Adverse Events Associated with the Clinical Use of Bee Venom: A Review

Jaehee Yoo 1 and Gihyun Lee 2,*

1 Department of Acupuncture and Moxibustion Medicine, Dongshin University, 67 Donshindaegil, Naju 58245, Korea
2 College of Korean Medicine, Dongshin University, 67 Donshindaegil, Naju 58245, Korea
* Correspondence: glee@khu.ac.kr

Abstract: Bee venom is used to treat various diseases but can cause a tickling sensation and anaphylaxis during clinical treatment. Adverse events (AEs) associated with bee venom may vary depending on the dosage, method, route of administration, and the country, region, and user. We summarized the AEs of bee venom used in various ways, such as by the injection of extracts, venom immunotherapy (VIT), live bee stings, or external preparations. We conducted a search in eight databases up to 28 February 2022. It took one month to set the topic and about 2 weeks to set the search terms and the search formula. We conducted a search in advance on 21 February to see if there were omissions in the search terms and whether the search formula was correct. There were no restrictions on the language or bee venom method used and diseases treated. However, natural stings that were not used for treatment were excluded. A total of 105 studies were selected, of which 67, 26, 8, and 4 were on the injection of extracts, VIT, live bee stings, and external preparation, respectively. Sixty-three studies accurately described AEs, while 42 did not report AEs. Thirty-five randomized controlled trials (RCTs) were evaluated for the risk of bias, and most of the studies had low significance. A large-scale clinical RCT that evaluates results based on objective criteria is needed. Strict criteria are needed for the reporting of AEs associated with bee venom.

Keywords: bee venom; bee venom acupuncture; adverse events; adverse effect

Key Contribution: Bee venom is stimulated in various ways, and the clinically used methods are largely classified into four types. This study summarizes the methods of clinical use and the occurrence of adverse events.

1. Introduction

Bee venom treatment uses the pharmacological effect of bee sting toxins and is widely used worldwide [1]. In addition to musculoskeletal diseases, bee venom is used for therapeutic purposes such as for uterine ovarian disease [2], cancer [3], and atopic dermatitis [4]. Bee venom treatment is performed in various ways, such as through apitoxin, bee venom acupuncture, venom immunotherapy (VIT), and live bee stings [5]. Among studies on the adverse events of bee venom, studies summarizing adverse events according to the type of paper have been conducted along with randomized controlled trials (RCTs) [6]. However, no studies have reported the side effects of bee venom treatment.

The toxin component of bee venom is presented to T cells by antigen-presenting cells in the skin and eventually causes an allergic reaction by producing IgE [7]. The most serious adverse event of bee venom treatment is anaphylaxis; however, the incidence is not high [8]. If anaphylaxis occurs, epinephrine may be treated preferentially [9]. However, owing to practical and ethical issues, strong evidence on the diagnosis and management of anaphylaxis is lacking [10]. Anaphylaxis can present similarly to acute asthma, local angioedema, fainting, and anxiety/panic seizures [11].
Treatment with bee venom can often cause adverse events by generating IgE [2], and it can appear in different ways depending on how the bee venom is stimulated. We aimed to investigate which method could safely use bee venom by classifying the adverse events during clinical use. Our results will help clinical therapists using bee venom to choose the method of bee venom stimulation and prepare for adverse events.

2. Results
2.1. Descriptions of Trials
A total of 1410 papers were searched using PubMed (226 papers), Cochrane (7), EMBASE (420), CINAHL (40), CNKI (296), NDSL (261), OASIS (21), KISS (37), KoreaMED (16), and KMBASE (84). After the exclusion of papers that did not meet the extraction conditions, 105 papers were finally selected. Bee venom stimulation methods included extract injections (67 studies) [12–78], venom immunotherapy (VIT; 26 studies) [79–104], live bee stings (8 studies) [105–112], and external preparations (4 studies) [113–116].

Forty-nine, twenty-eight, six, five, four, three, two, two, one, one, and one studies were conducted in China, Korea, Germany, Australia, Poland, Turkey, the United States, Spain, the Czech Republic, Greece, Belgium, and France, respectively. There were 33 case reports (CRs), 15 case series (CS), 14 cohort studies, 6 non-randomized controlled trials (nRCTs), and 37 RCTs. In the case of VIT, the purpose of treatment was to lower hypersensitivity to venom, and the diseases to which treatment was applied were noticeably more musculoskeletal diseases such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, frozen shoulder, and lumbar disc herniation. In addition, neuropathy, urticaria, tonsillitis, rhinitis, acne, facial palsy, and menstrual pain were treated.

The venom type mainly used was bee venom, but 19 studies used wasp venom in VIT. In most studies, the results of the pre-skin test were not confirmed. In the case of extract injections, acupuncture, cupping, herbal medicine, acupotomy, moxibustion, and physical therapy were accompanied by bee venom treatment. In addition, drugs such as methotrexate, prednisolone acetate, seraxib capsules, and tramadol were identified. In the case of VIT, omalizumab was used when adverse events were severe during VIT rather than as a concomitant treatment. In the case of live bee stings, McKenzie’s methods, medication, and fluid were accompanied by the treatment. For external preparations, CO₂ lasers and medication were used. Only 27 studies specified the capacity of bee venom.

