



## Bee Venom Acupuncture for Rheumatoid Arthritis: A Systematic Review protocol

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Manuscripts

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4 **Bee Venom Acupuncture for Rheumatoid Arthritis:**  
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7 **A Systematic Review protocol**  
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26 **Short title:** A protocol of systematic review of bee venom acupuncture for RA  
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**Key words:** Bee venom acupuncture, rheumatoid arthritis, safety and efficacy, systematic review

**Abstract**

**Introduction:** This systematic review aims to analyse the trial data on the efficacy of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

**Methods and analysis:** The following 15 databases will be searched from their inception: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, and Century Journal Project), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

**Dissemination:** The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print.

**Trial registration number:** PROSPERO 2013: CRD42013005853

### Article focus

- This systematic review aims to analyse the trial data on the efficacy of bee venom therapy for rheumatoid arthritis.

### Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

### Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- A possible weakness may be the quality of the trials that we identify because the CAM research field has not been explored deeply.

## Introduction

### *Description of the condition*

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that results in the destruction of the musculoskeletal system. The disease is often progressive and results in pain, stiffness, and joint swelling. In late stages, deformity and ankylosis develop. Because of the complex, systemic nature of the disease, RA treatment is also complex and involves a variety of approaches. The major goals are to relieve pain, reduce inflammation, slow or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function.<sup>1</sup>

Untreated RA leads to joint destruction, functional limitation and severe disability<sup>23</sup> and has a significant impact on health-related quality of life (HRQoL).<sup>45</sup>

### *Description of the intervention*

Bee venom (BV) therapy has been used since ancient times, including the administration of honeybee stings, BV injection, and BV acupuncture (BVA).<sup>6</sup> Bee venom acupuncture (BVA) involves injecting purified, diluted bee venom into acupoints.<sup>7</sup>

### *How the intervention might work*

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritic, and anti-cancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.<sup>8</sup> The analgesic effects of BVA have been reported in animal experiments<sup>910</sup> and in the clinic.<sup>711</sup>

In many countries, including the United States, BV therapy has been used to treat multiple sclerosis and arthritis.<sup>1213</sup> However, most of these therapeutic uses are not based on evidence.

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4 ***Why is performing this review important?***  
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6 Currently, BVA for RA is widely used as an effective method. However, there is no critically  
7 appraised evidence, such as a systematic review or meta-analysis, of the potential benefits  
8 and harm of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for  
9 RA will help manage patients using BVA treatment.  
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17 ***Objectives***  
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19 We will perform a systematic review to assess the safety and efficacy of BVA for treating RA.  
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## Methods

### *Criteria for including studies in this review*

#### Types of studies

All prospective randomised controlled clinical trials (RCTs) will be included if they were randomised studies of BV injection at acupoints as the sole treatment or as an adjunct to other treatments if the control group received the same treatment as the BVA group. Trials comparing BVA with any type of control intervention will be included. We will exclude trials of BV injection into parts of the body other than acupoints. Trials will also be excluded if only immunological or biological parameters were assessed. We will also exclude trials comparing 2 different types of BVA. No language restrictions will be imposed. Hard copies of all articles will be obtained and read in full.

#### Types of participants

Patients suffering from RA will be included.

#### Types of interventions

We will include those trials on BVA used alone or as combination therapy with BVA and conventional therapy versus the same conventional therapy. BVA involves injecting purified, diluted BV into acupoints. Conventional therapy would include medications such as nonsteroidal anti-inflammatory drugs, steroids, disease-modifying anti-rheumatic drugs, immunosuppressants, and TNF-alpha inhibitors.

#### Types of outcome measures

##### *Primary outcomes*

Symptom (morning stiffness, pain, and joint swelling) evaluation



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### *Secondary outcomes*

The number of joints affected by RA

Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

Rheumatoid factor (RF)

### *Search methods for identifying the studies*

Electronic searches

We will search for trials in the following electronic databases: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and VIP.

Searching other resources

We will also perform non-electronic searches of conference proceedings, our own files of articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and

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4 Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean  
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6 Oriental Internal Medicine).

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11 Search strategy

12 The strategy for searching the MEDLINE database is presented in appendix 1. Similar search  
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14 strategies will be applied for the other databases.  
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20 ***Data collection and analysis***

21 Study selection

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23 The data screening and selection process will be performed independently by four authors  
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25 and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements  
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27 on the selection are not resolved through discussions, the arbiter (MSL) will decide.  
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33 Inclusion criteria

- 34  
35 1. Randomised controlled trials and quasi-randomised trials.  
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37 2. No language limitation  
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39 3. No publication status restriction  
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44 Exclusion criteria

- 45  
46 1. Animal experiments  
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48 2. Non-randomised clinical trials  
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50 3. Case report/series, news items, and letters  
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52 4. Qualitative studies  
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57 Data extraction and management  
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4 The data extraction and quality assessment will be conducted by three authors (JAL, MJS and  
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6 JHJ) using a predefined data extraction form.  
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8 Any disagreement among the authors will be resolved by discussion with all of the authors.  
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10 When the reported data are insufficient or ambiguous, MSL will contact the corresponding  
11  
12 authors by e-mail or telephone to request additional information or clarification.  
13  
14

