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BMJ Open Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials

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To cite: Lee JA, Son MJ, Choi J, *et al*. Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials. *BMJ Open* 2014;**4**:e006140. doi:10.1136/bmjopen-2014-006140

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2014-006140>).

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Received 18 July 2014
Revised 14 October 2014
Accepted 15 October 2014



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ABSTRACT

Objective: To assess the clinical evidence for bee venom acupuncture (BVA) for rheumatoid arthritis (RA).

Design: Systematic review of randomised controlled trials (RCTs).

Setting: We searched 14 databases up to March 2014 without a language restriction.

Participants: Patients with RA.

Intervention: BVA involved injecting purified, diluted BV into acupoints. We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone.

Primary outcomes: Morning stiffness, pain and joint swelling

Secondary outcomes: Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor, the number of joints affected by RA and adverse effects likely related to RA.

Results: A total of 304 potentially relevant studies were identified; only one RCT met our inclusion criteria. Compared with placebo, BVA may more effectively improve joint pain, swollen joint counts, tender joint counts, ESR and CRP but was not shown to improve morning stiffness.

Conclusions: There is low-quality evidence, based on one trial, that BVA can significantly reduce pain, morning stiffness, tender joint counts, swollen joint counts and improve the quality of life of patients with RA compared with placebo (normal saline injection) control. However, the number of trials, their quality and the total sample size were too low to draw firm conclusions.

Trial registration number: PROSPERO 2013: CRD42013005853.

INTRODUCTION

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that results in pain and stiffness, joint swelling, deformity of joints and the development of ankylosis. The complex, systemic nature of the disease makes RA treatment complex and involves a variety of approaches. The

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 was conducted independently by two authors.
- Use of the GRADE approach to assess confidence in estimates of effect.
- We identified only one study, hence we could not draw strong conclusions.

major aims of treatment are to relieve pain and swelling, reduce inflammation and joint damage, prevent disability and preserve or improve patients' well-being and function.¹

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

Description of the intervention

Bee venom (BV) therapy has been used since ancient times. Different forms of the therapy include the administration of live bee stings, injections of BV and BV acupuncture (BVA).⁶ BVA involves injecting purified and diluted BV into acupoints.⁷

How the intervention might work

BVA exhibits several pharmacological actions, including analgesic, anti-inflammatory, anti-arthritis and anticancer effects through multiple mechanisms, such as activation of the central inhibitory and excitatory systems and modulation of the immune system.⁸ The analgesic effects of BVA have been reported in animal experiments^{9 10} and clinical settings.^{7 11} According to animal experiments, BV exhibits antiarthritic, anti-inflammatory and analgesic effects attributable to the suppression of cyclo-oxygenase-2 and phospholipase A2 expression and a decrease in the levels of tumour necrosis factor α , interleukin (IL)-1, IL-6, nitric oxide and

oxygen-reactive species. It is also widely assumed that bioactive BV compounds, including enzymes (phospholipase A2), peptides (melittin, adolapin and apamin), and amines are associated with these actions.^{7 8 12-14} However, most therapeutic uses are not based on evidence.

One study was conducted to elucidate whether the synergistic antiarthritic effects produced by a combination of BV and conventional therapy enhances the therapeutic potency and minimises the adverse effects of methotrexate.¹⁵

Why this review is important

BV therapy or BVA has been used for reducing pain caused by inflammatory diseases such as osteoarthritis and RA in some Asian countries.¹¹

However, there is no critically appraised evidence, such as a systematic review or meta-analysis, of the potential benefits and risks of BVA for RA. A comprehensive evaluation of the efficacy and safety of BVA for RA will inform the recommendation to patients to pursue BVA treatment.

Objectives

Although BVA for RA is used as an effective method for reducing RA-related symptoms and improving functioning, there is no critically appraised evidence regarding the safety and effectiveness of BVA for RA from a systematic review or meta-analysis.

We performed a systematic review to assess the safety and efficacy of BVA for the treatment of RA.

MATERIALS AND METHODS

The protocol of this SR is registered on PROSPERO 2013 (registration number: CRD42013005853) and published as a protocol.¹⁶

Data source

The following electronic databases were searched from the study's inception to March 2014: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED and CINAHL. We also searched six Korean medical databases (OASIS, Korean Traditional Knowledge Portal, Korean Studies Information Service System, KoreaMed, Korean Medical Database and DBPIA) and three 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 the Century Journal Project), Wanfang and VIP. Further, we conducted non-electronic searches of conference proceedings, our own files of articles and nine 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 Nerves, *Korean Journal of Oriental Physiology and Pathology* and *The Journal of Korean Oriental Internal Medicine*). The strategy for searching the MEDLINE, EMBASE, Cochrane Library, and CINAHL database is presented in online supplement 1. Similar search strategies were applied for other databases.

