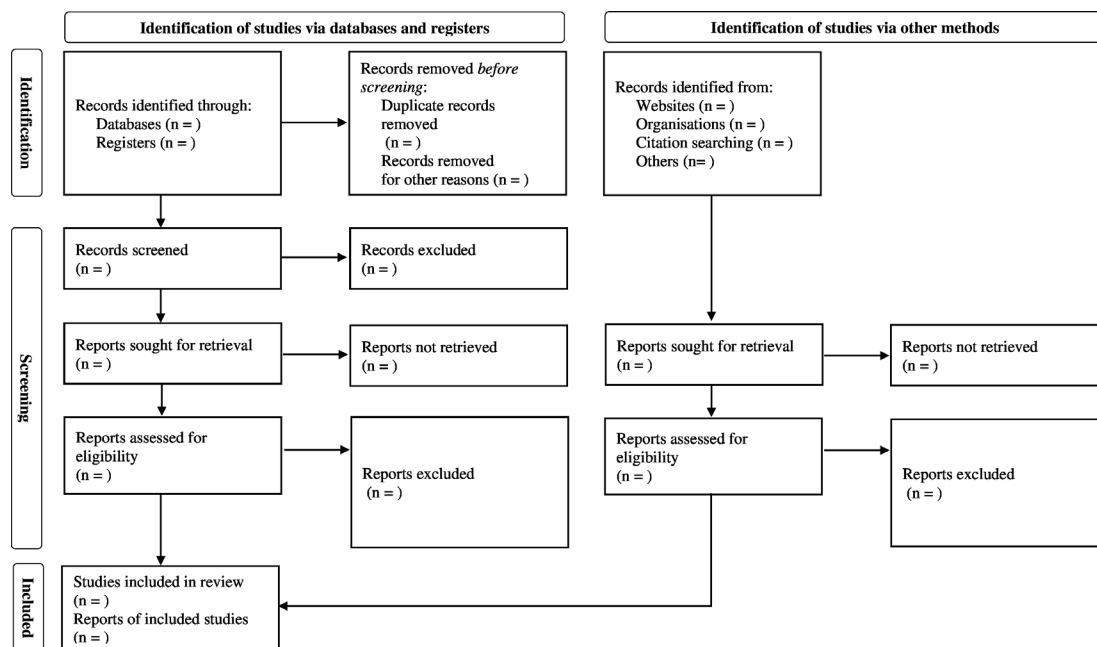
Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data management

Studies will be managed by using Endnote V.X9.

Data extraction

Reviewers will extract the information including first author, publication year, patients' characteristics, intervention in each group (process, treatment site and period), outcome measures, results and study quality. Disagreement will be resolved by the discussion or the mediation. If necessary, we will contact the corresponding author to obtain the incomplete data. If there is no response, we will describe this omission in the SR.

Data synthesis and analysis

We will use Review Manager software (V.5.3; Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014) for the meta-analysis. The changes from the baseline to the completion of the intervention will be used and the mean difference and 95% CIs in same outcome measures, and the standardised mean difference and 95% CI in different outcome measures will be calculated to estimate the effect. In the data analysis, a random-effects model will be based because the included studies may come from different population.

The heterogeneity will be determined by χ^2 and I-squared tests. The interpretation of the heterogeneity will be as follows: I-squared: 0%–40% unimportant heterogeneity; 30%–60% moderate heterogeneity; 50%–90% substantial heterogeneity and 75%–100% considerable heterogeneity.

If subgroup analysis is possible, it will be conducted based on the main intervention in control group. If quantitative synthesis is not possible, a narrative synthesis will be conducted using available data. Funnel plot will be applied to assess the publication bias by more than 10 included studies. The Grades of Recommendation, Assessment, Development and Evaluation method will also be used to determine the quality of evidence.[22]

Risk of bias assessment

Reviewers will assess independently the risk of bias by using the Cochrane Collaboration 'risk of bias', which consists of seven domains (sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other biases).[23] Disagreements will be resolved by discussion or medication as indicated above.

Patient and public involvement

No patient involved

ETHICS AND DISSEMINATION

RA is one of the most common immune disease that results in lower quality of life. Although previous DMARDs have been helpful for patients with RA, there are also needs for alternative options. BV had the possibility and several studies have been published. However, existing SR about BV on RA have limitations and this SR will suggest the clinical evidence. Also, we hope our review will be helpful for health policy makers, clinical practitioners, patients and further research. This review did not require the ethical approval since there was no need for personal information collection and patient recruitment. All of the results will be published in a peer-review journal.

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