

Trend Analysis of the Research on Bee Venom Acupuncture in South Korea, Based on Published Articles

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Background: This study investigated current research trends in bee venom acupuncture in Korea.

Materials and methods: The literature in Korea was reviewed using the search engines Science and Technology Society Village, Korean Studies Information Service System, National Discovery for Science Leaders, and Oriental Medicine Advanced Searching Integrated System. The keywords searched were “bee venom,” “apitoxin,” “apitherapy,” and “bee sting.” We selected 412 studies, which included Korean literary studies, experimental studies, and clinical studies.

Results: We classified them by publication year, research type, disease and topic, and quality assessment. Among bee venom-related studies, clinical studies (235 studies) outnumbered experimental studies (149 studies) and literary studies (28 studies). Nineteen experimental studies concentrated on the theme of “anticancer.” In the type analysis of clinical studies, lumbar disorders comprised 45 of 235 studies, followed by the effect on body. Forty-two randomized controlled trials (RCTs) have been published from 2003 to date (2015). Twenty-two studies used appropriate randomization methods. Fourteen studies had a Jadad score of 4–5 points; 15 studies, 1–3 points; and 13 studies, 0 points.

Conclusions: Bee venom treatment is based on Korean traditional medicine theory. Numerous research studies suggest its effectiveness. Effort and academic approach on bee venom are expected to receive a positive evaluation.

Key Words : Bee venom, Korean medicine, Pharmacopuncture

Introduction

Bee venom therapy is a new acupuncture method. It uses the effects of needling and the biochemical pharmacological reactions of bee venom in treating diseases by artificially extracting and purifying venom from the venom sac of live bees, and then injecting it into the area or the acupoints associated with a disease¹). In clinical practice, bee venom

acupuncture is applied to treat diseases such as musculoskeletal diseases, immune system diseases, and nervous system diseases through the use of its effective features such as anti-inflammatory effect, analgesic effect, and continuous thermal stimulation on the treated part, and immune function enhancement and activation²).

Under these changes, one of the largest features in the field of acupuncture in Korea is pharmacopuncture

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-related research. Bee venom acupuncture (BVA) is a treatment method that involves applying chemical stimulation and physical stimulation on the acupoints of the human body, along with the existing pharmacopuncture therapy. It originated from bee sting therapy, which has been used among ordinary people for a long time to stimulate an affected area or on acupoints with live bees. By collecting bee venom from bees with bee venom collectors and securing safety through a sterile purification process, pharmacopuncture preparations for treatment have become commercially available to Korean medicine doctors. Bee venom was successfully developed with significantly reduced allergic reaction, which is a substantial problem. In Korea, numerous studies have been conducted with this venom and good efficacy results are continuously reported³⁾. The authors aimed to report the results of an analysis on bee venom-related research studies published to date in Korea so as to investigate the current trends in research on bee venom and determine directions to move toward in the future.

Materials and Methods

1. Materials

To review current research articles, we used four databases in South Korea: Science and Technology Society Village (KISTI), Korean Studies Information Service System (KISS), National Discovery for Science Leaders (NDSL), and Oriental Medicine Advanced Searching Integrated System (OASIS). The key words were “bee venom,” “apitoxin,” “apitherapy,” and “bee sting.” Furthermore, studies published in 2015 that were not yet available in database systems were manually searched for inclusion by reviewing journals.

We included literary studies (e.g., review), experimental studies (e.g., *in vivo*, *in vitro*), and clinical studies (e.g., randomized clinical trials

[RCTs], non-RCTs, case reports or series, brief reports) on BVA. We excluded non-BVA-related studies, studies without full texts, and duplicate files. In the first step, the search focused on the titles and the abstracts. In the second step, studies were selected or extracted by reviewing the full texts.

As a result, 412 studies were selected for primary analysis. Based on the study method, clinical studies were then selected for secondary analysis. Forty-two RCTs, which excluded case studies and nonrandomized controlled trials (non-RCT), were selected for additional analysis (Figure 1).

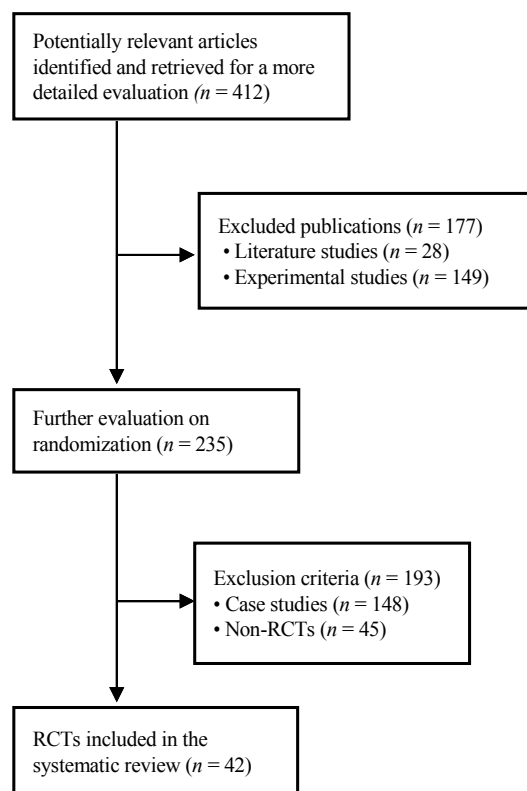


Fig. 1. Flowchart of the trial selection process.

2. Methods

Data extraction and analysis were performed by two authors (Dr. Han and Professor Lee), who read

and analyzed the full texts of the extracted data or abstracts when full texts were unavailable. The primarily selected studies were analyzed according to the year of publication and the type of study. The type of study was classified into three types: literature study, experimental study, and clinical study. A literature study was defined as a study that comprehensively investigated and described in the findings of various literature reports with respect to a certain disease or a study with a historical focus on the literature reports. An experimental study was defined as a study that released the results of experiments with animals or cells. A clinical study included case reports.

The secondarily selected RCTs were analyzed by subdividing them by general status and research quality assessment. The general status was analyzed with regard to the year of publication, target disease, bee venom treatment methods, control group setting, treatment and follow-up duration, assessment tools, treatment outcomes, ethical approval, and adverse event reports. The research quality assessment was performed using the modified Jadad score, as described in the study by White and Ernst ⁴⁾, which is slightly modified from the existing Jadad score because it is difficult for acupuncture practitioners to be blinded (Table 1).

Table 1. Modified Jadad Score.

Criteria	Points
Study is described as randomized	+1
Study used an appropriate randomization method	+1
Inappropriate randomization method	-1
Patient is blinded to the intervention	+1
Evaluator is blinded to the intervention	+1
Description of withdrawals and dropouts	+1
Total	5 points

In terms of measurement, a randomized study was assigned 1 point, a study that used an appropriate randomization method was assigned 1 point, a study

with inappropriate randomization was assigned -1 point (an undescribed randomization method was also assigned -1 point), a study in which the patients were blinded to intervention was assigned 1 point, a study in which the evaluator was blinded to the intervention was assigned 1 point, and a study that described withdrawals and dropouts was assigned 1 point.

Results

1. Study of bee venom

1) The number of published studies by year

Since 1976, when *Experimental Studies on the Effect of Bee Venom Therapy on the Analgesic, Anti-pyretic and Anti-inflammatory Action* by Koh⁵⁾ was published for the first time in Korea, the research of bee venom has steadily increased. Each year since 2000, related studies have been published in the double-digits. In 2003, more than 30 related studies were first published. In 2006, the number of published studies was the highest with 36 studies. Until 1999, experimental focused research was conducted; clinical studies began thereafter and have been conducted to a greater extent than literature or experimental research (Figure 2).