Types of studies

All prospective, randomised controlled clinical trials (RCTs) were included if they were randomised studies of BV injections 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 were also included. We excluded trials of BV injections into parts of the body other than acupoints. Trials were also excluded if only immunological or biological parameters were assessed. Trials comparing two different types of BVA were also excluded. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

Types of participants

Patients suffering from RA were included.

Types of interventions

We included trials on BVA used alone or in combination with a conventional therapy versus the conventional therapy alone. BVA involved injecting purified, diluted BV into acupoints. Conventional therapies included medications such as non-steroidal anti-inflammatory drugs, steroids, disease-modifying antirheumatic drugs, immunosuppressants and TNF- α inhibitors.

Types of outcomes measured

Primary outcomes were symptoms (morning stiffness, pain and joint swelling) experienced. Secondary outcomes included erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor, the number of joints affected by RA and adverse effects likely related to RA.

Data extraction and quality assessment

Hard copies of all articles were obtained and read in full. Two authors (MJS and JHJ) performed the data extraction and quality assessment using a predefined data extraction form. The risk of bias was assessed using the assessment tool for risk of bias from the Cochrane Handbook V.5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.¹⁷ Our review used 'L', 'U' and 'H' as results of the assessment; 'L' indicated a low risk of bias, 'U' indicated that the risk of bias was unclear and 'H' indicated a high risk of bias. Disagreements were resolved by a discussion between all of the authors. When disagreements on the selection were not resolved through discussions, the arbiter (MSL) made the final decision.

DATA COLLECTION AND SYNTHESIS

Data extraction and management

The data extraction and quality assessment were conducted by three authors (JAL, MJS and JHJ) using a pre-defined data extraction form. Any disagreement among the authors was resolved by a discussion between all of the authors. When the data were insufficient or ambiguous, MSL contacted the corresponding authors by email or telephone to request additional information or clarification. The data screening and selection process was performed independently by four authors and then was verified by a fifth author, JHJ, who is fluent in Chinese. We used GRADEpro software in the Cochrane Systematic Reviews to create a Summary of Findings table. When disagreements on the selections were not resolved through discussions, the arbiter (MSL) made the final decision.

Assessment of bias in the included studies

We independently assessed bias in the included studies according to criteria from the Cochrane Handbook, V.5.1.0, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias.¹⁷ The quality of each trial was categorised into a low, unclear or high risk of bias, and the authors of the assessed trials were contacted for clarification as needed. We resolved any differences in opinion through discussion or consultation with a third author.

Data synthesis

The differences between the intervention and control groups were assessed. For the continuous data, we used mean differences (MDs) with 95% CIs to measure the treatment effects. We converted other forms of data into MDs. In the case of outcome variables with different scales, we used the standard mean difference (SMD) with 95% CIs. For dichotomous data, we presented the treatment effect as a relative risk (RR) with 95% CIs. We converted other binary data into an RR value.

All of the statistical analyses were conducted using Cochrane Collaboration's software programme, Review Manager (RevMan), V.5.2.7 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012). For studies with insufficient information, we contacted the corresponding authors to acquire and verify data when possible. If appropriate, we pooled data across studies for a meta-analysis using fixed effects or random effects.

Unit of analysis issues

For cross-over trials, data from the first treatment period were used. For trials in which more than one control group was assessed, the primary analysis combined the data from each control group. Subgroup analyses of the control groups were performed. Each patient was counted only once in the analysis.

Addressing the missing data

Intention-to-treat analyses that included all of the randomised patients were performed. For patients with missing outcome data, a carry-forward of the last observed response was used. The individual patient data were sought from the original source or the published trial reports when the individual patient data were initially unavailable.