2.2. Adverse Events
The contents related to the reporting of adverse events are shown in Figure 1. The details are listed in Tables 1–4. Twenty-eight studies reported no adverse events, thirty-four studies specifically reported adverse events, and forty-three studies did not include adverse events. In one CR, no adverse events were reported. Seven of the forty-three studies reported the occurrence of adverse events using the terms “skin problem” or “systemic reaction,” without describing the specific symptoms. As a result of confirming the severity of adverse events through Spilker’s classification (Table 5), there were 26 mild, 4 moderate, and 11 severe adverse events. According to Mueller grading (Table 6), there were 23 grade I, 4 grade II, 0 grade III, and 4 grade IV cases (Figure 1).
Figure 1. Adverse events summary. The contents related to the reporting of adverse events of each stimulation type of procedure are described. There are 67 extract injections, 26 venom immunotherapy, 8 live bee stings, and 4 external preparations. It was classified into not reported, none, and Mueller grades, and if several types of Mueller grades occurred, it was classified as a high grade. Mueller grade III was not reported in the selected studies.
Table 1. Basic characteristics of extract injection type.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|-----------------|-----------------------|------------------------|-----------------------|-----------------|-----------------------|-----------|
| Han [12]     | Korea   | pain prevention therapy | CR          | 1              | bees       | NR        | NR              | NR                    | skin atrophy           | severe                | SP              | Gr1                   | probable  |
| Castro [13]  | U.S.A.  | multiple sclerosis       | CR          | 9              | bees       | NR        | NR              | NR                    | rash                  | -                     | -                | -                 | -          |
| Lee [14]     | Korea   | facial palsy cohort     | CR          | 108            | bees       | tested A: negative B: positive | 0.1–0.2 mL | -                  | rash                  | mild                  | SP              | Gr1                   | probable  |
| Jeong [15]   | Korea   | rotator cuff disease    | cohort      | 4              | bees       | tested (negative) | 0.1–0.5 cc | acupuncture, herbal medicine, physical therapy | none                  | -                     | -                | -                | -          |
| Kim [16]     | Korea   | CRPS                    | CR          | 1              | bees       | NR        | 0.15–0.4 mL    | anticonvulsant, tricyclic antidepressant analgesic | hypersensitivity, dyspepsia, rash, depression | mild                  | SP, SR          | Gr1                   | possible  |
| Kim [17]     | Korea   | allergic rhinitis       | CR          | 2              | bees       | NR        | 0.1–0.3 cc    | acupuncture           | none                  | -                     | -                | -                | -          |
| Moon [18]    | Korea   | Fibromyalgia            | CR          | 1              | bees       | NR        | 0.25 cc4      | acupuncture, pharmacopuncture, cupping, moxibustion, herbal medicine A: Shinbaro, acupuncture, cupping, moxibustion, herbal medicine, physical therapy B: acupuncture, cupping, moxibustion, herbal medicine, physical therapy | None                  | -                     | -                | -                | -          |
| Park [19]    | Korea   | lumbar disc herniation  | cohort      | A:12 B:10     | A:- B:bees | tested (negative) | A:1.0 cc B:1.0 cc | redness, itching     | mild                  | SP              | Gr1                   | possible  |
| An [20]      | Korea   | Systemic Lupus Erythematous | CR          | 1              | bees       | NR        | NR              | None                  | point pain            | -                     | -                | -                | -          |
| Kim [21]     | Korea   | survey study            | cohort      | A:132 B:336   | A:bees B:- | tested (negative) | NR          | A:- B:NR          | point pain, swelling, numbness | mild                  | SP              | Gr1                   | possible  |
| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|-----------------|-----------------------|---------------|------------------------|-------------------|------------------------|-----------|
| Lee [22]     | Korea   | refractory postherpetic neuralgia | CR          | 1              | Bees       | tested (negative) | NR          | NR                  | none           | -                      | -                  | -                      | -         |
| Kam [23]     | China   | lung cancer | nRCT       | A: 85 B: 82    | A: bees B: - | NR         | NR              | A: B: granulocyte colony-stimulating factor | NR           | NR                    | NR                 | NR                 | NR        |
| Gwo [24]     | China   | chronic urticaria | RCT         | A: 50 B: 50    | A: bees B: - | NR         | NR              | A: herbal medicine B: acupuncture, herbal medicine | NR           | mild                  | NR                 | NR                 | NR        |
| Gwo [25]     | China   | ankylosing | RCT         | A: 30 B: 30    | A: bees    | NR         | NR              | A: Bee’s oral medicine B: western medicine | NR           | NR                    | NR                 | NR                 | NR        |
| Chiu [26]    | China   | rheumatoid arthritis | RCT         | A: 35 B: 35    | A: bees B: - | NR         | NR              | A: methotrexine B: methotrexine, prednisolone acetate | NR           | NR                    | NR                 | NR                 | NR        |
| Qi [27]      | China   | rheumatoid arthritis | RCT         | A: 49 B: 49    | A: bees B: - | NR         | NR              | A: NR B: western medicine | NR           | NR                    | NR                 | NR                 | NR        |
| She [28]     | China   | ankylosing | nRCT        | A: 68 B: 38    | A: bees B: - | NR         | NR              | A: chuna B: oral seraxib capsules | stomachache  | mild                  | SR                 | Gr2                 | possible  |
| Su [29]      | China   | ankylosing | CR          | NR             | bees       | NR         | NR              | none               | -                      | -                      | -                  | -                  |
| Su [30]      | China   | enlargement of mammary gland | RCT         | A: 30 B: 30 C: 30 | A: bees B: bees C: - | NR         | NR              | A: B: acupuncture C: acupuncture fever urticaria lymphoma cirrhosis bleeding | moderate     | SP                    | SR                 | Gr1                 | probable  |
| An [31]      | China   | cancerous pain from lung cancer | RCT         | A: 39 B: 39    | A: bees B: - | NR         | NR              | A: hydroxycodone tablets B: hydroxycodone tablets | NR           | NR                    | NR                 | NR                 | NR        |
| Yang [32]    | China   | rheumatoid arthritis | RCT         | A: 46 B: 46    | A: bees B: - | NR         | NR              | A: Chinese medicine B: routine treatment | NR           | NR                    | NR                 | NR                 | NR        |
| Wen [33]     | China   | ankylosing | RCT         | A: 40 B: 40    | A: bees B: - | NR         | NR              | A: fentanil sulfasalazine, diclofenac | NR           | NR                    | NR                 | NR                 | NR        |
| Wang [34]    | China   | cancer pain | RCT         | A: 44 B: 43    | A: bees B: - | NR         | NR              | A: fentanyl percutaneous patch B: fentanyl percutaneous patch | NR           | NR                    | NR                 | NR                 | NR        |
Table 1. Cont.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|------------------|------------------------|------------------------|------------------------|----------------------|------------------------|-----------|
| Zhang [35]   | China   | frozen shoulder | RCT        | A:33 B:32       | A:bees B:   | NR        | NR               | A: acupotomy           | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Zhang [36]   | China   | facial palsy   | RCT        | A:36 B:35       | A:bees B:   | NR        | NR               | A: acupuncture         | redness itching        | mild                  | NR                   | NR                   | Sp Gr1    |
| Zhou [37]    | China   | ankylosing     | CS         | 40             | bees       | NR        | NR               | Chinese medicine       | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Zhou [38]    | China   | rheumatoid arthritis | RCT      | A:40 B:30 C:30 | A:bees B:  | NR        | NR               | B: electro acupuncture | None                   | -                     | -                    | -                    | -         |
| Zhu [39]     | China   | ankylosing     | CS         | 56             | bees       | tested (negative) | NR               | Chinese medicine       | fever itching urticaria pain anaphylaxis | severe | Sp SR | Gr4         |
| Zeng [40]    | China   | ankylosing seed | RCT        | A:54 B:54      | A:bees B:   | NR        | NR               | A: moxibustion B: acupuncture | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Chen [41]    | China   | leukocyte reduction after colorectal cancer chemotherapy | nRCT | A:33 B:33     | A:bees B:  | NR        | NR               | A: white elm tablets   | fever                  | mild                  | NR                   | Sp Gr1    |
| Chen [42]    | China   | rheumatoid arthritis | RCT     | A:30 B:30      | A:bees B:   | NR        | NR               | A: oral methotrexate, celecoxib | none                  | -                     | -                    | -                    | -         |
| Peng [43]    | China   | cancer pain    | RCT        | A:31 B:33      | A:bees B:   | NR        | NR               | A: tramadol 100 mg      | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Peng [44]    | China   | cancer pain    | RCT        | A:30 B:30      | A:bees B:   | NR        | NR               | A: pain medicine 3rd phase | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Huang [45]   | China   | rheumatoid arthritis | RCT     | A:30 B:30      | A:bees B:   | NR        | NR               | A: hemp tablet         | NR                     | NR                     | NR                   | NR                   | Gr2       |
| Guo [46]     | China   | ankylosing     | RCT        | A:36 B:36      | A:bees B:   | NR        | NR               | A: western treatment    | NR                     | NR                     | NR                   | NR                   | Gr2       |
Table 1. Cont.

| First Author | Country | Reason          | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|-----------------|------------|-----------------|------------|-----------|-----------------|------------------------|------------------------|------------------------|----------------------|------------------------|------------|
| Deng         | China   | RA              | RCT        | A:20 B:20 C:20 | A:bees B: C: | NR        | NR              | A: metrotrexate B: metrotrexate C: strong metrotrexate | NR                     | NR | NR | NR | NR | NR |
| Liu          | China   | RA              | RCT        | A:50 B:50      | A:bees B:  | NR        | NR              | A: western medicine B: western medicine A: epalrestat, methylcobalamin B: epalrestat, methylcobalamin | none                   | - | - | - | - | - |
| Yang         | China   | diabetic neuropathy | RCT    | A:25 B:25       | A:bees B: | NR        | NR              | A: herbal fumigation B: diclofenac sodium minidose | NR                     | NR | NR | NR | NR | NR |
| Wen          | China   | postpartum pain | RCT        | A:41 B:40      | A:bees B:  | NR        | NR              | A: metrotrexate B: metrotrexate C: strong metrotrexate | NR                     | NR | NR | NR | NR | NR |
| Wen          | China   | postherpetic neuralgia | RCT  | A:36 B:36       | A:bees B:  | NR        | NR              | A: unknown injection | NR                     | NR | NR | NR | NR | NR |
| Wei           | China   | rheumatoid arthritis | RCT  | A:30 B:30       | A:bees B:  | NR        | NR              | A: methotrexate B: Chinese medicine A: massage, acupuncture | NR                     | NR | NR | NR | NR | NR |
| Ying         | China   | shoulder pain   | RCT        | A:60 B:60       | A:bees B:  | NR        | NR              | A: heating needle B: flunarizine hydrochloride capsule, mecobalamin sodium | NR                     | NR | NR | NR | NR | NR |
| Zhou         | China   | neurotic tinnitus | RCT        | A:30 B:30      | A:bees B:  | NR        | NR              | chuna | NR | NR | NR | NR | NR |
| Chen         | China   | lumbar disc herniation | CS     | 4000           | bees       | NR        | NR              | chuna | NR | NR | NR | NR | NR |
| Chen         | China   | rheumatoid arthritis | RCT  | A:30 B:30 C:30 | A:bees (high) B:bees (low) C: | NR        | NR              | A: xianlong granule B: methotrexate C: methotrexate 10 mg, cerecoxib 0.2 g | NR                     | NR | NR | NR | NR | NR |
| Qin          | China   | rheumatoid arthritis | RCT  | A:32 B:28      | A:bees B: | NR        | NR              | A: xianlong granule B: methotrexate | NR                     | NR | NR | NR | NR | NR |
| Han          | China   | diabetes        | CS         | 80             | bees       | NR        | NR              | Chinese medicine | NR | NR | NR | NR | NR |
| Kim          | Korea   | NR              | CR         | 1              | bees       | NR        | NR              | papules crust | moderate | SP | Gr1 | probable |
| Jeong        | Korea   | NR              | CR         | 1              | bees       | NR        | NR              | mycobacterium massilense granulomatous | moderate | SP | Gr1 | probable |