2) The number of published studies, according to the study method

The included studies were classified into three types, according the study method: literature studies, experimental studies, and clinical studies. Among 412 studies, there were 235 clinical studies (accounting for 57%), 149 experimental studies (36%), and 28 literature studies (7%) (Figure 3).

2. Classification of the literature studies.

Literature studies related to bee venom can be largely classified into two categories. The first class of studies investigated research trends or analyzed

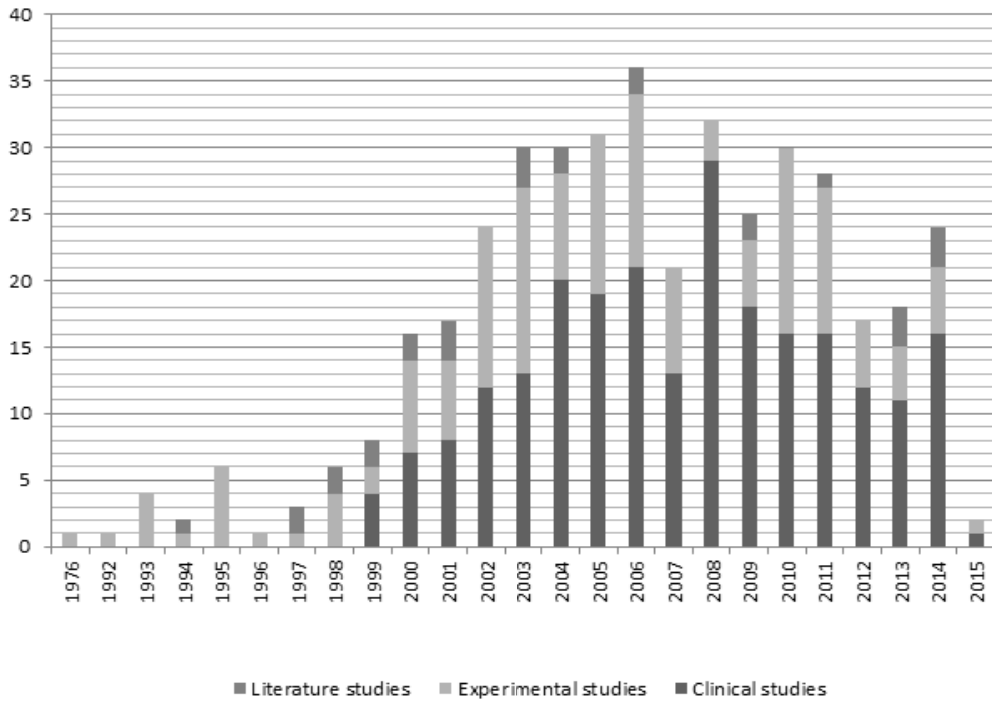


Fig. 2. Number of studies published on bee venom.

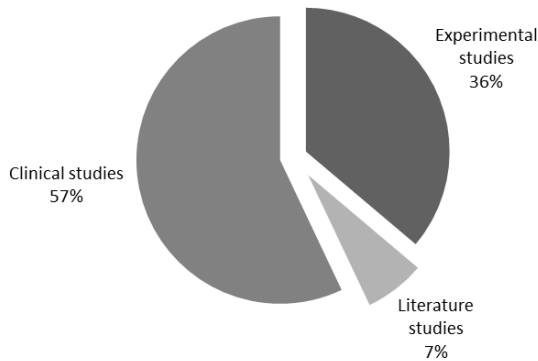


Fig. 3. The classification, according to the study method.

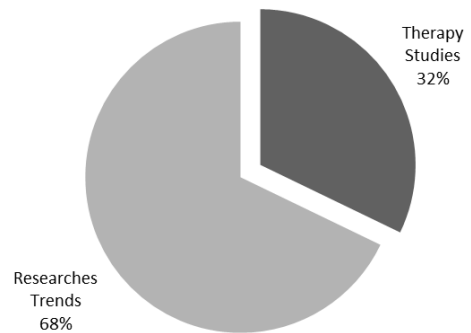


Fig. 4. The percentage of literature studies, classified by type.

studies obtained by searching the MEDLINE database (U.S. National Library of Medicine, Bethesda, MD) or journals; the second class of studies examined treatment theories with bee venom based on studies or past literature. The former class included 19

(68%) studies on research trends and literature analysis, whereas the latter class included nine (32%) studies on bee venom therapy (Figure 4).

3. The classification of the experimental studies, according to theme.

Experimental research papers related to bee venom were classified according to the purpose and theme. One study can have several purposes and themes; therefore, related studies were organized by allowing overlaps. The results were as follows: 19 studies most frequently dealt with the theme of anticancer, followed by 17 studies on pain control, 14 studies on apoptosis, 14 studies on anti-inflammatory effects, and 11 studies anti-arthritis effects. Overlapping may occur when classifying themes. For example, experiments on nitric oxide (NO) is often for its antioxidant effects and experiments on cyclooxygenase-2 (COX-2) is often to determine its anti-inflammatory analgesic action. In addition, experiments on apoptosis mostly use cancer cells, which may be intended to determine an anticancer effect (Figure 5).

4. Classification of clinical studies, according to the region of the disease.

The studies on diseases in clinical studies were classified by the region of the disease. It was difficult to classify the region of a disease because some cases involved multiple regions in a study; however, a widely covered region was classified as the region of a disease in the study and a region with an extensive range was classified as a systemic disease. The classified regions were largely divided into facial and head, neck, upper limb, spine and torso, lumbar, genitalia, pelvic limb, and systemic disease. The studies were divided by the subject of “nonpatients” or “hypersensitivity reactions.” The most studied region with a disease was the lumbar region with 45 (19%) studies, followed by systemic disease with 38 (16%) studies and the upper limb with 37 (16%) studies. It was followed by (in decreasing order) pelvic limb (13%), neck part (9%), facial and head (8%), hypersensitivity reaction (8%),

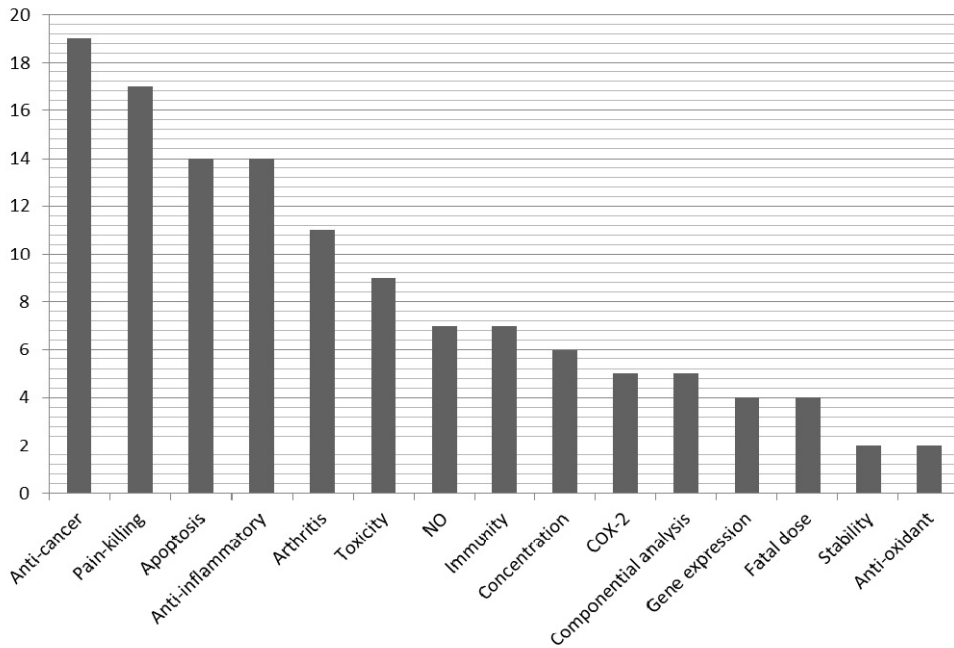


Fig. 5. The proportion of experimental papers, classified by theme.