Assessment of heterogeneity

We used the random-effect or fixed-effect model for the meta-analysis according to the data analysis. The χ^2 and I^2 tests were used to evaluate the heterogeneity of the included studies and $I^2 > 50$ were considered to have high heterogeneity. If heterogeneity was observed, we conducted a subgroup analysis to explore the possible causes.¹⁸

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) were available, we used funnel plots to detect reporting biases.¹⁹ However, funnel plot asymmetry was not the same as publication bias; therefore, we attempted to determine the possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity in the included studies.^{19 20}

RESULTS

Study selection and description

The search generated a total of 304 hits, of which only one met our inclusion criteria (figure 1). Thirteen RCTs were among the excluded articles for the following reasons: four RCTs, which were conducted in China, were excluded because the BVA was not made with purified, diluted BV but with live bee stings (see online supplements 2 and 3),^{21–24} four RCTs employed herbal medicine as coadministrator,^{25–28} two RCTs included herbal medicine as control treatment,^{29 30} one RCT compared two different acupoints,³¹ one RCT was not related to RA³² and one RCT was a duplicated publication.³³ The key data from the eligible RCT are summarised in table 1. This trial was conducted in Korea.³⁴

Risk of bias in the included studies

The RCT used³⁴ has an uncertain risk of bias due to its random sequence generation, allocation concealment, outcome assessment blinding, selective reporting and other biases. This study used blinding of participants and personnel employing placebo as a comparison and to address incomplete outcome data.

Outcomes

The study tested the efficacy of BVA on morning stiffness, Health Assessment Questionnaire (HAQ) scores, pain, tender joint counts, swollen joint counts, ESR and CRP in patients with RA.³⁴ Patients were randomised into two groups: one receiving BVA at ashi points and

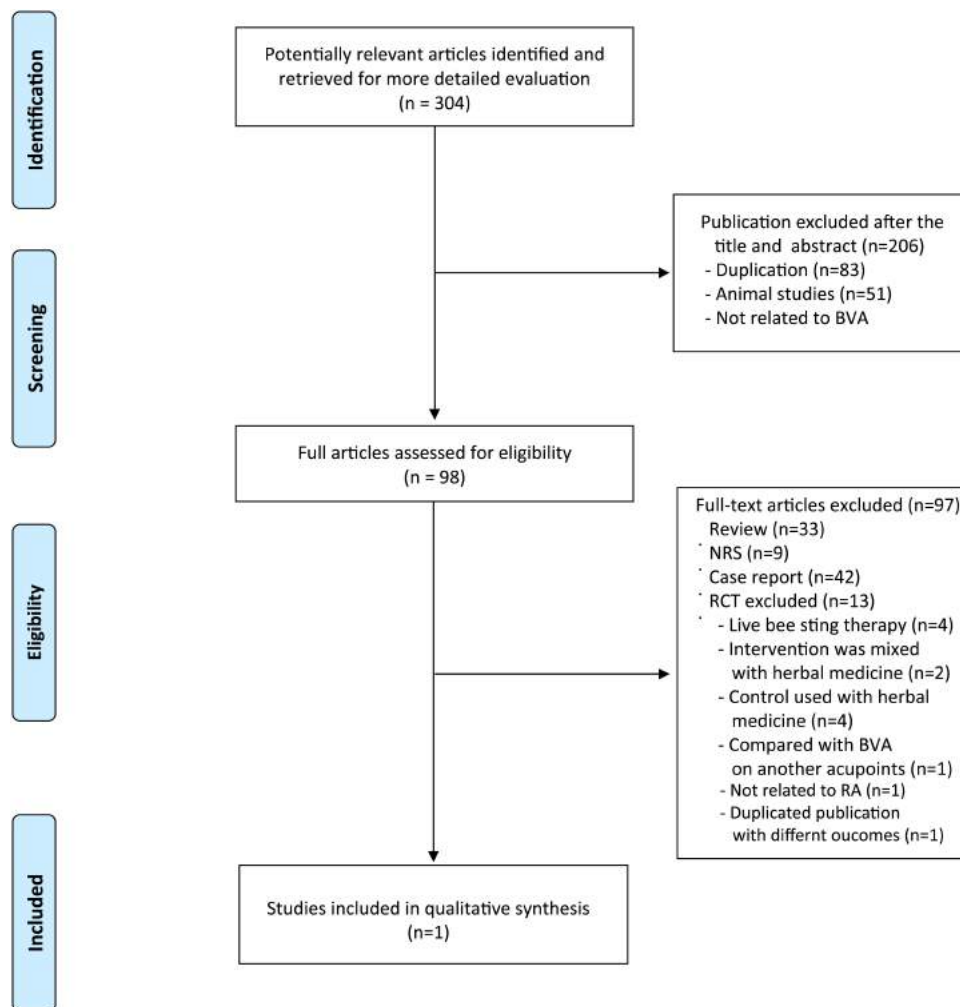


Figure 1 Flow chart of trial selection process. BVA, bee venom acupuncture; CCT, case series trials; NRS: Non-RCT; RA, rheumatoid arthritis; RCT, randomised controlled trials.

the other receiving normal saline injections at ashi points. After 2 months, the scores for morning stiffness, HAQ, pain on visual analogue scale, tender joint counts, swollen joint counts, ESR and CRP were significantly better in the BVA group than in the placebo control group.