Table 1. Cont.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|------------------|------------------------|------------------------|----------------------|----------------------|----------------------|------------|
| Lee [61]     | Korea   | NR     | cohort     | 8580          | bees       | NR        | NR               | NR                     | anaphylaxis            | severe               | SR                  | Gr4                   | probable  |
| Yook [62]    | Korea   | effect | nRCT       | A: 19         | A: bees    | B:-       | NR               | 0.05x4                  | A:-                 | mild                 | SP SR                | Gr2                   | possible  |
| Lee [63]     | Korea   | osteoarthritis | RCT       | A: 25         | A, B, C: bees | D:-      | NR               | A:-0.7 mg; B:-1.5 mg; C:-2.0 mg; D:1000 mg | A, B, C: nabumetone | mild                 | SP SR                | Gr1                   | possible  |
| Kim [64]     | Korea   | lower urinary tract symptoms | CS        | 41            | bees       | NR        | NR               | NR                     | itching, body ache    | severe               | SP SR                | (1) Gr4 (2) Gr3 | probable |
| Kim [65]     | Korea   | NR     | CR         | 2             | bees       | NR        | NR               | NR                     | (1) hypotension, drowsy mentality, dyspnea, vomiting (2) itching sensation, urticaria, breathlessness, abdominal pain | severe               | SP SR                | (1) Gr4 (2) Gr3 | probable |
| Li [66]      | China   | rheumatoid arthritis | CS        | 225           | bees       | NR        | NR               | NR                     | none                 | -                    | -                    | -                    | -         |
| Ma [67]      | China   | cancer pain | CR         | NR            | bees       | NR        | 0.5 mg          | morphine sulfate        | constipation drowsy   | mild                 | SPSR                 | Gr1                   | possible  |
| Yeon [68]    | Korea   | low back pain | CR         | 2             | bees       | tested (negative) | 0.2 cc | (1) fire needling (2) | none                 | -                    | -                    | -                    | -         |
| Lee [69]     | Korea   | trigger finger | CR         | 1             | bees       | tested (negative) | 0.3 cc | NR            | none                 | -                    | -                    | -                    | -         |
| Hwang [70]   | Korea   | systemic sclerosis | CR         | 1             | bees       | tested (negative) | NR         | NR            | none                 | -                    | -                    | -                    | -         |
| Lee [71]     | Korea   | non-specific neck pain | RCT       | A: 30 B: 30   | A: bees    | B:-       | NR               | A: NR B: 180 mg        | A:-                 | -                    | -                    | -                    | -         |
| Kim [72]     | Korea   | knee OA   | nRCT       | A: 40 B: NR   | A: bees    | B:-       | NR               | NR                     | B: acupuncture       | -                    | -                    | -                    | -         |
| Han [73]     | Korea   | OA with DM | CR         | 1             | bees       | NR        | NR               | NR                     | physical therapy      | -                    | -                    | -                    | -         |
Table 1. Cont.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|------------------|------------------------|------------------------|----------------------|---------------------|----------------------|-----------|
| Lee          | Korea   | lower back pain | cohort     | 523           | bees       | NR        | 0.1–1.2 mL       | NR                     | local hypersensitivity | moderate             | SP                  | Gr1                  | possible  |
| Lee          | Korea   | Raynaud’s disease | CR         | 1             | bees       | NR        | NR              | herbal medicine (Gamiguibi-tang) | none                  | -                     | -                   | -                    | -         |
| Park         | Korea   | chemotherapy-induced peripheral neuropathy | CR         | 5             | bees       | tested (negative) | NR            | NR                     | none                  | -                     | -                   | -                    | -         |
| Bong         | Korea   | acute low back pain | CR         | 3             | bees       | NR        | NR              | acupuncture cupping herbal medicine physical therapy | none                  | -                     | -                   | -                    | -         |
| Jo           | Korea   | periungual warts | CR         | 11            | bees       | NR        | NR              | acupuncture herbal medicine moxibustion | none                  | -                     | -                   | -                    | -         |
| Castro Neves | Turkey  | treatment of systematic allergic reactions | CR         | 1             | bees       | tested (positive) | 100 µg       | NR                     | none                  | -                     | -                   | -                    | -         |
| Da Silva     | Australia | treatment of systematic allergic reactions | CR         | 2             | bees       | tested (positive) | 100 µg       | NR                     | (1) none (2) NR       | (1) - (2) NR         | (1) - (2) NR | (1) - (2) NR | -         |
| Ekstrom      | Germany  | treatment of systematic allergic reactions | CS          | A:46 B:68     | bees       | tested (positive) | NR            | omalizumab (4 cases) | NR                    | NR                   | NR                  | NR                   | -         |
| Fok          | Australia | treatment of systematic allergic reactions | cohort     | A:5 B:1      | A:bees B:wasp | tested (positive) | 100 µg×2       | NR                     | hypotensive systemic reactions | severe               | SR                  | Gr 4                  | probable  |
| Gür Çetinkaya | Turkey  | treatment of systematic allergic reactions | cohort     | 107           | wasp       | tested (positive) | NR            | NR                     | local reactions systematic reactions | NR                   | SP                  | SR                  | possible  |

NR: not reported; CR: case report; CS: case series; nRCT: non-randomized controlled trial; RCT: randomized controlled trial; SP: skin problem; SR: systemic reaction; CRPS: complex regional pain syndrome; Adverse events severity: Spilker’s classification Section 5.2.4. Table 5; Muller classification: Section 5.2.4. Table 6.