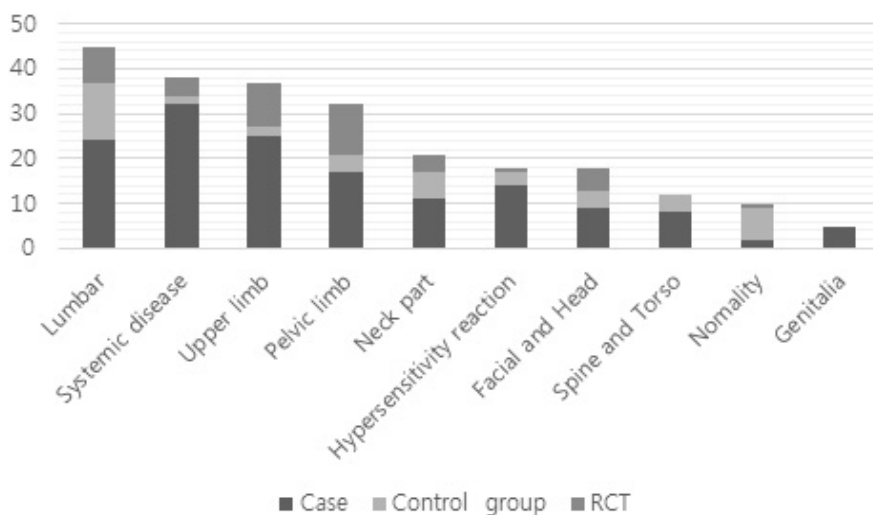


Fig. 6. The percentage of clinical studies, classified by the region of the disease.

spine and torso (5%). With regard to a single disease, lumbar herniation of the nucleus pulposus was the most commonly studied disease among lumbar diseases with 22 studies. When expanding the region of the disease to the entire spine (i.e., cervical, thoracic, lumbar), lumbar herniation of the nucleus pulposus had the highest number of clinical cases. In addition, 12 (8%) studies were related to bee venom hypersensitivity reaction, even if there was a single case per study. Musculoskeletal diseases (e.g., fracture, arthritis, ligament disease, herniation of the nucleus pulposus) overall accounted for approximately 66% of the total studies (Figure 6).

Random-controlled Trials of Bee Venom

1. The study diseases and the number of study participants

There were seven studies on degenerative knee osteoarthritis, six studies on shoulder pain caused by stroke sequelae, six studies on back pain and herniation of the nucleus pulposus, four studies on ankle sprain, five studies on facial paralysis, four

studies on neck disease, two studies on carpal tunnel disease, one study on patients with stroke and upper limb spasticity, one study on tennis elbow, one study on central post-stroke pain, one study on cancer pain, one study on heart rate variability, one study on musculoskeletal diseases, one study on rheumatoid arthritis, and one study on allergic reaction. With regard to the number of study participants, one study had fewer than 10 participants, three studies had 11–20 participants, 9 studies had 21–30 participants, 14 studies had 31–40 participants, 7 studies had 41–49 participants, 5 studies had 50–60 participants, 2 studies had 60–70 participants, and one study had more than 90 participants.

Bee venom treatment methods

1. Manufacturers and types.

There were 19 self-mixed studies that used dried bee venom. Seventeen studies were provided by the Korean Pharmacopuncture Institute, three studies were prepared by Kyunghee Medical Center, and three studies were prepared by Jsaeng Oriental

Medicine Hospital. Twenty-nine studies used bee venom (BV) only, 6 studies used sweet bee venom (SBV) only, and seven studies used both SBV and BV.

2. The injection site and the number of acupoints.

Four studies used one acupoint, nine studies used the A-shi point, and three studies used the joint cavity. Most studies used a variety of acupoints ranging from three points to 10 points or more.

3. The amount of injected BV into each acupoint.

Depending on the concentration, the amount of BV injection by acupoint varied from 0.01 cc to 0.1 cc, based on the study. In some studies that were included in the present study, the injected amount was changed, depending on the patients and the response.

4. The total amount of injected BV.

The total amount of injected BV also varied, and usually ranged from 0.1 cc to 1.0 cc. The highest amount used was 1.5 cc.

5. Needling depth.

In 11 studies, the needling depth was precisely indicated by the centimeter unit. However, in most studies the needling depth was ambiguously described as “subcutaneous,” “in blood,” or “intradermal,” or was not mentioned.

6. Treatment duration.

The treatment duration varied. Three studies evaluated one-time treatment. Two studies had a duration for a long-term period or 8 weeks or more; one study had a duration of 5 weeks; nine studies had a duration of 4 weeks; 10 studies had a duration

of 2 weeks to less than 4 weeks; and six studies had a duration of less than 2 weeks, except for the three studies with the one-time treatment. In 11 studies in which the treatment duration varied according to the individual patient, the treatment duration was not indicated or could not be determined.

7. The frequency of BVA treatments.

The frequency of BVA treatment varied: three studies examined one-time treatments only, four studies examined daily treatments, 15 studies examined three times weekly treatments or every other day treatments, eight studies examined twice weekly treatments, and five studies examined 2–3 times weekly treatments. Seven studies did not indicate the frequency of treatment.

8. Total number of BVA treatments.

The total number of BVA treatments was variously distributed, and the highest number of treatments was 16 sessions, which was reported in two studies. Nine studies reported more than 10 treatments; this number excludes the studies that reported 16 treatments. Seventeen studies reported five treatments to fewer than nine treatments, and accounted for most studies. Ten studies reported fewer than four treatments, except for the three studies that used a one-time treatment. In one study, the total number of treatments was unknown.

Control group setting and combined treatment

Most studies had one control group. Three studies had two control groups and one study had three control groups. Among studies having one control group, 10 studies adopted a saline solution to treat the control group; seven studies had no treatment, except for combined treatment; six studies adopted common acupuncture to treat the control group; seven studies compared SBV and BV, and eight

studies adopted other control group treatments.

Assessment tool

The visual analog scale (VAS) was the most commonly used assessment tool, which was used in 30 studies of the 42 included studies. In addition, a variety of assessment tools were used: five studies used the Yanagihara's unweighed grading system (Y-system), four studies used painless passive range of motion (ROM) of shoulder external rotation, three studies used the Ankle-Hindfoot Scale (AHS), five studies used the Oswestry Low Back Disability Questionnaire (ODI), three studies used the Numerical Rating Scale (NRS), three studies used the pain rating score, two studies used the Nine Point Scale, and three studies used the Neck Disability Index (NDI).

Treatment outcomes

Seventeen studies indicated that the results of the assessment as treatment results were statistically significant, eight studies indicated that the results of the assessment were partially effective, and 17 studies indicated no difference between the groups.

Ethical approval and skin test

With regard to ethical approval, four studies only were approved by the institutional review board (IRB) with consent, 10 studies received written consent, and three studies provided explanation and obtained verbal consent. However, in most studies information on written consent or IRB approval was not included.