Adverse events

This trial did not assess adverse events related to BVA used for RA.³⁴

DISCUSSION

Only one trial testing the effects of BVA for RA is currently available.³⁴ There is low-quality evidence based on this one trial that BVA significantly reduces pain, morning stiffness, tender joint counts, swollen joint counts and improves the quality of life of patients with RA compared with placebo (normal saline injection) control patients (table 2). To date, however, the effects of BVA for RA have not been confirmed because of small sample sizes and high risks of bias.

This systematic review has several limitations. First, although extensive efforts were made to retrieve all of the RCTs with no language and publication status limitations, only one study of BVA for RA qualified for our review. Second, the included RCT was conducted in East Asian countries, and studies from East Asian countries do not apply globally because of their lack of external validity. Third, Korean researchers tend to have positive results,³⁵ but we could not minimise the results because of the lack of methodology. Fourth, despite the possibility of delayed-type hypersensitivity occurring, there was no prolonged follow-up.

The included RCT used saline injections at the same acupoints used in the BVA group for the placebo control treatment.³⁴ The use of placebo is essential for differentiating non-specific from specific treatment effects. If we consider that the effects of BVA could come from stimulating acupoints with the immune-modulative effect of BV, it is necessary to implement further RCTs that use the appropriate placebo. This study has some potential caveats. One is that a normal saline injection at the same acupoints used in the experimental group could be an

Table 1 Characteristics of included randomised controlled trials of bee venom acupuncture for rheumatoid arthritis

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Methods	Design: prospective randomised controlled trial
Participants	Country: South Korea Number of patients included (completed/randomised): A. 37/40 B. 32/40 Mean age (years) A. 49.2±9.6 B. 47.3±8.9 Duration of disease (years) (A) 9.2±7.0 (B) 7.3±4.6 Follow-up: 1 and 2 months
Intervention	(A) BVA (ashi points, acupoints near the inflammation point, two times a week for 2 months)
Control	(B) Placebo (normal saline injection on ashi points, acupoints near the inflammation point, two times a week for 2 months)
Outcomes	Primary outcomes 1. Morning stiffness, MD, -0.70 (-2.00 to 0.60), p<0.05 2. HAQ, MD, 0.00 (-0.08 to 0.08), p<0.05 3. VAS-pain, MD, -18.10 (-23.71 to -12.49), p<0.05 Secondary outcomes 1. Tender joint count, MD, -1.30 (-1.91 to -0.69), p<0.0001 2. Swollen joint count, MD, -1.10 (-1.72 to -0.48), p=0.005 3. ESR, MD, 20.10 (-22.80 to -17.40), p<0.00001 4. CRP, MD, -1.90 (-2.86 to -0.94), p=0.0001
Note	Treatment rationale: TKM theory, clinical experience Adverse effect: NR Funding: Korea Research Foundation Grant and Kyung Hee University Language: Korean Publication: full paper Withdrawal/dropouts: yes Intention-to-treat: no Author comment: these results suggest that bee venom therapy could be an effective method in the treatment of patients with RA

Risk of bias

Item	Authors' judgement	Description
Random sequence generation (selection bias)	Unclear risk	Described as randomised but information not available
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) all outcomes	Low risk	Described as double blinding
Blinding of outcome assessment (detection bias), all outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias), all outcomes	High risk	Data from 11 participants were not included in the analysis
Selective reporting (reporting bias)	Low risk	Protocol not available, but all expected outcomes reported
Other bias	Unclear risk	Small sample size

BVA, bee venom acupuncture; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; MD, mean differences; NR, not reported; RA, rheumatoid arthritis; TKM, traditional Korean medicine; VAS, visual analogue scale.

inappropriate placebo. BVA combines biochemical effects of the BV and mechanical effects from the needles. As a result, this placebo could invoke mechanical effects from the acupoint injection. The other is that there was no reporting of previous experiences with