Table 2. Basic characteristics of VIT.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|------------------|------------------------|------------------------|----------------------|---------------------|----------------------|-----------|
| Castro Neves | Turkey  | treatment of systematic allergic reactions | CR         | 1             | bees       | tested (positive) | 100 µg       | NR                     | none                  | -                     | -                   | -                    | -         |
| Da Silva     | Australia | treatment of systematic allergic reactions | CR         | 2             | bees       | tested (positive) | 100 µg       | NR                     | (1) none (2) NR       | (1) - (2) NR         | (1) - (2) NR | (1) - (2) NR | -         |
| Ekstrom      | Germany  | treatment of systematic allergic reactions | CS          | A:46 B:68     | bees       | tested (positive) | NR            | omalizumab (4 cases) | NR                    | NR                   | NR                  | NR                   | -         |
| Fok          | Australia | treatment of systematic allergic reactions | cohort     | A:5 B:1      | A:bees B:wasp | tested (positive) | 100 µg×2       | NR                     | hypotensive systemic reactions | severe               | SR                  | Gr 4                  | probable  |
| Gür Çetinkaya| Turkey  | treatment of systematic allergic reactions | cohort     | 107           | wasp       | tested (positive) | NR            | NR                     | local reactions systematic reactions | NR                   | SP                  | SR                  | possible  |
| First Author          | Country   | Reason                                         | Paper Type | Number of Cases | Venom Type               | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|----------------------|-----------|-----------------------------------------------|------------|-----------------|--------------------------|-----------|------------------|------------------------|-------------------------|------------------------|----------------------|------------------------|------------|
| Gürçetinkaya         | Turkey    | treatment of systematic allergic reactions    | CS         | 107             | A:bees B:wasp C:bees,wasp | tested (positive) | NR                | NR                     | NR                      | NR                     | NR                   | SP SR                 | NR         | possible |
| Kappatou             | Greece    | treatment of systematic allergic reactions    | CR         | A:8 B:2        | A:wasp B:bees           | 6 tested (5 positive) | NR                | NR                     | NR                      | mild                   | SP SR                | NR                   | Gr1 Gr4     | possible |
| Kempinski            | Poland    | treatment of systematic allergic reactions    | CS         | 246             | wasp                    | NR                   | 100 µg           | NR                     | field re-stings          | mild                   | SR                   | Gr1 possible         | Gr1         | probable |
| Kochuyt              | Belgium   | treatment of systematic allergic reactions    | CS         | A:128 B:50     | A:wasp B:bees           | NR                   | 100 µg           | mild                   | 100–200 µg               | mild                   | SP SR                | Gr1 possible         | Gr1         | probable |
| Kolaczek             | Poland    | treatment of systematic allergic reactions    | cohort     | A:34 B:146     | A:bees B:wasp           | NR                   | ~100 mg          | mild                   | field stings anaphylaxis | severe                 | SP SR                | Gr1 possible         | Gr1         | possible |
| Mastnik               | Germany   | treatment of systematic allergic reactions    | cohort     | A:74 B:124     | A:bees B:wasp           | NR                   | ~100 µg          | mild                   | 100–400 µg               | mild                   | SR                   | Gr1 possible         | Gr1         | probable |
| Nittner-Marzalska     | Poland    | treatment of systematic allergic reactions    | cohort     | 341             | bees wasp               | NR                   | ~100 µg          | mild                   | 40–100 µg omalizumab (300 mg) | mild                   | SR                   | Gr1 possible         | Gr1         | possible |
| Puebla-Villaescusa    | Spain     | treatment of systematic allergic reactions    | CR         | 1               | bees                    | NR                   | ~100 µg          | mild                   | chest tightness oxygen desaturation hypotension | severe                 | SR                   | Gr4 probable         | -          | -        |
| Rettenèck            | Germany   | treatment of systematic allergic reactions    | cohort     | A:41 B:21 C:8  | A:bees B:wasp C:bees,wasp | NR                   | 100–200 µg      | mild                   | anaphylaxis              | mild                   | SP SR                | Gr1 possible         | Gr1         | probable |
| Sieber                | Germany   | treatment of systematic allergic reactions    | RCT        | A:30 B:30      | A:bees B:wasp           | NR                   | ~100 mg          | mild                   | anaphylaxis              | mild                   | SR                   | Gr1 possible         | Gr1         | probable |
| Treudler              | Germany   | treatment of systematic allergic reactions    | CS         | 20              | wasp                    | NR                   | ~210 mg          | mild                   | chest tightness oxygen desaturation hypotension | severe                 | SR                   | Gr4 probable         | -          | -        |
| Vachová              | Czech     | treatment of systematic allergic reactions    | nRCT       | A:80 B:65      | A:bees B:wasp           | NR                   | ~100 µg          | mild                   | anaphylaxis              | mild                   | SP SR                | Gr1 Gr4              | -          | -        |
| Vázquez-Revuelta      | Spain     | treatment of systematic allergic reactions    | CR         | 1               | NR                      | NR                   | ~100 µg          | mild                   | anaphylaxis              | severe                 | SR                   | Gr4 probable         | -          | -        |
| Wieczorek             | Germany   | treatment of systematic allergic reactions    | CR         | 1               | wasp                    | tested (positive)   | ~100 µg          | mild                   | anaphylaxis              | severe                 | SR                   | Gr4 probable         | -          | -        |

Table 2. Cont.
### Table 2. Cont.

| First Author          | Country     | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Mueller Classification | Causality |
|-----------------------|-------------|------------|-----------------|------------|-----------|-------------------|------------------------|------------------------|-------------------------|------------------------|-----------|
| Arzt-Gradwohl [98]    | Australia   | cohort     | 1425            | bees, wasp | NR        | NR                | NR                     | NR                     | NR                      | NR                     | GR1       |
| Hanzlikova [99]       | Czech       | CR         | 1               | wasp       | tested (positive) | NR                  | cetirizine 10 mg       | danazol 200 mg         | none                    | -                      | -         |
| Lanning [100]         | U.S.A.      | CR         | 1               | wasp       | NR         | 0.1–0.5 mL        | rash                   | mild                   | SP                      | GR1       | possible |
| Nittner-Marzaliska [101] | Poland      | CR         | 1               | wasp       | NR         | NR                | none                   | -                      | -                      | -         | -         |
| Pospischil [102]      | Australia   | cohort     | A:54 B:95       | A:bees, B:wasp | NR        | NR                | cluster rash ultra-rush | NR                     | SP                      | GR1       | possible |
| Toldra [103]          | France      | CR         | 1               | bees       | NR         | ~40 μg            | anaphylaxis            | severe                 | SR                      | GR4       | possible |
| Goh [104]             | Australia   | cohort     | 174             | bees       | NR         | NR                | rash                   | mild                   | SP                      | GR4       | probable |

VIT: venom immunotherapy

### Table 3. Basic characteristics of live bee sting.

| First Author | Country | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Mueller Classification | Causality |
|--------------|---------|------------|-----------------|------------|-----------|-------------------|------------------------|------------------------|-------------------------|------------------------|-----------|
| Utani [105]  | Japan   | CR         | 8               | bees       | NR        | -                 | -                      | erythema wheals anaphylaxis | mild severe             | SR                     | GR1       | GR4       | probable |
| Li [106]     | China   | RCT        | A:120 B:120     | bees       | NR        | A: lower B: higher | -                      | urticaria               | mild                   | SR                     | GR1       | possible |
| Wen [107]    | China   | CS         | 43              | tested (negative) | NR       | Chinese medicine | -                      | fever itching urticaria | mild                   | SR                     | GR1       | possible |
| Wen [108]    | China   | CS         | 40              | bees       | NR        | -                 | -                      | rash mild fever         | mild                   | SP                     | GR1       | possible |
| Chen [109]   | China   | RCT        | A:60 B:60       | A:bees, B:- | NR       | A:- B: oral methotrexate | none                | -                      | -                      | -                     | -         |
Table 3. Cont.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|-------------------|-----------------------|------------------------|----------------------|------------------|-----------------------|-----------|
| Qin [110]    | China   | shoulder-hand syndrome after CVA | RCT | A:36 B:36 | A:bees B:- | tested (negative) | 1~3 point | 1~3 ea | A: citicoline 0.75 g, DW5% or NS250 mL, rehabilitation treatment B: acupuncture, citicoline 0.75 g + DW5% or NS250 mL, rehabilitation treatment | none | - | - | - | - |
| Jiao [111]   | China   | primary menstrual pain | RCT | A:30 B:30 | A:bees B:- | NR | 1 ea~4 ea | A: oral ibuprofen capsule | none | - | - | - | - |
| Wu [112]     | China   | lumbar disc herniation | RCT | A:40 B:40 | A:bees B:- | NR | 1 ea~10 ea | A: Mckenzie methods, magneto thermal vibration therapy B: Mckenzie methods, magneto thermal vibration therapy | NR | NR | NR | NR | NR |

CVA: cerebrovascular accident

Table 4. Basic characteristics of external treatments.

| First Author | Country | Reason | Paper Type | Number of Cases | Venom Type | Skin Test | Injection Amount | Concomitant Treatment | Adverse Events Symptoms | Adverse Events Severity | Adverse Events Type | Mueller Classification | Causality |
|--------------|---------|--------|------------|----------------|------------|-----------|-------------------|-----------------------|------------------------|----------------------|------------------|-----------------------|-----------|
| Moon [113]   | Korea   | repigmentation of vitiligo | CR | 7 | bees | NR | NR | fractional CO2 laser | itching erythema | mild severe | SP | Gr1 | probable |
| Mo [114]     | China   | acne | CS | 40 | bees | NR | NR | - | burning itching desorption dryness | mild | SP | Gr1 | possible |
| Park [115]   | Korea   | chemotherapy-induced peripheral neuropathy | CR | 4 | bees | NR | NR | - | none | - | - | - | - |
| Yang [116]   | China   | tonsillitis | RCT | A:64B:61 | A:beesB:- | NR | NR | A: honey, oral ephelochal granules B: oral ephelochal granules | NR | NR | NR | NR | NR |
Table 5. Spilker’s adverse events classification.

| Mild       | Does Not Significantly Impair Daily Activities (Function) Nor Require Additional Medical Intervention |
|------------|--------------------------------------------------------------------------------------------------|
| Moderate   | Significantly impairs daily activities (function) and may require additional medical intervention but resolves afterwards |
| Severe     | Serious adverse events that requires intense medical intervention and leaves sequelae                |

Table 6. Classification of systemic reactions to insect stings by Mueller.

| Grade I          | Itch, Urticarial, Malaise, Anxiety                                                                 |
|------------------|---------------------------------------------------------------------------------------------------|
| Grade II         | Any of the above plus two or more of the following: angio-oedema, tight chest, nausea, vomiting, diarrhea, abdominal pain, dizziness |
| Grade III        | Any of the above plus two or more of the following: dyspnea, wheeze, stridor, hoarseness, weakness, feeling of impending doom |
| Grade IV         | Any of the above plus two or more of the following: hypotension, collapse, loss of consciousness, cyanosis |

2.3. Risk of Bias in Included Studies

Among the 37 RCTs, 1 study that used bee venom for the intervention group and wasp venom for the control group and 1 study that used different doses of bee venom for the intervention and control groups were excluded. For the remaining 35 RCTs, the interventions, control group treatment contents, evaluation index, results, and effective values were summarized. Subsequently, the risk of bias (RoB) was evaluated based on the content of the included studies.