The skin test and related information was described in 20 studies. However, it was not mentioned in the remaining 22 studies.

Modified Jadad score

1. Randomization.

All included studies reported being randomized. However, 21 studies were performed by appropriate randomization, and the remaining 21 studies merely reported that randomization was performed or were studied in an inappropriate way.

2. Blinding.

A total of 23 studies had patients blinded to the intervention, whereas the remaining 19 studies had patients unblinded to the intervention. Among the studies having patient blinding, only two studies had the evaluator blinded as well.

3. Dropouts or withdrawals.

Twenty-three studies mentioned dropouts, whereas the remaining 19 studies did not mention dropouts.

Discussion

Research articles related to bee venom began in France with the results of an experiment on applying bee stings to patients with rheumatoid disease, which was first reported in 1858 by Desjardin⁴⁸⁾. In 1968, Habermann⁴⁹⁾ reported the biochemical constituents of BV, and thereafter several experimental and clinical research studies with regard to the efficacy, effect, and allergic reaction of each constituent of BV have been actively published in many countries such as the United States, China, Russia, and Northern Europe. In addition, a recent attempt to analyze BVA for rheumatoid arthritis was performed through a systematic literature review and meta-analysis; however, there is low-quality evidence, based on one study, that BVA can significantly reduce pain and improve the quality of life of patients with rheumatoid arthritis, compared to the placebo control (i.e., a normal saline injection). However, the number

Table 2. Key data of random-controlled trials—comparative study between bee venom treatment and other treatments.

First author (year)	Conditions (sample size randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Lee (2014) ⁶⁾	Cervical pain caused by traffic accidents (44/40) both	5 blinding	Sweet bee venom (3 times weekly)	Hwangryunhaedoktang Pharamacupuncture (3times a week)	1. GA 2. herbal medicine 3. physical therapy	1. VAS (visual analogue scale) 2. Pain threshold 3. NDI (Neck Disability Index)	1. $p > 0.05$ 2. $p > 0.05$ 3. $p > 0.05$	We found that Hwangryunhaedoktang pharamacupuncture and essential bee venom pharamacupuncture treatment are considered effective and useful in cervical pain caused by traffic accident
Im (2014) ⁷⁾	Patients with facial paralysis (52/41) only	B.P.	Bee venom (daily for 12 days)	Jungsongoulyul Pharamacupuncture	1. GA 2. Herbal medicine	1. Y-System (Yanagihara's unweighted grading system) 2. H-B grade (gross grading system of House-Brackmann) 3. Lip-length and snout indices 4. FDI (facial disability index)	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p > 0.05$	<i>Jungsongoulyul</i> pharamacupuncture treatment appears to be as effective as bee venom pharamacupuncture treatment to improve symptoms of peripheral facial paralysis
Kim (2013) ⁸⁾	Patients with facial paralysis (60/40) n.r.	n.r.	Sweet bee venom (2-3times weekly for 4 weeks)	Needle-embedding therapy (3 times weekly for 4 weeks)	1. GA 2. herbal medicine	1. Y-System 2. H-B grade	1. $p < 0.05$ 2. $p < 0.05$	Needle-embedding Therapy would be as effective to improve symptoms of early stage of peripheral facial paralysis as sweet bee venom pharamacupuncture therapy
Ro (2012) ⁹⁾	Patient with spondylolisthesis (30/30)	0 n.r.	Bee venom (daily for 14days)	ShinBaro Pharamacupuncture (Daily for 14days)	1. GA 2. herbal medicine 3. physical therapy	1. NRS (numerical rating scale) 2. ODI (Oswestry Disability Index)	1. $p > 0.05$ 2. $p > 0.05$	The result suggest that ShinBaro pharamacupuncture treatment and bee venom pharamacupuncture treatment are considered effective and useful on low back pain and radicular pain caused by spondylolisthesis, although further study is needed
Cho (2012) ¹⁰⁾	Post-stroke shoulder pain (45/43)	3 n.r.	GA+bee venom+herbal medicine (Samgjeum) (GA: daily for 4 weeks; Bee venom: 3 times weekly for 4 weeks; HM: 2 times daily for 4 weeks)	1. GA 2. GA+bee venom 3. GA+herbal Medicine	1. herbal medicine 2. FMMA (Fugl-Meyer motor assessment) 3. PROM (painless passive external rotation) 4. MAS (Modified Ashworth sacle) 5. Satisfaction	1. VAS 2. FMMA (Fugl-Meyer motor assessment) 3. PROM (painless passive external rotation) 4. MAS (Modified Ashworth sacle) 5. Satisfaction	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ 4. $p > 0.05$ 5. $p < 0.05$	Cotreatment with Samgjeum-gagam, acupuncture and sweet bee venom acupuncture is more effective than acupuncture treatment only on post-stroke shoulder pain

First author (year)	Conditions sample size (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Lee (2011) ¹¹⁾	Low back pain caused by traffic accidents (34/34)	0 n.r.	Bee venom (2 times weekly for 4 weeks)	Only cotreatment	1. GA 2. Herbal medicine	1. VAS 2. ODI	1. $p < 0.05$ 2. $p < 0.05$	The results suggest that bee venom acupuncture was effective on low back pain resulting from traffic accidents
Park (2011) ¹²⁾	Post-stroke hemiplegic shoulder pain (41/40)	4 only B.P.	Sweet bee venom (3 times weekly for 1 week)	Normal saline (3 times weekly for 4 weeks)	1. GA 2. Herbal medicine 3. Physical therapy	1. VAS 2. PRS (pain rating score) 3. PROM 4. FMMA	1. $p < 0.05$ 2. $p < 0.05$ 3. NS 4. NS	Sweet bee venom pharmacopuncture has a significant analgesic effect on post-stroke hemiplegic shoulder pain
Ku (2010) ¹³⁾	Carpal tunnel syndrome (16/16)	4 only B.P.	Sweet bee venom (2 times weekly for 4 weeks)	Scolopendrid Pharmacopuncture treatment (2 times weekly for 4 weeks)	1. VAS 2. PRS 3. Tinell's Sign 4. Phalen's Sign 5. Nerve Conduction Velocity	1. VAS 2. PRS 3. Tinell's Sign 4. Phalen's Sign 5. Nerve Conduction Velocity	NS	These results showed that sweet bee venom pharmacopuncture and scolopendrid pharmacopuncture could decrease the symptoms of carpal tunnel syndrome. Further studies will be required to examine more cases in a long treatment period and the use of various concentrations and amount of pharmacopuncture for the effect on carpal tunnel syndrome
Park (2010) ¹⁴⁾	Patients with facial 3 paralysis (36/36)	3 only B.P.	Sweet bee venom (2-3times weekly for 4 weeks)	Hominis Placenta Pharmacopuncture treatment (2-3times weekly for 4 weeks)	1. GA 2. Herbal medicine	1. Y-System	NS	There were no significant differences statistically between Hominis Placenta pharmacopuncture therapy and sweet bee venom therapy on peripheral facial paralysis
Noh (2010) ¹⁵⁾	Stroke patients with upper limb spasticity (14/10)	4 only B.P.	Bee venom group (group I) and a normal saline group (group II). After 1 week resting phase; this trial was a cross-over trial. Bee venom treatments were three times weekly for 3 weeks	Normal saline	1. GA 2. Herbal medicine 3. Cupping 4. Moxibustion 5. Physical therapy	1. VAS 2. WMFT (Wolf Motor Function Test) 3. 10-sec Test	1. NS 2. $p < 0.05$ 3. $p < 0.05$	These results showed that bee venom acupuncture may decrease upper limb spasticity and increase arm motor function in stroke patients. Further studies will be required to examine more cases in a long treatment period for the effect on upper limb in spasticity by bee venom acupuncture
Choi (2009) ¹⁶⁾	Acute peripheral facial paralysis patient with post-auricular pain (30/30)	0 n.r.	Bee venom (3 times -hospitalization day, and after 3 days and 5 days)	Only cotreatment	1. GA 2. Herbal medicine	1. VAS 2. VAS reduction ratio 3. Post-auricular Pain Duration Time 4. Y-System	1. $p < 0.05$ 2. NS 3. $p < 0.05$ 4. NS	Bee venom pharmacopuncture on peripheral facial paralysis patient with post-auricular pain in the posterior ear was more effective in reducing the pain