BVA. BVA has uncomfortable sensations such as swelling and burning during the treatment. Some participants who have previously experienced BVA treatment could know what they were treated with, thereby interrupting patient blinding. To use normal saline injections as a

Table 2 Summary of findings

Bee venom acupuncture for patients with rheumatoid arthritis
 Patient or population: patients with rheumatoid arthritis
 Settings: Korea
 Intervention: bee venom acupuncture vs normal saline injection as placebo

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (Grade)	Comments
	Assumed risk Control (normal saline injection)	Corresponding risk Bee venom acupuncture			
Pain (VAS)		16.9 WMD lower† (26.57 to 7.23 lower)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month −10.40 (−16.47 to −4.33)
Morning stiffness		12.1 WMD higher† (11.61 to 12.59 higher)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month −0.30 (−1.01 to 0.41)
Swollen joint count		0.9 WMD lower† (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month 0.50 (−0.70 to −1.70)
Tender joint count		0.9 WMD lower† (1.97 lower to 0.17 higher)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month 0.50 (−0.73 to −1.73)
Quality of life (HAQ)		0.3 WMD higher† (0.08 to 0.52 higher)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month 0.20 (−0.06 to 0.46)
ESR		19.4 WMD lower† (28.51 to 10.29 lower)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month −2.30 (−10.17 to 5.57)
CRP		1.7 WMD lower† (2.6 to 0.8 lower)	69 (1 study)	⊕⊕⊕⊕ low‡§	After 1 month 1.40 (−8.27 to 5.47)

GRADE Working Group grades of evidence.

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low quality: we are very uncertain about the estimate.

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†After 2 months treatment.

‡Poorly reported paper (see 'Risk of bias' table).

§Small sample size.

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; VAS, visual analogue scale; WMD, weight mean difference.

placebo, it is important to recruit patients who have not experienced BVA.

In the absence of a sufficient number of RCTs, other types of evidence might be helpful. There was one observational study that showed favourable effects of BVA for several symptoms of RA (see online supplement 4).³⁶ However, this type of study, lacking in controls, was open to selection bias, which could lead to false-positive results.

Traditional BVA includes live bee sting acupuncture. It may be more commonly used when treating patients with RA in China. In considering traditional BVA, we found four additional RCTs that compared live bee sting acupuncture combined with conventional drugs with conventional treatments alone for the treatment of RA

symptoms.^{21–24} Three RCTs^{21–23} showed favourable effects of BVA on at least one of the main outcomes including total improvement, morning stiffness, pain, joint pain or joint swelling, while one RCT failed to do so.²⁴ These RCTs did not report serious adverse effects.

Both BVA (diluted or purified) and live bee stings can also cause diverse clinical responses depending on the amount of venom used and the frequency and duration of the treatment.^{37–39} The acute or delayed adverse reaction is an inflammatory reaction, such as anaphylaxis or urticarial.^{36–40} No studies were made comparing the occurrence of adverse events between traditional live bee sting acupuncture and BVA. Although trials are conducted safely, some problems remain in using BVA in clinical practice.

The injection parts may be one issue for the assessment. Although it is very common to inject on the painful point (ashi point) in patients with RA, we excluded studies using ashi points because of only assessing the evidence of efficacy of BV on acupoint. Even if we expand the inclusion criteria to these points, no further studies were found. However, many trials used acupoints with painful points. Further comparative studies are needed for finding the difference of effects of BVA on acupoints and painful points.

One could question the validity of the conclusion by pointing to the review method used (reviewing a small number of trials with many limitations). However, reasons for doing a systematic review would be to answer questions not posted by individual studies, to settle controversies arising from apparently conflicting studies, or to generate new hypotheses.⁴¹ A systematic review with a small number of trials can be done.

In conclusion, currently, very few trials have tested the effects of BVA in the management of RA. Collectively, the evidence is insufficient to suggest that BVA is an effective therapy for RA. Further studies should be of high quality, with a particular emphasis on designing adequate and appropriate control groups.

Contributors MSL and JAL conceived and designed the review. JHJ and MJS extracted the data. MJS, JC and J-IK analysed the data. JAL, MJS, JC, J-IK and MSL wrote the paper. JHJ, MJS and JC searched and selected studies. JAL and MSL revised the paper. MSL monitored data collection.

Funding JAL, JC, JHJ and MSL were supported by Korea Institute of Oriental Medicine (K14281, K14400). MJS was supported by the same institute (K14380).

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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