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Review

Beneficial Effect of Bee Venom Therapy as an Adjunctive Treatment of Parkinson's Disease: A Systematic Review & Meta-Analysis

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Abstract

The second most prevalent progressive neurodegenerative disorder in the world is Parkinson's disease (PD). According to many studies, the majority of the existing PD therapies are symptomatic and may result in motor problems, such as dyskinesia and fluctuations. To overcome these complications, various reports have proposed the use of bee venom as an effective treatment. Bee venom can suppress the neuroinflammation effect in PD mouse models, indicating its potential as an effective adjuvant treatment for the disease in humans. Thus, the purpose of this study was to evaluate the therapeutic potential of bee venom treatment (BVT) as a PD adjuvant. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards were followed during the processes. In addition, a literature search was performed on various electronic databases, including PubMed, EBSCO, and ProQuest. After evaluating the included papers' quality using the Risk of Bias Tool 2.0 (RoB 2) as well as RoB In Non-randomized Studies of Interventions (ROBINS-I), a meta-analysis was carried out using Review Manager (RevMan) 5.4. Four publications in total have been analyzed in the systematic review as well as meta-analysis based on the inclusion criteria. The results showed that three and one articles had low and moderate risk of bias, respectively. The BDI score between the bee venom and control groups had a statistically significant p-value (SMD=-0.52, 95%CI= -0.93 to -0.11, p=0.01) according to the meta-analysis. Nevertheless, following the therapy, there were no discernible improvements in UPDRS II, III, and II+III, as well as PDQL, gait speed & number, MXE, and DCL. The findings also showed that bee venom significantly improved BDI scores in PD patients. Although the positive trends observed in other outcomes were not statistically significant, further investigation with larger cohorts is required to validate these findings.

Keywords: Acupuncture therapy; Apitherapy; Bee venom therapy; Parkinson's disease

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Introduction

The second most prevalent progressive neurodegenerative disorder in the world is Parkinson's disease (PD) [1]. According to the UK Parkinson's Disease Society Brain Bank, the clinical criteria for diagnosing PD require the presence of bradykinesia along with rigidity, 4–6 Hz rest tremor, or postural instability presence [2]. The incidence and prevalence of this disorder have been reported to increase with age. This is consistent with a previous study, where 25% of affected individuals experience PD before the age of 65 years, with 5-10% being under the age of 50. In addition, individuals under the age of 40 years have been shown to have the potential to develop PD, known as young-onset PD [3].

At present, the treatments for PD are predominantly focused on controlling motor symptoms using pharmacological therapy [1]. In addition, there are two major types of medications commonly used for the disease, namely drugs based on exogenous administration of compounds with dopaminergic activity (e.g. levodopa, dopamine agonists) and those that inhibit the metabolism of endogenous dopamine (e.g. COMT, MAO-B inhibitors) [4]. Levodopa is a medication that is frequently used to treat PD and has been shown to be beneficial. But after using levodopa for five years, around half of the patients usually experience side effects from the drug, such as dyskinesia and motor irregularities [5]. A previous report revealed that certain non-motor symptoms, such as orthostatic hypotension or psychosis were often worsened by dopaminergic treatment, and several features of PD did not respond adequately to optimal pharmacotherapy. As the disease progresses, these difficulties usually worsen because neurodegeneration progressively damages non-dopaminergic brain regions [3]. Due to these difficulties, a novel therapeutic approach and adjuvant medications with fewer side effects are needed to reduce the dependence on levodopa. Consequently, several studies have proposed the use of complementary and alternative medicine (CAM), particularly bee venom, which has recently gained popularity as an adjunctive drug.

In line with previous studies, apitherapy comprises the use of honeybee products, particularly bee venom for the treatment of various diseases in humans [6]. Bee venom treatment (BVT) can be carried out using different approaches, including live bee stings, topical application of bee venom ointments, bee venom acupuncture (BVA), or injections [6]. In addition, bee venom is typically secreted by female worker bees and has been reported to contain various active ingredients. These include peptides (macrolactone, adolapin, melittin, including apamin), enzymes (hyaluronidase and phospholipase A2), as well as volatile compounds, and amino acids [7]. Several studies have also assessed the therapeutic potential of the constituents in human inflammatory disorders and central nervous system diseases, such as PD, Alzheimer's, and amyotrophic lateral sclerosis [8]. Bee venom is also known to have various pharmaceutical effects, such as analgesic, anti-inflammatory, and anti-apoptotic [9]. According to previous studies, microglial activation is a major indicator showing the presence of neurodegenerative disorders. Forbye, bee venom and MEL typically have a strong inhibitory impact on BV2 microglia pro-inflammatory responses, demonstrating the substantial therapeutic value of these compounds [10].