First author (year)	Conditions sample size (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Gwak (2009) ¹⁷⁾	Central post-stroke pain (25/19)	4 only B.P.	Bee venom (2 times weekly for 3 weeks)	Normal saline treatment (2 times weekly for 3 weeks)	1. Drugs for central pain	1. VAS scale 2. CBS (Categorical rating scale) 3. MBI 4. MRS (Modified Rankin Scale)	NS	There are positive effect on central post-stroke pain patients in pain and stroke recovery when treated with bee venom acupuncture, compared to the control group
Kang (2008) ¹⁸⁾	Lateral ankle pain 1 patients (60/52)	n.r.	Bee venom (1 time for 3 days or 4 days)	1. GA 2. Hwangryunhaedo-akang herbal acupuncture (one time for 3 days or 4 days)		1. AHS (Ankle-Hind foot Scale) 2. NRS	NS	When treating patients with acute ankle pain, acupuncture, bee venom acupuncture, hwangryunhaedokang herbal acupuncture each has a clinical effect
Kim (2008) ¹⁹⁾	Knee osteoarthritis 4 patients (45/32)	4 only B.P.	Intramuscular bee venom treatment (2 times weekly for 4 weeks)	Intra-articular bee venom treatment (2 times weekly for 4 weeks)	1. Drugs for knee arthritis	1. Korean Pain Assessment Card 2. KWOMAC (Korean Western Ontario and McMaster Universities Osteoarthritis Index) 3. VAS 4. 36-Items Short-Form Health Survey 5. Nine Point Scale	1. Unknown 2. NS 3. NS 4. NS 5. NS	This study suggests that, in the treatment of knee osteoarthritis patients, the effects of "intramuscular bee venom herbal acupuncture" were not statistically different from "intraarticular bee venom herbal acupuncture." However, both treatments showed effects on pain and physical function in knee osteoarthritis patients
Yang (2008) ²⁰⁾	Knee osteoarthritis 5 patients (49/33)	blinding both	Bee venom (twice weekly for an 8-week period)	Warm needling (twice weekly for 8-week period)		1. KWOMAC 2. 36-Items Short-Form Health Survey 3. Patient Global Assessment	1. $p < 0.05$ 2. NS 3. $p < 0.05$	BVP was more effective in relieving pain of knee osteoarthritis (OA) than WN. These findings suggest that BVP is a promising alternative for treating knee OA
Kim (2008) ²¹⁾	the osteoarthritis of the knee joint patients (30/30)	1 only B.P.	Sweet bee venom (3 times weekly for 2 weeks)	Bee venom (3 times weekly for 2 weeks)		1. VAS 2. Oddy test	1. $p < 0.05$ 2. Be effective	Sweet bee venom had a significant effect on suppressing the local immediate hypersensitivity reaction. The effect on reducing osteoarthritis of the knee joint pain was better than the same concentration of bee venom
Kim (2008) ²²⁾	Chronic lower back pain (52/39)	2 only B.P.	Sweet bee venom (2 times weekly for 2 weeks)	Bee venom (2 times weekly for 2 weeks)	1. GA	1. VAS 2. ODI 3. Pruritus VAS	1. $p < 0.05$ 2. $p < 0.05$ 3. $p < 0.05$ (less pruritus to sweet bee venom)	According to the study, sweet bee venom therapy shows a more effective result than bee venom therapy in controlling itching. However, bee venom therapy is more effective than sweet bee venom therapy in controlling pain and promoting function

First author (year)	Conditions sample size (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Yook (2008) ²³	Heart rate variability (22/22)	1 only B.P.	Sweet bee venom (one time)	Bee venom (one time)		1. HRV by QEEG-3LXC3203	NS	The results suggest that, compared to bee venom, sweet bee venom in healthy adult men tend to activate the autonomic nervous system within the normal range
Lee (2008) ²⁴	Patients with a stiff neck (41/41)	3 only B.P.	Sweet bee venom (one time)	bee venom (one time)	1. Cupping 2. GA	1. VAS 2. NDI (Neck Disability Index) 3. CEG	NS	It seems that there are no substantially different treatment effects between the two groups. Sweet bee venom pharmacopuncture appears to be a more effective measurement against allergic reactions than the bee venom pharmacopuncture. Further studies are needed for a comparison of bee venom pharmacopuncture and sweet bee venom pharmacopuncture
Yoo (2008) ²⁵	Cancer-related pain (11/9)	4 only B.P.	Sweet bee venom (daily for five days)	normal saline treatment (Daily for five days)		1. NRS	1. Short-term: $p < 0.5$ Long-term: NS	Although further study will be needed on a large scale, sweet bee venom pharmacopuncture shows potential as an effective treatment for immediate relief of cancer-related pain
Lee (2007) ²⁶	Herniation of the nucleus pulposus comparison (60/60)	0 n.r.	Bee venom (Group 2)	1. Oshiyul herbal acupuncture treatment (Group 3) 2. No treatment (Group 1)	1. GA 2. Physical therapy	1. VAS 2. Clinical symptoms rating 3. SLRT	NS	In this study, there were different effects among the three groups, according to the treatment period. Further study on various treatment for herniation of the nucleus pulposus is required
Na (2007) ²⁷	Osteoarthritis of the knee joint (36/36)	1 only B.P.	Sweet bee venom (3 times weekly for 2 weeks)	bee venom (3 times weekly for 2 weeks)		1. VAS 2. Oddy test	1. NS 2. Allergic responses were significantly lower in the sweet bee venom group	We could not get a significant difference in the whole score between the two pharmacopuncture groups. On the other hand other allergic responses such as edema, itchiness, pain were significantly lower in the sweet bee venom group
Lee (2007) ²⁸	Low back pain with radiating pain (24/24)	3 only B.P.	Sweet bee venom (4 times)	bee venom (4times)	1. GA	1. VAS 2. SLRT	NS	Using sweet bee venom may have equal effects as using bee venom to treat low back pain with radiation pain. We can try to treat other diseases known to be affected by bee venom