All 35 studies in the first domain of random allocation and double blindness were evaluated as “some concerns.” In all studies, participants were randomly assigned. However, there was no information on blinding after the random assignment. All 35 studies were evaluated as “some concerns” in the second domain because there were dropouts, the sample size was not sufficient, or the caregiver was not blinded to the group assignment of the participants. In all 35 studies, the results of the study participants were evaluated as “low risk” because they appeared to be universally available to all participants. In the fourth domain, 8 studies were “low risk” because there was an objective outcome measurement method, but 27 studies were “high risk” because only scales based on the subjective symptoms of participants were used. All 35 studies were evaluated as having “some concerns” because no implementation plan or protocol was mentioned. The details are presented in Table 7 and Figures 2 and 3.
Figure 2. Risk of bias graph. Domain 1 (randomization process): random allocation and double blindness. Domain 2 (deviations from intended interventions): dropouts, insufficient sample size, and caregiver blindness. Domain 3 (missing outcome data): availability of results to all participants. Domain 4 (measurement of the outcome): appropriation or diversity of measurement methods. Domain 5 (selection of the reported result): this is performed by the implementation plan or protocol. Domain 6 (overall bias): combination of the five domains.
Figure 3. Risk of bias summary Domain 1 (randomization process): random allocation and double blindness. Domain 2 (deviations from intended interventions): dropouts, insufficient sample size, and caregiver blindness. Domain 3 (missing outcome data): availability of results to all participants. Domain 4 (measurement of the outcome): appropriation or diversity of measurement methods. Domain 5 (selection of the reported result): this is performed by the implementation plan or protocol. Domain 6 (overall bias): combination of the five domains.
Table 7. Characteristics of included RCTs.

| Author [Ref] | Condition                           | Sample Size | Treatment Time | Treatment Period | Intervention                  | Control                    | Evaluation Index | Results | p-Value (Significance) |
|--------------|-------------------------------------|-------------|----------------|------------------|--------------------------------|----------------------------|-------------------|---------|------------------------|
| Gwo [24]     | chronic urticaria                   | (A) 50      | NR             | NR               | (A) -bee venom injection       | (B) -herbal medicine       | (1) Efficacy rate |         | (1) p < 0.05           |
|              |                                     | (B) 50      |                |                  | (B) -acupuncture               |                           | (2) Recurrence rate |         | (2) p < 0.05           |
| Gwo [25]     | ankylosing spondylitis              | (A) 30      | NR             | NR               | (A) -bee venom injection       | (B) -western medicine      | Efficacy rate     | (A) 80.03% | significant             |
|              |                                     | (B) 30      |                |                  | (B) -bee’s oral medicine       |                           |                   | (B) 66.67% |                       |
| Chiu [26]    | rheumatoid arthritis                | (A) 35      | NR             | NR               | (A) -bee venom injection       | (B) -methotrexine prednisolone acetate | (1) Efficacy rate |         | (1) p < 0.05           |
|              |                                     | (B) 35      |                |                  | (B) -methotrexine              |                           | (2) Recurrence rate |         | (2) p > 0.05           |
| Qi [27]      | rheumatoid arthritis                | (A) 49      | NR             | NR               | (A) -bee venom injection       | (B) -western medicine      | (1) Efficacy rate |         | (1) p > 0.05           |
|              |                                     | (B) 49      |                |                  | (B) -methotrexine              |                           | (2) Recurrence rate |         | (2) p < 0.05           |
| Su [30]      | enlargement of mammary gland        | (A) 30      | 10             | NR               | (A) -bee venom injection       | (C) -acupuncture           | (1) Efficacy rate |         | (1) (A),(C) p > 0.05   |
|              |                                     | (B) 30      |                |                  | (B) -bee venom injection       |                           | (2) Breast pain, menstruation |         | (2) (A),(B) p > 0.05   |
|              |                                     | (C) 30      |                |                  | (C) -acupuncture               |                           | (3) Breast mass   |         | (3) (A),(B) p < 0.05   |
|              |                                     |             |                |                  |                               |                           | (4) Emotional changes |         | (4) (A),(B),(C) p > 0.05|
| An [31]      | cancerous pain from lung cancer     | (A) 39      | NR             | 20 days          | (A) -bee venom injection       | (B) -hydroxycode tablets  | Efficacy rate     | (A) 82.05% | p < 0.05               |
|              |                                     | (B) 39      |                |                  | (B) -hydroxycode tablets       |                           |                   | (B) 61.54% |                       |
| Yang [32]    | rheumatoid arthritis                | (A) 46      | NR             | 30 days          | (A) -bee venom injection       | (B) -routine treatment     | (1) Efficacy rate |         | (1) p < 0.05           |
|              |                                     | (B) 46      |                |                  | (B) -herbal medicine           |                           | (2) Recurrence rate |         | (2) p < 0.05           |
| Wen [33]     | ankylosing spondylitis              | (A) 40      | NR             | 12 weeks         | (A) -bee venom injection       | (B) -sulfasalazine         | (1) Efficacy rate |         | (1) p > 0.05           |
|              |                                     | (B) 40      |                |                  | (B) -diclofenac                |                           | (2) Adverse events rate |         | (2) NR                  |
### Table 7. Cont.