Over the past 30 years, there has been a significant increase in the use of bee venom as a complementary therapy for PD in various animal studies. These reports have revealed the neuroprotective properties of bee venom as well as its constituents, such as apamin, which specifically target inflammatory responses by reducing neuroinflammation in PD rat models [11–13]. Moreover, the material has been reported to have the potential to enhance locomotor activity and coordination [14]. Despite its widespread utilization, the translation of preclinical findings to clinical trials has yielded varied results. Epidemiological studies among beekeepers have also reported the absence of a correlation between reduced risk for PD and bee venom exposure [15]. Conflicting findings have been reported from various clinical trials, with some reporting improvements in motor function, quality of life, and non-motor symptoms; while others show less pronounced or inconclusive benefits. According to two Randomized Control Trials (RCTs) [1,16], BVA group had a significant improvement in the UPDRS score; while one RCT by Hartmann et al. [17] reported that BVA did not differ significantly from placebo. These discrepancies show the need for a comprehensive systematic review to investigate the beneficial effect of BVT as an adjunctive treatment of PD.

Methods

This review was designed and conducted under the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement [18]. In addition, the protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number: CRD42023470298.

Eligibility criteria

Research Type

The review consisted of published articles examining the impact of BVA on idiopathic PD and written in English. The articles were designed as interventional studies, either RCTs or non-RCTs (quasi-experimental and multiple-arm studies), without publication year

restrictions. The following types of articles were excluded: book sections, conference abstracts, reviews, cross-sectional, cohort research, case reports as well as case series, and commentary or editorials. Moreover, those lacking the entire text and having nothing to do with the pertinent topic were also disqualified.

Participants

Patients having an idiopathic PD diagnosis, regardless of age or gender, and with or without anti-parkinsonian treatment were eligible for participation. People with somatic diseases, dementia, alcohol abuse/narcotic drug addiction, along with organic neurological disorders other than PD, past or present disease, epilepsy, a typical Parkinsonism, allergies to bee venom confirmed by skin allergy testing, women who were pregnant or nursing, and people deemed unfit for participation by the assessor were all excluded.

Variable and interest outcome

The primary outcome of interest was the effect of bee venom acupuncture as an adjunctive treatment of PD compared to control, in the form of Unified Parkinson's Disease Rating Scale III (UPDRS III), which was reported in numerical data. Meanwhile, the secondary outcomes were UPDRS II, total UPDRS, Parkinson's Disease Quality of Life Questionnaire (PDQL), Beck's Depression Inventory (BDI), gait speed, gait number, Maximum Excursion (MXE), and Directional Control (DCL), which were only reported in some articles.

Search strategy and study selection

Eligible studies were found using PubMed/MEDLINE, EBSCO-Host, and ProQuest search engines. The papers were identified using medical subject headings, and the keywords used while accessing PubMed in the literature search were *((Parkinson Disease[MeSH Terms]) OR (Parkinson Disease[Title/Abstract])) AND ((((((Apitherapy[MeSH Terms]) OR (Apitherapy [Title/Abstract])) OR (Bee Venom[MeSH Terms])) OR (Bee Venom[Title/Abstract])) OR (Acupuncture Therapy[MeSH Terms])) OR (Acupuncture Therapy[Title/Abstract])).* Detailed information on the PICOTS-SD criteria, search terms, and strategy were available in Tables 1 and 2 of the supplementary materials.

All obtained studies were imported to the Zotero 6.0.30 version as the reference manager. Seven authors separately vetted and examined the article titles and abstracts after making sure there were no duplicates. The full-texts were assessed based on the eligibility criteria, and any distinctions among the authors were resolved by consensus.