#### 15 16 17 Assessment of bias in the included studies 18

19 We will independently assess bias in the included studies according to the criteria from the  
20  
21 Cochrane Handbook version 5.1.0, which include random sequence generation, allocation  
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23 concealment, blinding of participants and personnel, blinding of outcome assessment,  
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25 incomplete outcome data, selective reporting and other sources of bias.<sup>14</sup> The quality of each  
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27 trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact  
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29 the authors of the assessed trials for clarification. We will resolve any differences in opinion  
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31 through discussion or consultation with a third author.  
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#### 38 Measurement of the treatment effect

39 For the continuous data, we will use the mean difference (MD) with 95% confidence  
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41 intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs.  
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43 In the case of outcome variables with different scales, we will use the standard mean  
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45 difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect  
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47 as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.  
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#### 53 **Unit of analysis issues**

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55 For cross-over trials, data from the first treatment period will be used. For trials in which  
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57 more than one control group was assessed, the primary analysis will combine the data from  
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4 each control group. Subgroup analyses of the control groups will also be performed. Each  
5  
6 patient will be counted only once in the analysis  
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#### 10 Dealing with the missing data

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12 Intention-to-treat analyses that include all of the randomised patients will be performed. For  
13  
14 patients with missing outcome data, a carry-forward of the last observed response will be  
15  
16 used. The individual patient data will be sought from the original source or the published trial  
17  
18 reports when the individual patient data are unavailable.  
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#### 22 Assessment of heterogeneity

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24 We will use the random-effect or fixed-effect model for the meta-analysis according to the  
25  
26 data analysis. If a meta-analysis is possible, we will use the  $I^2$  statistic to quantify the  
27  
28 inconsistencies among the included studies. According to the guidance given in *the Cochrane*  
29  
30 *Handbook for Systematic Reviews of Interventions*, 50% will be the cut-off point for  
31  
32 meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis  
33  
34 to explore the possible causes.<sup>15</sup>  
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#### 42 Assessment of reporting biases

43  
44 If a sufficient number of included studies (at least 10 trials) are available, we will use funnel  
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46 plots to detect reporting biases.<sup>16</sup> However, funnel plot asymmetry is not the same as  
47  
48 publication bias; therefore, we will attempt to distinguish the possible reasons for the  
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50 asymmetry, such as small-study effects, poor methodological quality and true heterogeneity  
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52 in the included studies.<sup>16 17</sup>  
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#### 57 Data synthesis

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4 The differences between the intervention and control groups will be assessed. The relative  
5 risk (RR) and 95% confidence intervals will be assessed for the effect size of each included  
6 study. All of the statistical analyses will be conducted using Cochrane Collaboration's  
7 software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen,  
8 The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient  
9 information, we will contact the corresponding authors to acquire and verify the data when  
10 possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the  
11 included studies. Unless excessive statistical heterogeneity is present, we will then pool the  
12 data across studies for a meta-analysis using a random-effects or fixed-effect model.  
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#### 24 25 26 Subgroup analysis and investigation of heterogeneity

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28 If there are an adequate number of studies, we will conduct subgroup analyses to interpret the  
29 heterogeneity between the studies, including the following:  
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- 32 1. Bee-venom therapy used alone or as combination therapy with bee-venom and  
33 conventional therapy;  
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- 36 2. Type of control.  
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#### 41 42 Sensitivity analysis

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44 Sensitivity analysis will be conducted according to the following criteria:  
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- 46 1. Methodological quality (sequence generation, allocation concealment, or blinding);  
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- 49 2. Sample size (small sample studies, e.g., less than 30 subjects in each group, or large  
50 sample studies, e.g., more than 30 subjects in each group);  
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- 53 3. Analysis-related issues (e.g., processes to handle the missing data).  
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### **Ethics and dissemination**

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

### **Discussion**

This systematic review will provide a detailed summary of the current state of evidence for the effectiveness of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

For peer review only

**Contribution of authors**

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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**Conflict of interest**

None declared

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**Appendix 1. Search Strategy****MEDLINE(Pubmed)**

1. arthritis, rheumatoid
2. arthritis, juvenile rheumatoid
3. nodule, rheumatoid
4. felty\$ adj2 syndrome
5. caplan\$ adj2 syndrome
6. sjogren\$ adj2 syndrome
7. sicca adj2 syndrome
8. still\$ disease.
9. bechterew\$ disease.
10. or/1-9
11. bee venom
12. bee sting
13. wasp venom
14. bee venom acupuncture
15. bee venom therapy
16. apitoxin
17. apitherapy
18. or/11-17
19. 9 and 18

**EMBASE**

- #1 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis'
- #2 'rheumatoid arthritis juvenile'/exp OR 'rheumatoid arthritis juvenile'
- #3 'rheumatoid nodule'/exp OR 'rheumatoid nodule'
- #4 'felty syndrome'/exp OR 'felty syndrome'
- #5 'caplan syndrome'/exp OR 'caplan syndrome'
- #6 'sjogren s syndrome'/exp OR 'sjogren s syndrome'
- #7 'sicca syndrome'/exp OR 'sicca syndrome'
- #8 'still disease'/exp OR 'still disease'
- #9 'bechterew disease'/exp OR 'bechterew disease'
- #10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11 'bee venom'/exp OR 'bee venom'
- #12 'bee sting'/exp OR 'bee sting'
- #13 'wasp venom'/exp OR 'wasp venom'
- #14 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('acupuncture'/exp OR acupuncture)
- #15 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('therapy'/exp OR therapy)