| Author [Ref] | Condition                  | Sample Size | Treatment Time | Treatment Period | Intervention                                                      | Control                                  | Evaluation Index | Results | p-Value (Significance) |
|--------------|----------------------------|-------------|----------------|------------------|------------------------------------------------------------------|------------------------------------------|------------------|---------|------------------------|
| Wang [34]    | cancer pain                | (A) 44 (B) 43 | NR             | NR               | (A) -bee venom injection -fentanyl percutaneous patch (B) -fentanyl percutaneous patch | (1) Efficacy rate (2) Quality of life (3) Pain intensity (4) Adverse event rate | NR               | (1) p < 0.01 (2) p < 0.05 (3) p < 0.05 (4) p < 0.01 |
| Zhang [35]   | frozen shoulder            | (A) 33 (B) 32 (C) 32 | NR             | NR               | (A) -bee venom injection -acupotomy (B) -triamcinolone acetonide -acupotomy | Efficacy rate                                  | (A) 100% (B) 100% (C) 93.75% | NR               |
| Zhang [36]   | facial palsy               | (A) 36 (B) 35 | 4 weeks        | (A) -bee venom injection (B) -acupuncture                      | (1) H-B Grade (2) Sunnybrook scale (3) Efficacy rate | (1) NR (2)NR (3) | (1) p > 0.05 (2) p < 0.05 (3) p < 0.05 |
| Zhou [38]    | rheumatoid arthritis       | (A) 40 (B) 30 (C) 30 | NR             | NR               | (A) -bee venom injection -electro acupuncture -western medicine | Blood test level                              | NR               | NR               |
| Zeng [40]    | ankylosing spondylitis     | (A) 54 (B) 54 | NR             | NR               | (A) -bee venom injection -acupotomy -moxibustion (B) -acupuncture | Efficacy rate                                  | (A) 74.07% (B) 42.31% | p < 0.05 |
| Chen [42]    | rheumatoid arthritis       | (A) 30 (B) 30 | NR             | NR               | (A) -bee venom injection -oral methotrexate -celecoxib | (1) Efficacy rate (2) VAS                      | NR               | (1) p < 0.05 (2) p < 0.05 |
| Peng [43]    | cancer pain                | (A) 31 (B) 33 | NR             | NR               | (A) -bee venom injection -tramadol 100 mg (B) -tramadol 100 mg | (1) Pain relief (2) Quality of life (3) Adverse event relief (4) Systemic symptoms | NR               | (1) p < 0.01 (2) p < 0.05 (3) p < 0.05 (4) p < 0.05 |
| Peng [44]    | cancer pain                | (A) 30 (B) 30 | 30             | 30 days          | (A) -bee venom injection -pain medicine 3rd phase (WHO recommended) (B) -pain medicine 3rd phase (WHO recommended) | (1) Efficacy rate (2) Adverse event rate | (A) 96.67% (B) 90.03% (2)NR | (1) p < 0.05 (2) p < 0.05 |
| Huang [45]   | rheumatoid arthritis       | (A) 30 (B) 30 | 30             | NR               | (A) -bee venom injection -hemp tablets | Efficacy rate                                  | (A) 100% (B) 86.7% | p < 0.01 |
| Guo [46]     | ankylosing spondylitis     | (A) 36 (B) 36 | NR             | NR               | (A) -bee venom injection -western treatment | Efficacy rate                                  | (A) 94.44% (B) 72.22% | significant |
| Deng [47]    | rheumatoid arthritis       | (A) 20 (B) 20 (C) 20 | 60 days        | (A) -bee venom injection -metrotrexate (C) -strong metrotrexate | (1) Clinical symptoms (2) Blood test level | NR               | NR               |
| Author [Ref] | Condition | Sample Size | Treatment Time | Treatment Period | Intervention | Control | Evaluation Index | Results | p-Value (Significance) |
|--------------|-----------|-------------|----------------|------------------|--------------|---------|------------------|---------|----------------------|
| Liu [48]     | rheumatoid arthritis | (A) 50 (B) 50 | NR | 3 months | (A) -bee venom injection -western medicine | (B) -western medicine | (1) Efficacy rate (2) Symptoms (3) Adverse event and recurrence rate | NR | (1) p < 0.05 (2) p < 0.05 (3) p < 0.05 |
| Yang [49]    | diabetic neuropathy | (A) 25 (B) 25 | 15 | 15 days | (A) -bee venom injection -epalrestat -methylcobalamin | (B) -epalrestat -methylcobalamin | (1) Neurotransmission speed (2) Hydrogen peroxide enzyme level (3) Glutathione level | NR | (1),(2),(3) p < 0.05 |
| Wen [50]     | postpartum pain | (A) 41 (B) 40 | NR | 8 weeks | (A) -bee venom injection -herbal fumigation | (B) -diclofenac natrium minidose | Efficacy rate | (A) 95.2% (B) 77.5% | p < 0.01 |
| Wen [51]     | postherpetic neuralgia | (A) 36 (B) 36 | NR | 12 weeks | (A) -bee venom injection | (B) -injection(unknown) | (1) Efficacy rate (2) Blood serum test (3) Adverse event rate | (A) (1) 97.22% (2) 77.7% (3) NR | (1) p < 0.05 (2) p < 0.05 (3) p > 0.05 |
| Wei [52]     | rheumatoid arthritis | (A) 30 (B) 30 | NR | NR | (A) -bee venom injection | (B) -Chinese medicine | (1) Efficacy rate (2) VAS (3) Blood serum test (4) Adverse event rate | (A) (1) 90.00% (2) 66.66% (B) (3) NR | (1) p < 0.05 (2) p < 0.05 (3) p > 0.05 (4) p > 0.05 |
| Ying [53]    | Shoulder pain | (A) 60 (B) 60 | NR | 4 weeks | (A) -bee venom injection -massage -acupuncture | | (1) Efficacy rate (2) McGill pain scale (3) Constant-Murley score (4) Rådlett analysis | (A) (1) 95.00% (2) 83.33% (B) (3) NR | (1) p < 0.05 (2) p < 0.01 (3) p > 0.05 (4) p < 0.05 |
| Zhou [54]    | neurotic tinnitus | (A) 30 (B) 30 | NR | 4 weeks | (A) -bee venom injection -heating needle | (B) -flunarizine hydrochloride capsule -mecobalamin minidose | (1) Hearing impairment threshold level (2) Tinnitus (3) SDS level (4) Efficacy rate | (1),(2),(3) NR (4) (A) (1) 83.33% (2) 66.67% | (1) p < 0.01 (2) p < 0.01 (3) p > 0.05 (4) p < 0.05 |
| Chen [56]    | Rheumatoid arthritis | (A) 30 (B) 30 (C) 30 | (A),(B) 24 (C) 56 | 8 weeks | (A) -bee venom injection (high dose) -methotrexate 10 mg -diclofenac 0.2 g | (B) -bee venom injection (low dose) -cerecoxib 0.2 g | Efficacy rate | (A) 86.67% (B) 70.00% (C) 76.67 | p < 0.05 |
| Qin [57]     | rheumatoid arthritis | (A) 32 (B) 28 | NR | 3 months | (A) -bee venom injection -xianlong granule | (B) -methotrexate | (1) Efficacy rate (2) TCM syndrome score (3) VAS (4) DAS (5) HAQ score (6) Adverse event rate | (A) (1) 90.6% (2) 85.7% (3) NR | (1) p > 0.05 (2) p > 0.05 (3) p > 0.05 (4) p > 0.05 (5) | (1),(2),(3),(4),(5),(6) p < 0.05 (7) p < 0.05 |
Table 7. Cont.

| Author [Ref] | Condition                | Sample Size | Treatment Period | Intervention                                                                                       | Control                      | Evaluation Index                        | Results                                      | p-Value (Significance) |
|--------------|--------------------------|-------------|------------------|--------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------|----------------------------------------------|------------------------|
| Won [63]     | osteoarthritis           | (A) 25      | 6 weeks          | (A) -bee venom injection (~0.7 mg)                                                               | (D) -nabumetone 1000 mg     | Efficacy rate                            | NR                                           | (A) (B) (C) (D) p < 0.01 (B) (C) (A) p < 0.01 |
|              |                          | (B) 26      |                  | (B) -bee venom injection (~1.5 mg)                                                                |                              |                                          |                               |                        |
|              |                          | (C) 26      |                  | (C) -bee venom injection (~2.0 mg)                                                                |                              |                                          |                               |                        |
|              |                          | (D) 24      |                  | (D) -nabumetone 1000 mg                                                                        |                              |                                          |                               |                        |
| Lee [71]     | non-specific neck pain   | (A) 30      | ≥ 3 months       | (A) -bee venom injection                                                                      | (B) -loxoprofen 180 mg      | Clinical symptoms                        | NR                                           | NR                     |
|              |                          | (B) 30      |                  | (B) -loxoprofen 180 mg                                                                         |                              |                                          |                               |                        |
| Chen [109]   | rheumatoid arthritis     | (A) 60      | 8 weeks          | (A) -live bee sting                                                                            | (B) -oral methotrexate     | (1) Efficacy rate (2) Morning stiffness,  | (1) (A) 83.33% (B) 80.00% (2) NR | (1) p > 0.05 (2) p > 0.05 |
|              |                          | (B) 60      |                  | (B) -oral methotrexate                                                                        |                              |                                          |                               |                        |
| Qin [110]    | shoulder–hand syndrome   | (A) 36      | 3 weeks          | (A) -live bee sting, acupuncture, citalcine 0.75 g, DW5% or NS250 mL, rehabilitation treatment | (B) -acupuncture, citalcine 0.75 g, DW5% or NS250 mL, rehabilitation treatment | (1) Efficacy rate                  | (1) (A) 93.75% (B) 73.53% (2) NR   | (1) p > 0.05 (2) p > 0.01 |
|              | after CVA                | (B) 36      |                  | (B) -acupuncture, citalcine 0.75 g, DW5% or NS250 mL, rehabilitation treatment                    |                              |                                          |                               |                        |
| Jiao [111]   | primary menstrual pain   | (A) 30      | 3 months         | (A) -live bee sting                                                                            | (B) -oral ibuprofen capsules | (1) Efficacy rate                        | (1) (A) 93.3% (B) 76.6% (2) (A) 100% (B) 0% | (1) p < 0.05 (2) p < 0.05 |
|              |                          | (B) 30      |                  | (B) -oral ibuprofen capsules                                                                    |                              |                                          |                               |                        |
| Wu [112]     | lumbar disc herniation   | (A) 40      | 2 weeks          | (A) -live bee sting, magneto thermal vibration therapy, Mckenzie methods 7                      | (B) -Mckenzie methods, Magneto thermal vibration therapy    | (1) VAS (2) ODI (3) TCM score (4) Clinical efficacy rate | (1) (2) (3) NR (4) (A) 95% (B) 80% | (1) p < 0.05 (2) p < 0.05 (3) p < 0.05 (4) p < 0.05 |
|              |                          | (B) 40      |                  | (B) -Mckenzie methods, Magneto thermal vibration therapy, Mckenzie methods 7                    |                              |                                          |                               |                        |
| Yang [116]   | Tonsillitis              | (A) 64      | 5 days           | (A) -bee venom externals, oral cephalocolonal granules                                         | (B) -oral cephalocolonal granules | (1) Efficacy rate                        | (1) (A) 100% (B) 90.2% (2) (A) 3.1% (B) 1.6% | (1) p < 0.05 (2) p < 0.05 |
|              |                          | (B) 61      |                  | (B) -oral cephalocolonal granules                                                               |                              |                                          |                               |                        |

NR: not reported; H-B grade: House–Brackmann grade; VAS: Visual Analog Scale; SDS: Self-Depression Scale; TCM syndrome score: Traditional Chinese Medicine syndrome score; DAS: Diseases Activity Score; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein; ODI: Oswestry Low Back Pain Disability Index.
3. Discussion

We conducted a literature search using eight databases: PubMed, Cochrane, EMBASE, CINAHL, CNKI, NDSL, OASIS, KISS, KoreaMED, and KMBASE. However, there were many cases in which access to Chinese-based databases was not possible, so an additional literature search could not be performed. Ultimately, 105 studies were included. There were forty-nine, twenty-eight, six, five, four, three, two, two, one, one, one, and one studies from China, Korea, Germany, Australia, Poland, Turkey, Spain, Czech Republic, Greece, Belgium, France, and Japan, respectively. As for the paper type, there were 37 RCTs, 33 CRs, 15 CSs, 14 cohort studies, and 6 nRCTs.