First author (year)	Conditions sample size (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Ko (2007) ²⁹⁾	Shoulder pain after stroke (46/43)	blinding both	Bee venom (3 times weekly for 2 weeks)	normal saline treatment (3 times weekly for 2 weeks)	1. GA 2. Herbal medicine 3. Kinesiatrics 4. Physical therapy 5. Moxibustion	1. VAS 2. PRS 3. PROM 4. FMMA	1. $p < 0.05$ 2. $p < 0.05$ 3. NS 4. NS	This study suggests that bee venom injection has a significant analgesic effect on hemiplegic shoulder pain. Further study based in multiple centers with a larger population, and long-term following-up is needed to confirm this suggestion
Song (2007) ³⁰⁾	Patients with whiplash injury (25/25)	0 n.r.	Sweet bee venom (5 times)	normal saline treatment (5 times)	1. GA 2. Herbal medicine 3. Physical therapy	1. VAS 2. Neck ROM scale	1. $p < 0.05$ 2. $p < 0.05$	This study suggests that sweet bee venom herbal acupuncture can improve symptoms in patients with acute whiplash injury by traffic accident
Seo (2006) ³¹⁾	Acute ankle sprain (60/20)	3 n.r.	Bee venom (more than three times)	GA(more than 3times)	1. GA 2. Physical therapy 3. Infrared irradiation 4. Brace appliance	1. NRS 2. AHS	NS	Both bee venom acupuncture therapy and single acupuncture therapy were effective to treat the acute ankle sprain but there were no significant data to prove that bee venom acupuncture therapy is more effective than single acupuncture therapy
An (2006) ³²⁾	Patients with sprain of the wrist joint (38/31)	3 n.r.	Bee venom (more than 3times)	GA(more than 3times)	1. Herbal medicine	1. VAS	1. $p < 0.05$	These results suggested that bee venom acupuncture treatment should be more effective in patients with sprain of the wrist joint
An (2006) ³³⁾	Patients with osteoarthritis of the knee joint (36/30)	3 n.r.	Bee venom (more than 3times)	GA(more than 3times)	1. Herbal medicine	1. The WOMAC Index (Appendix 1)	1. $p < 0.05$	These results suggested that bee venom acupuncture treatment should be more effective in the patient with osteoarthritis of knee joint
Eom (2006) ³⁴⁾	Post-stroke hemiplegic shoulder pain (30/30)	0 n.r.	Bee venom—syringe (3 times weekly for 4 weeks)	1. bee venom (3 times weekly for 2weeks) 2. GA (3 times weekly for 4weeks)	1. VAS 2. FMMA 3. PROM 4. Modified Ashworth Scale	NS	Bee venom acupuncture and bee venom herbal acupuncture appears to be an effective in treating post-stroke hemiplegic shoulder pain. Further clinical studies must be performed to obtain more concrete findings	
Lee (2006) ³⁵⁾	Shoulder pain patients in stroke sequelae (40/40)	0 n.r.	Bee venom (3 times weekly for 3 weeks)	GA (3 times weekly for 3weeks)	1. Moxibustion 2. Physical therapy 3. Kinesiatrics	1. VAS 2. PROM 3. Muscular strength rating	1. $p < 0.05$ 2. NS 3. NS	We suggest that GDS oral administration and electro-acupuncture at BJ.52 and GB39 are available for prevention and curing postmenopausal osteoporosis
Lee (2006) ³⁶⁾	Allergic responses (95/95)	4 only B.P.	Sweet bee venom (one time)	bee venom (one time)	1. VAS	1. VAS	1. Except for whole body allergic	As a result of the removed allergen, sweet bee venom significantly inhibits allergic responses locally and throughout the body.

First author (year)	Conditions sample size (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
Choi (2005) ³⁷⁾	Post-stroke hemiplegic shoulder pain (23/23)	0 n.r.	Bee venom (3 times a week for 2 weeks)	Zingiberis Rhizoma herbal acupuncture treatment (3times a week for two weeks)	1. GA 2. Herbal medicine 3. Kinesiatrics	1. Manual muscle test 2. VAS 3. ROM	NS	In the study, both herbal acupuncture therapies were effective on the post-stroke hemiplegic shoulder pain, but bee venom herbal acupuncture was more effective on the pain level
Kim (2005) ³⁸⁾	Sprain of the cervical spine (26/21)	4 only B.P.	Bee venom (more than two times)	normal saline treatment (more than two times)	1. GA 2. Infrared irradiation	1. VAS 2. NDI	1. $p < 0.05$ 2. $p < 0.05$	After the end of treatment, bee venom group showed a significant reduction in NDI- VAS than general acupuncture
Kim (2005) ³⁹⁾	Sprain of the lumbar spine (30/24)	4 only B.P.	Bee venom (5 times)	normal saline treatment (5times)	1. GA 2. infrared irradiation	1. VAS 2. ODI	1. $p < 0.05$ 2. $p < 0.05$	Bee venom acupuncture therapy can be used with acupuncture therapy for a high index score
Song (2005) ⁴⁰⁾	Acute ankle sprain (30/24)	4 only B.P.	Bee venom (daily for a week)	normal saline treatment (Daily for a week)	1. GA	1. AHS 2. VAS	1. $p < 0.05$ 2. $p < 0.05$	Bee venom acupuncture was thought to be effective alternatives for relieving symptoms of acute ankle sprain, although further study was needed on the large scale
Kim (2004) ⁴¹⁾	Peripheral facial paralysis (30/30)	0 n.r.	Bee venom (2 times weekly—approximately 10 times)	only cotreatment	1. Basic Oriental medicine treatment 2. GA	1. Y-System	NS	Combining Bee venom aqua-acupuncture therapy on peripheral facial paralysis more efficacious than the only use of basic oriental medicine treatment
Ryu (2004) ⁴²⁾	Osteoarthritis of the knee (51/51)	0 n.r.	Intra-articular bee venom injection (3 times weekly for 4 weeks)	GA venom injection (3 times weekly for 4 weeks)	1. VAS 2. WOMAC 3. Lequesne's index	1. VAS 2. WOMAC 3. Lequesne's index	1. $p < 0.05$ 2. Overall evaluations: $p < 0.05$ Pain and function: $p < 0.05$ Ankylosis: NS 3. $p < 0.05$	In this clinical study, Intra-articular bee venom injection therapy was more effective in improving pain and disability of the knee joint caused by osteoarthritis, compared to traditional needle acupuncture therapy alone

First author (year)	Conditions (randomized/analyzed)	Quality score, blinding	Experimental treatment (regimen)	Control treatment (regimen)	Concomitant treatment	Main outcomes	Intergroup difference	Authors' conclusion
An (2004) ⁴³	Tennis elbow (24/24)	0 n.r.	Bee venom (more than six times)	GA (More than six times)	Infrared irradiation	1. VAS	1. $p < 0.05$	In the study, both bee venom therapies and general acupuncture were effective on tennis elbow. But after four times of treatment, bee venom therapy is more effective in reducing the pain
Lee (2004) ⁴⁴	Acute ankle sprain (32/32)	0 n.r.	Bee venom (More than four times)	GA (More than four times)		1. VAS 2. ROM	NS	There was a good effect on the ankle sprain in both two groups. There were no significant difference at the ROM of ankle joint in either of the two groups. Common acupuncture therapy had a quicker effect on joint swelling. In the VAS score, bee venom therapy had a quicker effect on total improvement of the ankle sprain
Lee (2003) ⁴⁵	Osteoarthritis of the knee joint (50/50)	0 n.r.	Bee venom (2-3 times weekly)	GA (2-3 times weekly)		1. Clinical rating 2. Nine point scale 3. Degree of favorable for clinical symptoms rating	1. More than favorable: bee venom-88%; GA-68% 2. $p < 0.05$ 3. $p < 0.05$	In the treatment of osteoarthritis of knee joint, bee venom acupuncture can be regarded as more effective treatment than Filiform acupuncture in clinical practice. This is expected to be available for clinical use
Chung (2003) ⁴⁶	Patient with herniation of nucleus pulposus of the lumbar spine (45/41)	1 n.r.	Bee venom (2-3 times weekly)	GA (2-3 times weekly)	1. GA 2. Physical therapy 3. Manipulation therapy	1. VAS 2. ROM 3. ODI	1. $p < 0.01$ 2. $p < 0.05$ 3. $p < 0.01$	In this clinical study, bee venom acupuncture was more effective in improving pain, disability of daily life and limited range of movement caused by HIVD than simple acupuncture therapy
Lee (2003) ⁴⁷	Rheumatoid arthritis (80/69)	2 only B.P.	Bee venom (2 times weekly for 8 weeks)	normal saline treatment (2 times weekly for 8 weeks)		1. VAS	1. $p < 0.05$	These results suggest that bee venom therapy could be an effective method in the treatment of patients with rheumatoid arthritis