#16 'bee'/exp OR bee AND ('sting'/exp OR sting) AND ('therapy'/exp OR therapy)

#17 apitoxin

#18 'apitherapy'/exp OR apitherapy

#19 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#20 #10 AND #19

### The Cochrane Library (Wiley InterScience)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\* or reumat\* or revmarthrit\*) near/3(arthrit\* or artrit\* or diseas\* or condition\* or nodule\*)):ti,ab,kw

#3 felty\* NEAR/2 syndrome:ti,ab,kw

#4 caplan\* NEAR/2 syndrome:ti,ab,kw

#5 sjogren\* near/2 syndrome:ti,ab,kw

#6 sicca near/2 syndrome:ti,ab,kw

#7 still\* next disease:ti,ab,kw

#8 bechterew\$ disease

#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

#10 MeSH descriptor: [Bee venoms] explode all trees

#11 bee venom\* :ti,ab,kw

#12 bee sting\* :ti,ab,kw

#13 wasp venom\* :ti,ab,kw

#14 bee venom\* acupuncture :ti,ab,kw

#15 bee venom\* therapy:ti,ab,kw

#16 bee sting\* therapy:ti,ab,kw

#17 apitoxin:ti,ab,kw

#18 apitherapy:ti,ab,kw

#19 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)

#20 #9 AND #19

### CINAHL (EBSCOhost)

S1 (MM "Arthritis, Rheumatoid+") OR (MM "Arthritis, Juvenile Rheumatoid") OR (MM "Rheumatoid Nodule")

S2 (MM "Caplan syndrome") OR (MM "Felty's Syndrome") OR (MM "Still's Disease, Adult-Onset")

S3 TI arthritis N2 rheumat\* OR AB arthritis N2 rheumat\* OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI Arthritis, Juvenile Rheumatoid OR AB Arthritis, Juvenile Rheumatoid OR TI felty\* N2 syndrome OR AB felty\* N2 syndrome OR TI caplan\* N2 syndrome OR AB caplan\* N2 syndrome

S4 TI sjogren\* N2 syndrome OR AB sjogren\* N2 syndrome OR TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew\* disease OR AB bechterew\* disease

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4 S5 S1 OR S2 OR S3 OR S4

5 S6 (MM"Apitherapy")

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7 S7 TI bee venom\* OR AB bee venom\* OR TI bee sting\* OR AB bee sting\* OR TI wasp venom\* OR AB wasp  
8 venom\* OR TI bee venom\* acupuncture OR AB bee venom\* acupuncture OR TI bee venom\* therapy OR AB  
9 bee venom\* therapy

10  
11 S8 TI apitherap\* OR AB apitherap\* OR TI apitoxin\* OR AB apitoxin\*

12 S9 S6 OR S7 OR S8

13 S10 S5 AND S9

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18 **AMED (EBSCOhost)**

19 S1 TX Arthritis, Rheumatoid OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI arthritis N2 rheumat\*  
20 OR AB arthritis N2 rheumat\* OR TI felty\* N2 syndrome OR AB felty\* N2 syndrome OR TI caplan\* N2  
21 syndrome OR AB caplan\* N2 syndrome OR TI sjogren\* N2 syndrome OR AB sjogren\* N2 syndrome

22 S2 TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew\* disease OR AB bechterew\* disease

23 S3 S1 OR S2

24 S4 TI bee venom OR AB bee venom OR TI bee sting OR AB bee sting OR TI wasp venom OR AB wasp  
25 venom

26 S5 TI apitoxin OR AB apitoxin TI apitherapy OR AB apitherapy

27 S6 bee venom therapy OR bee venom acupuncture

28 S7 S4 OR S5 OR S6

29 S8 S3 AND S7  
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# BMJ Open

## Bee Venom Acupuncture for Rheumatoid Arthritis: A Systematic Review Protocol

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Complete List of Authors:	Lee, Ju Ah; Korea Institute of Oriental Medicine, Son, Mi-Ju; Korea Institute of Oriental Medicine, Literature & Informatics Research Division Choi, Jiae; Korea Institute of Oriental Medicine, Yun, Kyung-Jin; Korea Institute of Oriental Medicine, Jun, Ji Hee; Korea Institute of Oriental Medicine, Lee, Myeong Soo; Korea Institute of Oriental Medicine,
<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Rheumatology
Keywords:	COMPLEMENTARY MEDICINE, RHEUMATOLOGY, PAIN MANAGEMENT

SCHOLARONE™  
Manuscripts

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4 **Bee Venom Acupuncture for Rheumatoid Arthritis:**  
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7 **A Systematic Review Protocol**  
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12 Ju Ah Lee, Mi Ju Son, Jiae Choi, Kyung-Jin Yun, Ji Hee Jun, Myeong Soo Lee\*  
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17 *Korea Institute of Oriental Medicine, Daejeon, South Korea*  
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21 **Short title:** A protocol of systematic review of bee venom acupuncture for RA  
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## Abstract

**Introduction:** This systematic review aims to analyse the trial data on the effects of bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

**Methods and analysis:** The following 15 databases will be searched from their inception to March 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, CINAHL, 6 Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database, China Proceedings of Conference Full Text Database, and Century Journal Project), Wanfang and VIP. The methodological quality will be assessed using the Cochrane risk of bias tool.