When classified according to the stimulation method of bee venom, there were 67, 26, 8, and 4 studies on extract injections, VIT, live bee stings, and external preparations, respectively. Twenty-seven studies described the injection capacity of bee venom, but few studies specifically described the dose that was injected into how many acupoints.

Twenty-eight studies reported no adverse events, thirty-four specifically reported adverse events, and the remaining forty-three studies partially or failed to describe adverse events. Seven of the forty-six studies did not describe specific symptoms of adverse events but described adverse events such as “skin problem” and “systemic reaction”. Based on Mueller’s classification, twenty-nine cases were grade I and two cases were grade II with the patients complaining of abdominal pain, chest pain, and vomiting. There was also one case of grade III, with the patient presenting with weakness and dyspnea, and eleven cases of grade IV, with patients suffering from hypotension and cyanosis. According to Spilker’s classification, 26 cases were “mild” with no functional disruption to daily activities, 4 cases were “moderate” with symptoms disappearing over time when additional treatment was applied, and 11 cases were “severe” with immediate treatment required or after-effects. Regarding “mild” symptoms, there were cases where it was accompanied by “moderate” to “severe” symptoms.

Bee venom injections are performed using refined bee venom. In this process, active ingredients can be extracted separately and allergens can be removed. Moreover, the capacity and concentration of the bee venom injections can be easily controlled [117]. Depending on the venom to be purified, snakes [118] and jellyfish [119] can be used instead of bees. However, as an invasive treatment, there may be a risk of infection, depending on the injection site. In addition, since the unification of terms, such as bee venom acupuncture and bee venom pharmacopuncture, has not been achieved, it is necessary to establish appropriate terminology.

VIT is a prophylactic method that aims to reduce hypersensitivity in individuals with hypersensitivity to venom [120]. If adverse events occur during follow-up, additional treatment such as the oral administration of omalizumab, an anti-IgE, may be introduced [121]. However, in the case of VIT, since it is targeted at people who have already experienced adverse events or hypersensitivity, it seems that the definition of an adverse event should be different.

Live bee stings may have similar effects to bee venom injections but are clinically impractical because they require live bees [122]. Bees vary slightly in composition and concentration, depending on the type and growth area [123]. In addition, live-bee dermatitis may occur if infected [124]. Since this method directly uses bees to sting, criteria that detail the infection control process, effective bee type, recommended time, and/or the number of stings are needed.

Bee venom is sometimes used as an external preparation, and honey, royal jelly, and bee venom are used to treat and prevent oral diseases [125], while cream containing bee venom is used to improve wrinkles [126]. A direct correlation between bee venom allergy and bee products has not been revealed, but some people are allergic to honey or propolis [127]. In the case of external preparations, more clinical studies are needed to determine the correlation between the concentration of ingredients, the amount of application, and allergies.
Of the 105 studies included in this review, only 63 reported specifically on the adverse events that occurred. VIT seems to be used in many Western countries, whereas bee venom injections and live bee stings seem to be used in many Eastern countries. Since the method of bee venom stimulation differs by country and culture, it is thought that the reporting method for the adverse events that occur may be different. There are criteria such as Mueller’s and Spilker’s classification, but these criteria do not appear to be essential in the reporting of venom treatment. Since bee venom has the potential to cause anaphylaxis, reports of side effects must be included in venom clinical trials.

RoB evaluation was conducted on 35 RCT studies. Each domain explains a randomization process, deviations from intended interventions, missing outcome data, a measurement of the outcome, selection of the reported result and overall bias. As shown in the RoB results, there were no studies with a low RoB. To supplement this study, objective and diverse scales are required in large RCTs to evaluate the effectiveness of bee venom, and a rigorous reporting framework for adverse events should be presented.

From the 105 studies reviewed, there were 10 studies in which Mueller’s grade IV adverse events occurred (3 extract injection studies, 6 VIT studies, and 1 live bee sting study). Only 2 studies were conducted in advance. The most serious adverse events that can occur with bee venom treatment were anaphylaxis and unrecoverable sequelae. Since there is a possibility of anaphylaxis, it is recommended that a person with medical knowledge manages patients undergoing a bee venom procedure. Further research is needed on the relationship between skin test results and serious adverse events. However, to reduce the occurrence of serious adverse events in clinical practice, skin tests should be conducted prior to treatment. In addition, since skin tests are used to adjust the concentration and capacity of the active ingredient, the live bee sting type is not recommended. In the selected papers, the capacity of bee venom was expressed in various ways, such as mL and cc. When researchers write papers or conduct experiments, it is necessary to use general units such as mg/kg, or to specify capacity units and concentrations of effective ingredients according to the purpose of the study. This study focuses on the adverse events of bee venom. If an additional comparative study on the effect, adverse events rate, and fatality rate according to the stimulation type is conducted, the clinician may use bee venom in consideration of the effect and adverse events.

4. Conclusions

This study reviewed the adverse effects of bee venom stimulation. Most of the RoB evaluations of RCT studies were not significant, and large-scale RCT studies with a system for reporting adverse events of bee venom are required. A skin test is needed to reduce the occurrence of adverse events, and a person who can cope with anaphylaxis should perform a bee venom procedure. It was confirmed that many studies omitted reports of adverse events. In order to analyze the occurrence and fatality rate of adverse events according to the stimulation type, it is essential to include a report of adverse events when using bee venom.

5. Methods

5.1. Search Method for Identifying Studies

This study included eight databases: PubMed (National Center for Biotechnology Information, Bethesda, Maryland, U.S.A.), Cochrane (John Wiley & Sons, Inc., London, UK, 2000), CINAHL (EBSCO Industries, Birmingham, AL, USA), CNKI (Tongfang Knowledge Network Technology Co., Ltd., Beijing, China, 2014), NDSL (Korea Institute of Science and Information Technology, Daejeon, Korea), OASIS (Korea Institute of oriental medicine, Daejeon, Korea, 2016), KISS (Korea Studies Information Co., Ltd., Paju, Gyeonggi-do, Korea), KoreaMED (Korea Association of Medical Journal Editors, Seoul, Korea), and KMBASE (MedRIC, Cheongju, Chungcheongbuk-do, Korea, 2000). The search was conducted using “bee venom acupuncture” and “adverse events” as keywords. There were no restrictions on the country or the language of the issue. The search was conducted up to 28 February 2022.
5.2. Inclusion Criteria

5.2.1. Types of Studies

CRs, CSs, and nRCTs were included. Experimental, animal, and protocol studies were excluded.

5.2.2. Types of Participants

There were no special restrictions on the diseases treated and patient characteristics.

5.2.3. Types of Interventions

All treatments using bee venom were included in the intervention group. Non-intervention cases were excluded even if bee venom was used. In the case of RCTs, group classification according to the capacity of bee venom was included. Studies that included individuals who were accidentally stung by a bee (i.e., the sting was not part of their treatment) were excluded. There were no restrictions on the comparison group.

5.2.4. Types of Outcome Measures

Contents related to adverse events were also extracted. The symptoms were classified into skin problems, systemic reactions, and others. The severity of the symptoms was classified as mild, moderate, and severe according to Spilker’s classification (Table 5) [128] and grades I to IV according to Mueller’s classification (Table 6) [129]. Causality was classified as certain, probable, possible, unlikely, unclassified, and unclassifiable according to the WHO-UMC causality scale (Table 8) [130]. No adverse events were described as “non-reported,” and no adverse events were “none”.