^a Quality Score: Jadad score.
 AHS: Ankle-Hindfoot Scale; B.P: blinding patients; FDI: facial disability index; FIMMA: Fugl-Meyer motor assessment; GA: general acupuncture; H-B grade: gross grading system of House-Brackmann; HM: herbal medicine; MAS: Modified Ashworth scale; NDI: Neck Disability Index; n.r.: not reported; NPS: numerical rating scale; NS: no significant; ODI: Oswestry Low Back Disability Questionnaire; PPS: pain rating score; ROM: range of motion; SBV: sweet bee venom; VAS: visual analog scale; Y-System: Yanagihara's unweighed grading system

Table 3. Quality scores for the included randomized-controlled trials, according to the modified Jadad score.

First Author (year)	Randomization			Blinding		Description of dropouts or withdrawals	Modified Jadad total	Ethical approval
	Described as randomized	Appropriate method	Inappropriate method	Subject	Evaluator			
Lee (2014) ⁶⁾	Yes	Yes Random-number table		Yes	Yes	Yes	5	consent form (IRB approval)
Im (2014) ⁷⁾	Yes	Yes Toss-up		Yes	No	Yes	4	consent form
Kim (2013) ⁸⁾	Yes	Yes Random-number table		No	No	Yes	3	n.r
Ro (2012) ⁹⁾	Yes		Yes	No	No	No	0	n.r
Cho (2012) ¹⁰⁾	Yes	Yes Block-randomized (block size 8)		No	No	Yes	3	consent form
Park (2011) ¹²⁾	Yes		Yes	No	No	No	0	verbal consent
Ku (2010) ¹³⁾	Yes	Yes Random-number table		Yes	No	Yes	4	n.r
Roh (2010) ¹⁵⁾	Yes	Yes Random-number table		Yes	No	Yes	4	consent form
Choi (2009) ¹⁶⁾	Yes	Yes Random-number table		Yes	No	No	3	n.r
Gwak (2009) ¹⁷⁾	Yes	Yes Random-number table		Yes	No	Yes	4	consent form
Kim (2008) ¹⁹⁾	Yes		Yes	No	No	No	0	n.r
Yang (2008) ²⁰⁾	Yes	Yes Block-randomized (block size 4)		Yes	No	Yes	4	consent form
Kim (2008) ²²⁾	Yes		Yes	No	No	Yes	1	n.r
Yook (2008) ²³⁾	Yes	Yes Block-randomized (block size 4)		Yes	no	Yes	4	consent form (IRB approval)
Lee (2008) ²⁴⁾	Yes	Yes Random-number table		Yes	Yes	Yes	5	consent form (IRB approval)
Yoo (2008) ²⁵⁾	Yes		Yes	Yes	No	No	1	consent form
Lee (2007) ²⁶⁾	Yes		Yes	Yes	No	Yes	2	n.r
Na (2007) ²⁷⁾	Yes		Yes	Yes	No	No	1	n.r
Lee (2007) ²⁸⁾	Yes	Yes Random-number table		Yes	No	No	3	n.r
Ko (2007) ²⁹⁾	Yes	Yes Random-number table		Yes	No	Yes	4	consent form
Lee (2006) ³⁵⁾	Yes		Yes	No	No	No	0	n.r.
Cho (2005) ³⁷⁾	Yes		Yes	Yes	No	No	1	Consent form (IRB approval)
Kim (2005) ³⁸⁾	Yes	Yes Drawing lots		Yes	No	No	3	n.r

First Author (year)	Described as randomized	Randomization		Blinding		Description of dropouts or withdrawals	Modified Jadad total	Ethical approval
		Appropriate method	Inappropriate method	Subject	Evaluator			
Song (2005) ⁴⁰⁾	Yes	Yes Random-stratified sampling		Yes	Yes	Yes	5	verbal consent
An (2004) ⁴³⁾	Yes		Yes	No	No	No	0	verbal consent
Lee (2003) ⁴⁵⁾	Yes	Yes Toss-up		No	No	Yes	3	n.r.
Chung (2003) ⁴⁶⁾	Yes	Yes Toss-up		No	No	Yes	3	n.r.
Lee (2003) ⁴⁷⁾	Yes	Yes Toss-up		No	No	Yes	3	n.r.
Lee (2014) ⁶⁾	Yes		Yes	No	No	No	0	consent form
Im (2014) ⁷⁾	Yes		Yes	No	No	No	0	n.r.
Kim (2013) ⁸⁾	Yes	Yes Random-number table		Yes	No	Yes	4	consent form
Lee (2011) ¹¹⁾	Yes		Yes	No	No	No	0	n.r.
Park (2011) ¹²⁾	Yes	Yes Toss-up		Yes	No	Yes	4	n.r.
Ku (2010) ¹³⁾	Yes	Yes Toss-up		Yes	No	Yes	4	n.r.
Park (2010) ¹⁴⁾	Yes	Yes Toss-up		Yes	No	Yes	4	n.r.
Choi (2009) ¹⁶⁾	Yes		Yes	No	No	No	0	n.r.
Gwak (2009) ¹⁷⁾	Yes		Yes	No	No	No	0	n.r.
Kang (2008) ¹⁸⁾	Yes		Yes	No	No	No	0	n.r.
Kim (2008) ¹⁹⁾	Yes		Yes	No	No	No	0	n.r.
Kim (2008) ²¹⁾	Yes		Yes	No	No	No	0	n.r.
Kim (2008) ²²⁾	Yes		Yes	No	No	Yes	1	n.r.
Yook (2008) ²³⁾	Yes		Yes	Yes	No	Yes	2	Consent form

IRB: institutional review board; n.r.: not reported.

of studies, their quality, and the total sample size were too low to draw firm conclusions⁵⁰⁾. Since a thesis by Kweon⁵¹⁾ in 1992, many studies have been published to date in Korea.

In this regard, the authors attempted to conduct a typical analysis of BV-related studies to analyze and classify comprehensively the trends and content of

BV-related studies published until 2015, and thereby to explore the directions of BV-related studies and address problems. In addition, the authors analyzed research trends and the research quality of RCT-designed studies by using various assessment criteria and the modified Jadad scale.

An examination of the number of studies by type

Table 4. Summary of methods in the included random-controlled trials.

Categories	Number of RCTs
Number of included trials	42
Objective of the trials	
To determine efficacy of SBV or BV	20
To compare efficacy between SBV and BV	7
To compare efficacy with other treatments	13
Other	2
Quality of trials (average of Jadad score)	2.190476
4-5	14
1-3	15
0	13
Randomization methods	
Appropriate	22
Inappropriate	20
Blinding	
Subject-blinded	22
Evaluator-blinded	3
Operator-blinded	13
Description of Informed consent	17
Fully described with ethical approval	4
Just for informed consent	13
Type of control	
Compared with SBV	7
Compared with normal saline	10
Compared with other treatments	25
Sample size	
Over 50	8
10 < N < 50	33
Under 10	1

BV: bee venom; RCT: random-controlled trial; SBV: sweet bee venom.

published from the 1990s to 2015 showed that, since the 2000s, full-fledged clinical studies have been conducted, based on basic research and early literature. Beginning in 2002, more than 25 BV-related studies have been published every year, and account for a considerable proportion of studies in the Korean medicine community.