**Dissemination:** The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print.

**Trial registration number:** PROSPERO 2013: CRD42013005853

**Key words:** Bee venom acupuncture, rheumatoid arthritis, complementary and alternative medicine, systematic review

## Article focus

- This systematic review aims to analyse the trial data on the effects of bee venom acupuncture for rheumatoid arthritis.

## Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.



### Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.
- A possible weakness may be the quality of the trials that we identify because the complementary and alternative medicine research field has not been explored deeply.

## Introduction

### *Description of the condition*

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that results in the destruction of the musculoskeletal system. The disease is often progressive and results in pain, stiffness, and joint swelling. In late stages, deformity and ankylosis develop. Because of the complex, systemic nature of the disease, RA treatment is also complex and involves a variety of approaches. The major goals are to relieve pain, reduce inflammation, slow or stop joint damage, prevent disability, and preserve or improve the person's sense of well-being and ability to function.<sup>1</sup>

Untreated RA leads to joint destruction, functional limitation and severe disability<sup>2,3</sup> and has a significant impact on health-related quality of life (HRQoL).<sup>4,5</sup>

### *Description of the intervention*

Bee venom (BV) therapy has been used since ancient times, including the administration of honeybee stings, BV injection, and BV acupuncture (BVA).<sup>6</sup> Bee venom acupuncture (BVA) involves injecting purified, diluted bee venom into acupoints or ashi-points on the body.<sup>7</sup>

### *How the intervention might work*

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritis, and anti-cancer effects through multiple mechanisms, such as the activation of the central inhibitory and excitatory systems and modulation of the immune system.<sup>8</sup> The analgesic effects of BVA have been reported in animal experiments<sup>9,10</sup> and in the clinic.<sup>7,11</sup>

In many countries, including the United States, BV therapy has been used to treat multiple sclerosis and arthritis.<sup>12,13</sup> However, most of these therapeutic uses are not based on evidence.

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4 ***Why is performing this review important?***  
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6 Currently, BVA for RA is widely used as an effective method. However, there is no critically  
7 appraised evidence, such as a systematic review or meta-analysis, of the potential benefits  
8 and harm of BVA for RA. A comprehensive evaluation of the effects of BVA for RA will  
9 help manage patients using BVA treatment.  
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17 ***Objectives***  
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19 We will perform a systematic review to assess the effects of BVA for treating RA.  
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## Methods

### *Criteria for including studies in this review*

#### Types of studies

All prospective randomised controlled clinical trials (RCTs) and quasi-RCTs will be included.

#### Types of participants

Patients suffering from RA will be included.

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We will include RCTs of BV injection at acupoints or ashi-points on the body as the sole treatment or as an adjunct to other treatments if the control group received the same treatment as the BVA group. Trials comparing BVA with any type of control intervention will be included. We will exclude trials of BV injection into parts of the body or ashi-points. Trials will also be excluded if only immunological or biological parameters were assessed. We will also exclude trials comparing 2 different types of BVA.

#### Types of outcome measures

##### *Primary outcomes*

Symptom (morning stiffness, pain, and joint swelling) evaluation

##### *Secondary outcomes*

The number of joints affected by RA

Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

1  
2  
3  
4 C-reactive protein (CRP)  
5

6 Rheumatoid factor (RF)  
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### 10 *Search methods for identifying the studies*

#### 11 Electronic searches

12  
13 We will search for trials in the following electronic databases from their inception to March  
14  
15 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL),  
16  
17 AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean  
18  
19 Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed,  
20  
21 Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China  
22  
23 Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database,  
24  
25 China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and  
26  
27 VIP.  
28  
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31

#### 32 Searching other resources

33  
34 We will also perform non-electronic searches of conference proceedings, our own files of  
35  
36 articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal  
37  
38 of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of  
39  
40 Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental  
41  
42 Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and  
43  
44 Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean  
45  
46 Oriental Internal Medicine).  
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#### 52 Search strategy

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4 The strategy for searching the MEDLINE database is presented in appendix 1. Similar search  
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6 strategies will be applied for the other databases.  
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### 10 ***Data collection and analysis***

#### 11 Study selection

12  
13 The data screening and selection process will be performed independently by four authors  
14  
15 and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements  
16  
17 on the selection are not resolved through discussions, the arbiter (MSL) will decide. No  
18  
19 language restrictions will be imposed. Hard copies of all articles will be obtained and read in  
20  
21 full. The details of selection process will be shown in PRISMA flow diagram (Figure 1).  
22  
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#### 28 Data extraction and management

29  
30 The data extraction and quality assessment will be conducted by three authors (JAL, MJS and  
31  
32 JHJ) using a predefined data extraction form.  
33  
34