Table 8. WHO-UMC causality categories.

| Causality Term          | Assessment Criteria                                                                 |
|------------------------|---------------------------------------------------------------------------------------|
| Certain                | -Event or laboratory test abnormality, with plausible time relationship to drug intake |
|                        | -Cannot be explained by disease or other drugs                                        |
|                        | -Response to withdrawal plausible (pharmacologically, pathologically)                 |
|                        | -Event definitive pharmacologically or phenomenologically (i.e., and objective and specific medical disorder or a recognized pharmacological phenomenon) |
|                        | -Rechallenge satisfactory, if necessary                                               |
| Probable/Likely        | -Event or laboratory test abnormality, with reasonable time relationship to drug intake |
|                        | -Unlikely to be attributed to disease or other drugs                                   |
|                        | -Response to withdrawal clinically reasonable                                         |
|                        | -Rechallenge not required                                                             |
| Possible               | -Event or laboratory test abnormality, with reasonable time relationship to drug intake |
|                        | -Could also be explained by disease or other drugs                                     |
|                        | -Information on drug withdrawal may be lacking or unclear                             |
| Unlikely               | -Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) |
|                        | -Disease or other drugs provide plausible explanations                                 |
| Conditional/Unclassified | -Event of laboratory test abnormality                                                |
|                        | -More data for proper assessment needed, or                                           |
|                        | -Additional data under examination                                                    |
| Unassessable/Unclassifiable | -Report suggesting and adverse reaction                                               |
|                        | -Cannot be judged because information is insufficient or contradictory                |
|                        | -Data cannot be supplemented or verified                                              |

5.3. Data Selection and Extraction

5.3.1. Selection of Studies

Two authors (JY and GL) independently searched each of the eight databases based on the abstracts. The full text was checked for papers for which the abstract was insuffi-
cient. The entire process was summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 4) [131].

Figure 4. PRISMA flow diagram of the study selection. EMBASE: Excerpta Medica database; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNKI: China National Knowledge Infrastructure; NDSL: National Discovery for Science Library; OASIS: Oriental Medicine Advanced Searching Integrated System; KISS: Korean Studies Information Service System; KMBASE: Korea Medical database.

The study selection process is summarized in Figure 4. Duplicate studies and those that did not meet the selection criteria were excluded.
5.3.2. Data Extraction

One author (JY) extracted the data, and the other (GL) inspected the extracted data. The number of participants, type of bee venom treatment method, outcomes, and the information related to adverse events were recorded.

5.3.3. Assessment RCTs

Two reviewers evaluated the bias of RCT studies using the RoB evaluation [132]. The bias evaluation item consisted of five categories: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. The first domain is whether random assignments and double blindness are properly performed, and the second domain is whether the dropout rate is high, the sample size is sufficient, or the caregiver is aware of the group assignment of the participants. The third domain concerned whether the results of the study were all available to the study participants. The fourth domain relates to whether the method of measuring results is the same and appropriate between groups, and the fifth domain relates to whether the research results were conducted using a pre-protocol. In addition, overall bias was evaluated by synthesizing five evaluation items. In each item, if there is no RoB, it is marked as “low risk”, if the RoB was high as “high risk”, and if there is no information on the item, it was marked as “some concerns”.

Author Contributions: Manuscript draft version writing, J.Y. Manuscript editing, supervision and project administration, G.L. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT)—No. NRF-2022R1I1A3068255.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data used in this study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflict of interest regarding the publication of this paper.

References

1. Ahn, C.B.; Youn, H.M.; Cho, E.J. An Investigation of Directions of Research on Bee Venom in the Sphere of Oriental Medicine in Korea in Last Decade. Dong-Eui-Han-Eui-Yeon 2011, 5, 23–42.
2. Karimzadeh, L.; Nabiuni, M.; Kouchesfehani, H.M.; Adham, H.; Bagheri, A.; Sheikholeslami, A. Effect of bee venom on IL-6, COX-2 and VEGF levels in polycystic ovarian syndrome induced in Wistar rats by estradiol valerate. J. Venom. Anim. Toxins Incl. Trop. Dis. 2013, 19, 32. [CrossRef] [PubMed]
3. Oršolić, N. Bee venom in cancer therapy. Cancer Metastasis Rev. 2012, 31, 173–194. [CrossRef] [PubMed]
4. An, H.J.; Kim, J.Y.; Kim, W.H.; Gwon, M.G.; Gu, H.M.; Jeon, M.J.; Han, S.M.; Pak, S.C.; Lee, C.K.; Park, I.S.; et al. Therapeutic effects of bee venom and its major component, melittin, on atopic dermatitis in vivo and vitro. Br. J. Pharmacol. 2018, 175, 4310–4324. [CrossRef]
5. Park, J.H.; Yim, B.K.; Lee, J.-H.; Lee, S.H.; Kim, T.-H. Risk Associated with Bee Venom Therapy: A Systematic Review and Meta-Analysis. PLoS ONE 2015, 10, e0126971. [CrossRef]
6. Jang, S.B.; Kim, K.H. Clinical Effectiveness and Adverse Events of Bee Venom Therapy: A Systematic Review of Randomized Controlled Trials. Toxins 2020, 12, 558. [CrossRef]
7. Elieh Ali Komi, D.; Shafaghat, F.; Zwiener, R.D. Immunology of Bee Venom. Clin. Rev. Allergy Immunol. 2018, 54, 386–396. [CrossRef]
8. Ko, S.-H.; Oh, H.-M.; Kwon, D.-Y.; Yang, J.-E.; Kim, B.-J.; Ha, H.-J.; Lim, E.-J.; Oh, M.-S.; Son, C.-G.; Lee, E.-J. Incidence Rate of Bee Venom Acupuncture Related Anaphylaxis: A Systematic Review. Toxins 2022, 14, 238. [CrossRef]
9. Liberman, P. Anaphylaxis. Med. Clin. N. Am. 2006, 90, 77–95. [CrossRef]
10. Silva, D.; Singh, C.; Muraro, A.; Worm, M.; Alviani, C.; Cardona, V.; DunnGlvin, A.; Garvey, L.H.; Riggioni, C.; Angier, E.; et al. Diagnosing, managing and preventing anaphylaxis: Systematic review. Allergy 2021, 76, 1493–1506. [CrossRef]
11. Hernandez, L.; Papalia, S.; Pujalte, G.G.A. Anaphylaxis. Prim. Care 2016, 43, 477–485. [CrossRef]
124. Park, J.S.; Lee, M.J.; Chung, K.H.; Ko, D.K.; Cung, H. Live bee acupuncture (Bong-Chim) dermatitis: Dermatitis due to live bee acupuncture therapy in Korea. *Int. J. Dermatol.* **2013**, *52*, 1519–1524. [CrossRef]

125. Otreba, M.; Marek, L.; Tyczynska, N.; Stojko, J.; Stojko, A.R. Bee Venom, Honey, and Royal Jelly in the Treatment of Bacterial Infections of the Oral Cavity: A Review. *Life* **2021**, *11*, 1311. [CrossRef]

126. Samanci, A.E.T.; Kekecoglu, M. Development of a cream formulation containing bee venom and other bee products. *J. Cosmet. Dermatol.* **2022**. [CrossRef]

127. Cifuentes, L. Allergy to honeybee not only stings. *Curr. Opin. Allergy Clin. Immunol.* **2015**, *15*, 364–368. [CrossRef] [PubMed]

128. Spilker, B. Interpretation of Adverse Reactions. In *Guide to Clinical Trials*; Raven Press, Ltd.: New York, NY, USA, 1991; pp. 565–587.

129. Mueller, H.L. *Insect Sting Allergy*; Gustav Fischer: Stuttgart, Germany, 1990.

130. World Health Organizations. *The Use of the WHO-UMC System for Standardized Case Causality Assessment*; World Health Organizations: Uppsala, Sweden, 2005.

131. Shamseer, L.; Moher, D.; Clarke, M.; Chersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* **2015**, *349*, g7647. [CrossRef] [PubMed]

132. Higgins, J.P.T.; Savovic, J.; Page, M.J.; Elbers, R.G.; Sterne, J.A.C. Chapter 8: Assessing risk of bias in a randomized trail. In *Cochrane Handbook for Systematic Reviews of Interventions, Version 6.2*; Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., Eds.; (Updated February 2021); Cochrane: London, UK, 2021.