Based on the type of study, the number of past literature studies related to BV was very small, compared to other Korean medicine therapy-related literature; thus, studies based on the literature

accounted for a small proportion, and most of the development is achieved in the areas of experimental and clinical studies.

For basic research papers, experiments have been conducted in diverse ways from the pharmacological reactions of cell units to efficacy with injections on acupoints in animals. When dealing with a wide range of topics, the contents of such diverse topics may often overlap because the topics have been examined for similar purposes, even though the main subject of each study is different.

It was too complicated to classify clinical studies by disease because such studies have dealt with a variety of diseases from nervous system disorders such as stroke and facial nerve paralysis; adverse reaction reports, which include BV hypersensitivity reactions in clinical studies of normal persons; and the same diseases often become separate diseases because in many cases a mix of Western diagnoses and Korean medicine diagnoses is used in practice. Therefore, it was in reality difficult to obtain statistical data.

From 2003 until 2008, related RCTs have generally been on an increasing trend. However, since 2009, a small number of related studies have been released. This may be because studies related to BV have been conducted over a certain level and there have been increased restrictions in RCTs because of reinforced IRB standards. Related studies have been conducted on a variety of disease, but most studies have been conducted with a focus on musculoskeletal diseases because of the nature of BV.

With regard to the number of study participants in the included studies, for a considerable number of studies, there was a concern whether the number of clinical study participants as presented in the results of related studies could be a sufficient number of samples as the evidence of study results. For example, if the number of participants in a study is fewer than 20, the number of individuals per group

is fewer than 10 subjects per group, and thus any changes in the results of a small number of patients may easily reverse the study's conclusion.

An examination of the experimental methods showed that, because there were differences in the experimental methods between studies, it may be necessary to establish standards for BV-related studies. Several studies also lacked a detailed description of the experimental design, which decreased the accuracy and reliability of the studies. This may subsequently affect the reproducibility of studies and, at the same time, pose questions about their results. The amount of BV injection is critical because of the characteristics of BV. However, there were significant deviations in the injection amount between studies, which showed there was no unified recognition of the appropriate injection amount among researchers. Furthermore, the effects of BVA may vary, according to the needling depth; however, the needling depth was precisely described in only 11 studies, which may make it difficult to reproduce or verify the related studies objectively. The number of acupoints and injected amount by acupoint were different, depending on the study. Thus, consistent standards for BV-related studies seem to be required.

The treatment duration and the number of treatments are to be adjusted, according to the response to BV and the severity of diseases. The number of treatments, treatment intervals, and treatment duration should be controlled for each study. In view of the fact that the exact treatment interval was not specified or that the number of treatments, treatment interval, and treatment duration were different (depending on the patient), the control variables were inconsistent, and thereby lowered the reliability of the studies as a whole.

The VAS was the most used assessment tool. When assessing statistical effectiveness with this tool, BV has a therapeutic effect, according to the control group results. However, its efficacy may not be statistically significant because there is no

difference between the treatment group and the control group. Considering such relativity, the control groups in the included studies could be classified in studies that compared SBS and BV, studies that adopted saline solution as the control group treatment, and studies that adopted other treatments (e.g., general acupuncture, pharmacopuncture) for the control group. In spite of clinical studies having similar themes, there were studies that showed significant differences in the results. This may be further verified through more sophisticated study designs and appropriate study methods in the future.

In clinical studies, the objectivity and science of study are important. However in an experimental study, in which certain factors are artificially manipulated or intervened, these factors are likely to cause a greater risk. Thus, concerned parties such as researchers, study sponsors, ethics committee, and research institution are further required to comply with ethics and to have responsibility. In particular, in a randomized study design, it is considered a matter of "equivalence," and thus study participants should be informed of the risks associated with their allocation to a placebo group. Information on consent or IRB approval was not included in 25 studies of 42 RCTs. After 2007, investigators gradually tended to set a high value on written consent or ethical approval. Clinical studies in the future should be conducted after obtaining IRB approval.

A universal tool that determines the quality of study methods is the Jadad score. However, in the present study a slightly modified Jadad score was used because it is difficult to have acupuncture practitioners blinded to an intervention. In this regard, specific randomization methods were described in 22 studies (i.e., more than one-half of the included studies), which used a random-number table, randomization by computer, or coin tossing. In 20 studies, the investigators simply mentioned that the study was randomized. Randomization by

computer program is recommended in view of the fact that coin tossing or random-number table has no reproducibility. However, in the present study, these randomization methods were considered appropriate because a study was evaluated only as to whether it mentioned randomization.

Twenty-two studies had the patients blinded to the intervention, 13 studies were double-blinded, and two studies were evaluator-blinded. For patient-blinded or double-blinded studies, it is easy for patients and practitioners to identify by the naked eye the treatment received, except for saline and acupuncture in which the same kind of syringe can be used. Thus, it is difficult to assess BV-related studies with blinding only. Furthermore, for patients are able to recognize whether BV was injected who experience BV reactions or symptoms such as redness, itching and swelling, which makes it impossible to determine if a blinding was properly achieved. On the other hand, for evaluator blinding, a study that is in progress in a double-blind fashion can be performed sufficiently and avoid selection bias, and therefore the quality of evaluator-blinded studies would be excellent. In fact, evaluator-blinded studies by Yang and Song²⁰⁾ and Ko et al.²⁹⁾ were appropriately conducted for different diseased areas.

A description about dropouts is a good way to assess studies objectively. If the reasons for dropouts and the number of dropouts are not described, dropouts can be determined by the researcher's intention, which may cause bias and thereby affect the reliability of the whole study. Twenty studies did not mention dropouts from which it can be judged that an undetailed study design, progress, and description of the whole study were collectively formed.

The quality assessment of study methods in the included studies revealed that a considerable number of studies had low scores, which may deteriorate the quality of studies and raise questions about the reliability and validity of results of related studies.

Therefore, efforts may be needed to describe study methods accurately. The use of the CONSolidated Standards of Reporting Trials (CONSORT) form or checklists for reporting RCTs, including the RCT checklist of the Scottish Intercollegiate Guidelines Network (SIGN) can be an option^{52,53)}. In addition, when using recommendations such as the Standard for Reporting Intervention in Controlled Trials of Acupuncture (STRICTA)⁵⁴⁾ or the influencing Factors which Affect the Effectiveness of Acupuncture Scale (FEAS)⁵⁵⁾ as the study methods in acupuncture-related clinical studies, the provisions of such recommendations may affect the results of BV therapy such as acupuncture. Thus, BV-related RCTs in the future may require considering these methodologies.

Because BVA has not been standardized, significant differences in selecting medications and treatment methods exist among practitioners. It is necessary to verify the efficacy of BV through well-designed clinical studies rather than through clinical experience or literature evidences in accordance with EBM, but the number of high-quality clinical studies is absolutely lacking. In addition, there have been no unified study method in previous clinical studies conducted to date, which may lower the reliability of results. This factor makes it difficult to apply a meta-analysis as a means of setting treatment guidelines by integrating and analyzing several RCT results, which recently have been increasingly utilized. Therefore, clinical studies should be conducted using a standardized study method suited for the characteristics of BVA so that BVA can be positioned as an efficacious therapy, based on EBM. Studies for demonstrating the efficacy and safety of BVA should be actively performed, and its treatment methods should be standardized through integrating and analyzing the results of the studies.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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