35 Any disagreement among the authors will be resolved by discussion with all of the authors.  
36  
37 When the reported data are insufficient or ambiguous, MSL will contact the corresponding  
38  
39 authors by e-mail or telephone to request additional information or clarification.  
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#### 44 Assessment of bias in the included studies

45  
46 We will independently assess bias in the included studies according to the criteria from the  
47  
48 Cochrane Handbook version 5.1.0, which include random sequence generation, allocation  
49  
50 concealment, blinding of participants and personnel, blinding of outcome assessment,  
51  
52 incomplete outcome data, selective reporting and other sources of bias.<sup>14</sup> The quality of each  
53  
54 trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact  
55  
56 the authors of the assessed trials for clarification. We will resolve any differences in opinion  
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4 through discussion or consultation with a third author.  
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#### 8 Measurement of the treatment effect 9

10 For the continuous data, we will use the mean difference (MD) with 95% confidence  
11 intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs.  
12

13 In the case of outcome variables with different scales, we will use the standard mean  
14 difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect  
15 as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.  
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#### 24 Unit of analysis issues 25

26 For cross-over trials, data from the first treatment period will be used. For trials in which  
27 more than one control group was assessed, the primary analysis will combine the data from  
28 each control group. Subgroup analyses of the control groups will also be performed. Each  
29 patient will be counted only once in the analysis  
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#### 46 Dealing with the missing data 47

48 We will contact the original authors for missing data whenever possible. If it is not possible  
49 to get the missing data, we will only analyse the available data.  
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#### 56 Assessment of heterogeneity 57

58 We will use the random-effect or fixed-effect model for the meta-analysis according to the  
59 data analysis. If a meta-analysis is possible, we will use the  $I^2$  statistic to quantify the  
60 inconsistencies among the included studies. According to the guidance given in the Cochrane  
Handbook for Systematic Reviews of Interventions, 50% will be the cut-off point for

1  
2  
3  
4 meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis  
5  
6 to explore the possible causes.<sup>15</sup>  
7  
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9

#### 10 Assessment of reporting biases

11  
12 If a sufficient number of included studies (at least 10 trials) are available, we will use funnel  
13  
14 plots to detect reporting biases.<sup>16</sup> However, funnel plot asymmetry is not the same as  
15  
16 publication bias; therefore, we will attempt to distinguish the possible reasons for the  
17  
18 asymmetry, such as small-study effects, poor methodological quality and true heterogeneity  
19  
20 in the included studies.<sup>16 17</sup>  
21  
22  
23  
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#### 26 Data synthesis

27  
28 The differences between the intervention and control groups will be assessed. The relative  
29  
30 risk (RR) and 95% confidence intervals will be assessed for the effect size of each included  
31  
32 study. All of the statistical analyses will be conducted using Cochrane Collaboration's  
33  
34 software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen,  
35  
36 The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient  
37  
38 information, we will contact the corresponding authors to acquire and verify the data when  
39  
40 possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the  
41  
42 included studies. Unless excessive statistical heterogeneity is present, we will then pool the  
43  
44 data across studies for a meta-analysis using a random-effects or fixed-effect model.  
45  
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#### 50 Subgroup analysis and investigation of heterogeneity

51  
52 If the data are available, we will conduct subgroup analyses to assess the heterogeneity  
53  
54 between the studies, including the following:  
55

- 56 1. Type of BVA;  
57  
58  
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1  
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4 2. Type of control.  
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6 3. Duration of RA  
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8 4. Laterality of RA; bilateral RA vs. unilateral RA  
9

10 Sensitivity analysis  
11

12 Sensitivity analysis will be conducted according to the following criteria:  
13

- 14  
15 1. Sample size (small sample studies, e.g., less than 40 subjects in each group, or large  
16  
17 sample studies, e.g., more than 40 subjects in each group);  
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19 2. Analysis-related issues (e.g., processes to handle the missing data).  
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### **Ethics and dissemination**

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

### **Discussion**

This systematic review will provide a detailed summary of the current state of evidence for the effects of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

**Contribution of authors**

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

**Funding**

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**Conflict of interest**

None declared

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**Figure legends**

**Figure 1.** Study selection flow diagram

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Adverse effects likely to be related to RA

Quality of life

Erythrocyte sedimentation rate (ESR)

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2  
3  
4 C-reactive protein (CRP)

5  
6 Rheumatoid factor (RF)

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10  
11 *Search methods for identifying the studies*

12  
13 Electronic searches

14  
15 We will search for trials in the following electronic databases from their inception to March  
16  
17 2014: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL),  
18  
19 AMED, and CINAHL. We will also search 6 Korean medical databases (OASIS, Korean  
20  
21 Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed,  
22  
23 Korean Medical Database, and DBPIA), and 3 Chinese databases including CNKI (China  
24  
25 Academic Journal, China Doctoral Dissertations and Master's Theses Full-text Database,  
26  
27 China Proceedings of Conference Full Text Database, Century Journal Project), Wanfang and  
28  
29 VIP.  
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31

32  
33  
34  
35 Searching other resources

36  
37 We will also perform non-electronic searches of conference proceedings, our own files of  
38  
39 articles, and 9 Korean traditional medical journals (Journal of Korean Medicine, The Journal  
40  
41 of Korean Acupuncture and Moxibustion Society, Korean Journal of Acupuncture, Journal of  
42  
43 Acupuncture and Meridian Studies, Journal of Pharmacopuncture, Journal of Oriental  
44  
45 Rehabilitation Medicine, The Journal of Korea Chuna Manual Medicine for Spine and  
46  
47 Nerves, Korean Journal of Oriental Physiology and Pathology and The Journal of Korean  
48  
49 Oriental Internal Medicine).  
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55 Search strategy  
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4 The strategy for searching the MEDLINE database is presented in appendix 1. Similar search  
5  
6 strategies will be applied for the other databases.  
7  
8

### 9 10 *Data collection and analysis*

#### 11 Study selection

12  
13 The data screening and selection process will be performed independently by four authors  
14  
15 and will be verified by the fifth author (JHJ), who is fluent in Chinese. When disagreements  
16  
17 on the selection are not resolved through discussions, the arbiter (MSL) will decide. No  
18  
19 language restrictions will be imposed. Hard copies of all articles will be obtained and read in  
20  
21 full. The details of selection process will be shown in PRISMA flow diagram (Figure 1).  
22  
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#### 28 Data extraction and management

29  
30 The data extraction and quality assessment will be conducted by three authors (JAL, MJS and  
31  
32 JHJ) using a predefined data extraction form.  
33

34  
35 Any disagreement among the authors will be resolved by discussion with all of the authors.  
36  
37 When the reported data are insufficient or ambiguous, MSL will contact the corresponding  
38  
39 authors by e-mail or telephone to request additional information or clarification.  
40  
41  
42

#### 43 Assessment of bias in the included studies

44  
45 We will independently assess bias in the included studies according to the criteria from the  
46  
47 Cochrane Handbook version 5.1.0, which include random sequence generation, allocation  
48  
49 concealment, blinding of participants and personnel, blinding of outcome assessment,  
50  
51 incomplete outcome data, selective reporting and other sources of bias.<sup>14</sup> The quality of each  
52  
53 trial will be categorised into a low, unclear, or high risk of bias. If necessary, we will contact  
54  
55 the authors of the assessed trials for clarification. We will resolve any differences in opinion  
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4 through discussion or consultation with a third author.  
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7

#### 8 Measurement of the treatment effect 9

10 For the continuous data, we will use the mean difference (MD) with 95% confidence  
11 intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs.  
12

13 In the case of outcome variables with different scales, we will use the standard mean  
14 difference (SMD) with 95% CIs. For dichotomous data, we will present the treatment effect  
15 as a relative risk (RR) with 95% CIs. We will convert other binary data into a RR value.  
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#### 24 Unit of analysis issues 25

26 For cross-over trials, data from the first treatment period will be used. For trials in which  
27 more than one control group was assessed, the primary analysis will combine the data from  
28 each control group. Subgroup analyses of the control groups will also be performed. Each  
29 patient will be counted only once in the analysis  
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#### 37 Dealing with the missing data 38

39 We will contact the original authors for missing data whenever possible. If it is not possible  
40 to get the missing data, we will only analyse the available data.  
41  
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45

#### 46 Assessment of heterogeneity 47

48 We will use the random-effect or fixed-effect model for the meta-analysis according to the  
49 data analysis. If a meta-analysis is possible, we will use the  $I^2$  statistic to quantify the  
50 inconsistencies among the included studies. According to the guidance given in the Cochrane  
51 Handbook for Systematic Reviews of Interventions, 50% will be the cut-off point for  
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1  
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4 meaningful heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis  
5  
6 to explore the possible causes.<sup>15</sup>  
7  
8  
9

#### 10 Assessment of reporting biases

11  
12 If a sufficient number of included studies (at least 10 trials) are available, we will use funnel  
13  
14 plots to detect reporting biases.<sup>16</sup> However, funnel plot asymmetry is not the same as  
15  
16 publication bias; therefore, we will attempt to distinguish the possible reasons for the  
17  
18 asymmetry, such as small-study effects, poor methodological quality and true heterogeneity  
19  
20 in the included studies.<sup>16 17</sup>  
21  
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24

#### 25 Data synthesis

26  
27  
28 The differences between the intervention and control groups will be assessed. The relative  
29  
30 risk (RR) and 95% confidence intervals will be assessed for the effect size of each included  
31  
32 study. All of the statistical analyses will be conducted using Cochrane Collaboration's  
33  
34 software program, Review Manager (RevMan), Version 5.2.7 for Windows (Copenhagen,  
35  
36 The Nordic Cochrane Centre, the Cochrane Collaboration 2012). For studies with insufficient  
37  
38 information, we will contact the corresponding authors to acquire and verify the data when  
39  
40 possible. Chi-squared and I-squared tests will be used to evaluate the heterogeneity of the  
41  
42 included studies. Unless excessive statistical heterogeneity is present, we will then pool the  
43  
44 data across studies for a meta-analysis using a random-effects or fixed-effect model.  
45  
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48

#### 49 Subgroup analysis and investigation of heterogeneity

50  
51  
52 If the data are available, we will conduct subgroup analyses to assess the heterogeneity  
53  
54 between the studies, including the following:

55  
56  
57 1. Type of BVA;  
58  
59  
60

1  
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4 2. Type of control.  
5

6 3. Duration of RA  
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8 4. Laterality of RA; bilateral RA vs. unilateral RA  
9

10 Sensitivity analysis  
11

12 Sensitivity analysis will be conducted according to the following criteria:  
13

- 14  
15 1. Sample size (small sample studies, e.g., less than 40 subjects in each group, or large  
16  
17 sample studies, e.g., more than 40 subjects in each group);  
18  
19 2. Analysis-related issues (e.g., processes to handle the missing data).  
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### **Ethics and dissemination**

Ethical approval is not required, given that this protocol is for a systematic review. The findings of this review will be disseminated widely through peer-reviewed publications and conference presentations.

### **Discussion**

This systematic review will provide a detailed summary of the current state of evidence for the effects of BVA in treating symptoms in RA patients. The review will benefit patients and practitioners in the fields of traditional and complementary medicine.

**Contribution of authors**

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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**Conflict of interest**

None declared

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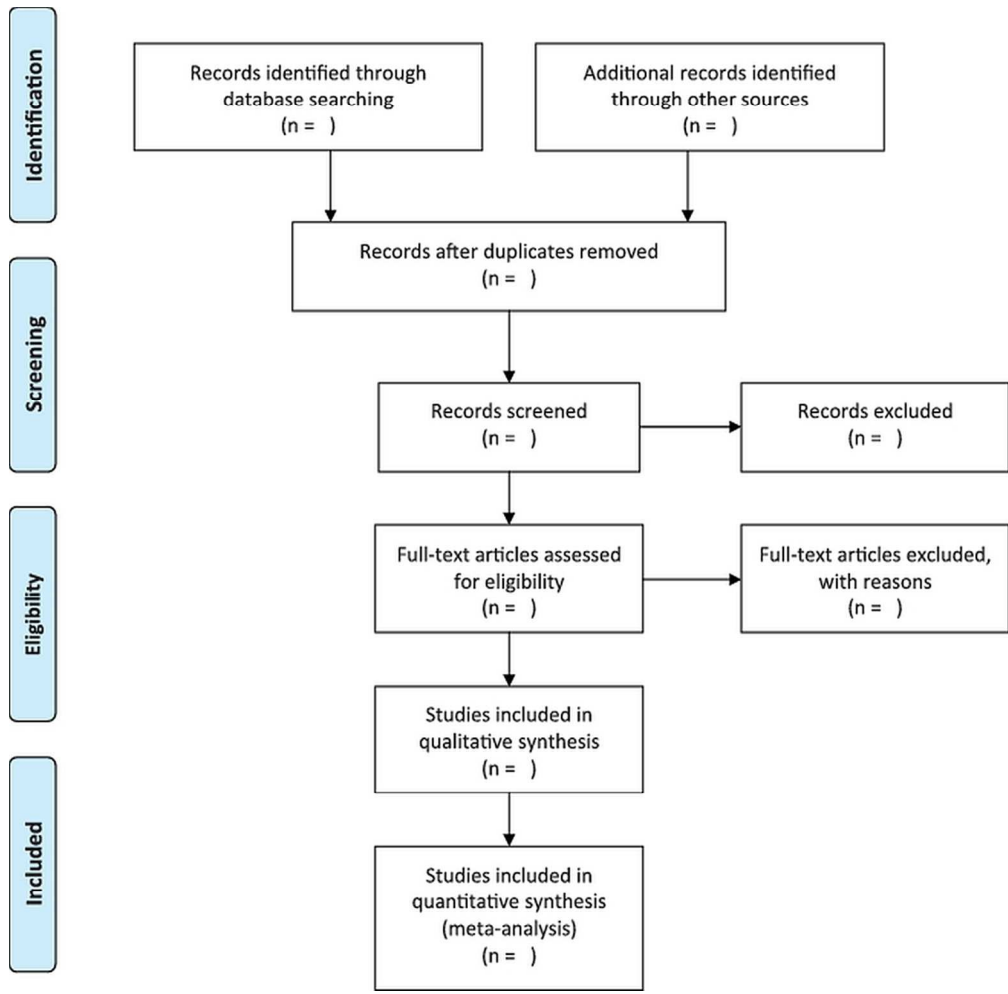
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4 **Figure legends**  
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6 **Figure 1.** Study selection flow diagram  
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For peer review only

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90x88mm (300 x 300 DPI)

Preprint



**Appendix 1. Search Strategy****MEDLINE(Pubmed)**

1. arthritis, rheumatoid
2. arthritis, juvenile rheumatoid
3. nodule, rheumatoid
4. felty\$ adj2 syndrome
5. caplan\$ adj2 syndrome
6. sjogren\$ adj2 syndrome
7. sicca adj2 syndrome
8. still\$ disease.
9. bechterew\$ disease.
10. or/1-9
11. bee venom
12. bee sting
13. wasp venom
14. bee venom acupuncture
15. bee venom therapy
16. apitoxin
17. apitherapy
18. or/11-17
19. 9 and 18

**EMBASE**

- #1 'rheumatoid arthritis'/exp OR 'rheumatoid arthritis'
- #2 'rheumatoid arthritis juvenile'/exp OR 'rheumatoid arthritis juvenile'
- #3 'rheumatoid nodule'/exp OR 'rheumatoid nodule'
- #4 'felty syndrome'/exp OR 'felty syndrome'
- #5 'caplan syndrome'/exp OR 'caplan syndrome'
- #6 'sjogren s syndrome'/exp OR 'sjogren s syndrome'
- #7 'sicca syndrome'/exp OR 'sicca syndrome'
- #8 'still disease'/exp OR 'still disease'
- #9 'bechterew disease'/exp OR 'bechterew disease'
- #10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11 'bee venom'/exp OR 'bee venom'
- #12 'bee sting'/exp OR 'bee sting'
- #13 'wasp venom'/exp OR 'wasp venom'
- #14 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('acupuncture'/exp OR acupuncture)
- #15 'bee'/exp OR bee AND ('venom'/exp OR venom) AND ('therapy'/exp OR therapy)

1  
2  
3  
4 #16 'bee'/exp OR bee AND ('sting'/exp OR sting) AND ('therapy'/exp OR therapy)

5 #17 apitoxin

6 #18 'apitherapy'/exp OR apitherapy

7 #19 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

8 #20 #10 AND #19

9  
10  
11  
12  
13 **The Cochrane Library (Wiley InterScience)**

14 #1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

15 #2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat\* or reumat\* or

16 revmarthrit\*) near/3(arthrit\* or artrit\* or diseas\* or condition\* or nodule\*)):ti,ab,kw

17 #3 felty\* NEAR/2 syndrome:ti,ab,kw

18 #4 caplan\* NEAR/2 syndrome:ti,ab,kw

19 #5 sjogren\* near/2 syndrome:ti,ab,kw

20 #6 sicca near/2 syndrome:ti,ab,kw

21 #7 still\* next disease:ti,ab,kw

22 #8 bechterew\$ disease

23 #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

24 #10 MeSH descriptor: [Bee venoms] explode all trees

25 #11 bee venom\* :ti,ab,kw

26 #12 bee sting\* :ti,ab,kw

27 #13 wasp venom\* :ti,ab,kw

28 #14 bee venom\* acupuncture :ti,ab,kw

29 #15 bee venom\* therapy:ti,ab,kw

30 #16 bee sting\* therapy:ti,ab,kw

31 #17 apitoxin:ti,ab,kw

32 #18 apitherapy:ti,ab,kw

33 #19 (#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)

34 #20 #9 AND #19

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46 **CINAHL (EBSCOhost)**

47 S1 (MM "Arthritis, Rheumatoid+") OR (MM "Arthritis, Juvenile Rheumatoid") OR (MM "Rheumatoid

48 Nodule")

49 S2 (MM "Caplan syndrome") OR (MM "Felty's Syndrome") OR (MM "Still's Disease, Adult-Onset")

50 S3 TI arthritis N2 rheumat\* OR AB arthritis N2 rheumat\* OR TI rheumatoid nodule OR AB rheumatoid nodule

51 OR TI Arthritis, Juvenile Rheumatoid OR AB Arthritis, Juvenile Rheumatoid OR TI felty\* N2 syndrome OR

52 AB felty\* N2 syndrome OR TI caplan\* N2 syndrome OR AB caplan\* N2 syndrome

53 S4 TI sjogren\* N2 syndrome OR AB sjogren\* N2 syndrome OR TI sicca N2 syndrome OR AB sicca N2

54 syndrome OR TI bechterew\* disease OR AB bechterew\* disease

1  
2  
3  
4 S5 S1 OR S2 OR S3 OR S4

5 S6 (MM"Apitherapy")

6  
7 S7 TI bee venom\* OR AB bee venom\* OR TI bee sting\* OR AB bee sting\* OR TI wasp venom\* OR AB wasp  
8 venom\* OR TI bee venom\* acupuncture OR AB bee venom\* acupuncture OR TI bee venom\* therapy OR AB  
9 bee venom\* therapy

10  
11 S8 TI apitherap\* OR AB apitherap\* OR TI apitoxin\* OR AB apitoxin\*

12 S9 S6 OR S7 OR S8

13 S10 S5 AND S9

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18 **AMED (EBSCOhost)**

19 S1 TX Arthritis, Rheumatoid OR TI rheumatoid nodule OR AB rheumatoid nodule OR TI arthritis N2 rheumat\*

20 OR AB arthritis N2 rheumat\* OR TI felty\* N2 syndrome OR AB felty\* N2 syndrome OR TI caplan\* N2

21 syndrome OR AB caplan\* N2 syndrome OR TI sjogren\* N2 syndrome OR AB sjogren\* N2 syndrome

22 S2 TI sicca N2 syndrome OR AB sicca N2 syndrome OR TI bechterew\* disease OR AB bechterew\* disease

23 S3 S1 OR S2

24 S4 TI bee venom OR AB bee venom OR TI bee sting OR AB bee sting OR TI wasp venom OR AB wasp  
25 venom

26 S5 TI apitoxin OR AB apitoxin TI apitherapy OR AB apitherapy

27 S6 bee venom therapy OR bee venom acupuncture

28 S7 S4 OR S5 OR S6

29 S8 S3 AND S7  
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