Data Collection

First author, nation, participant numbers, baseline attributes (age and sex), publication year, design, as well as subject eligibility and exclusion criteria, PD evaluation tools, BVT preparation, BVT administration protocol, duration of treatment or follow-up, and their outcome of interest were all extracted from the analyses of the included studies.

Summary measures

Every result was quantified and presented as continuous-numerical data. Furthermore, data that were normally distributed were displayed as the average ± standard deviation (SD); while data that were not normally distributed were displayed as median (interquartile range). Standardized Mean Differences (SMDs) along with the 95% Confidence Interval (CI) were extracted to show the effect magnitude, and a p-value of 0.05 or less was deemed statistically significant.

RoB Assessment

The Cochrane RoB 2 was used to evaluate three studies [1,16,17] pertaining to randomized controlled trials, and a single study [19] for non-randomized one was assessed using ROBINS-I. The five primary domains of the Cochrane RoB 2 tool, which each was categorized as low, high, or some concern [20] were the following: (a) The randomization of data process; (b) Differences from intended treatments; (c) Defective result data; (d) Quantification process; along with (e) Assortment of disclosed outcome. Based on the revealed bias levels, each trial was categorized into one of three groups: (1) low (low in all), (2) moderate (some concerns in at least one, but not at high risk in any), or (3) high (high risk in a minimum of one or moderate in multiple).

The Cochrane ROBINS-I [21] comprised of seven major domains grouped into three main categories, namely (1) Pre-intervention, consisting of (a) Bias because of confounding, (b) Bias in the participants' selection; (2) Intervention, consisting of (c) Bias in interventions classification; (3) Post-intervention, comprising (d) Bias because intended interventions deviations, (e) Bias because of missing data, (f) Bias in outcomes measurement, and (g) Bias in reported result selection. From each domain, the bias risk was considered as low, moderate, serious, critical risk, and no information. The overall quality of each trial was categorized into five groups based on the degree of bias presented, including (1) low risk of bias (low for all domains), (2) moderate risk of bias (low or moderate for all domains), (3) serious risk (serious in at least 1 domain, but not at critical risk in any domain), (4) critical risk (critical in at least one domain), (5) no information (lack of information in 1 or more key domains where judgment was required). Each article was evaluated separately by two reviewers, and any disagreements were then addressed among the whole

review team until agreement was obtained.

Result synthesis & statistical analysis

The information was extracted for quantitative synthesis using Review Manager (RevMan; Cochrane Collaboration) 5.4 ver. To determine the disparity among the intervention (bee venom treatment) as well as control groups, all participants were separated into two groups for the analysis. In order to compare groups, statistical analyses were performed using totals as well as subtotals with a 95% CI. An independent *t*-test was utilized to compute the values for each group pertaining to the missing changes in certain reported outcomes from the beginning of the research period to the conclusion. It also converted values from studies that did not report in the form of mean as well as standard deviation using the formula suggested by [22] and [23]. Subsequently, its needed information that could be taken out of each original study, including sample size (N), as well as quartiles on lower (Q1), and middle (Median/Q2), and upper (Q3) categories.

Some studies reported primary outcomes using different evaluation or calculation methods, hence, meta-analyses were conducted with a random effects model. This model presupposed that the treatment impact was distributed over certain populations and offered each study a more equal weighting. Moreover, it enabled extrapolation to a larger sample of the population in cases where new studies were subsequently performed. The combined effect measured from an individual intervention was compared by the inverse variance method for numerical (continuous) data. The SMDs were used as the most appropriate effect size for continuous data.

Confidence in cumulative evidence

By employing the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method, the confidence in cumulative evidence was calculated [24]. For every outcome, the GRADE method involved assessing the caliber of an evidence body. At the same time, the RoB of publication, heterogeneity, transparency, accuracy of impact estimates, and RoB within the research (methodological quality) all influenced the quality of an evidence body. It was classified with varying degrees of overall certainty, ranging from high to moderate, and even to low or extremely low levels [24].

Registration of the review protocol

The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), with the following registration number: CRD42023470298.

Results

Study Selection

The study selection process and the results obtained were summarized in a flowchart as shown in figure 1. A total of 519 articles were identified using the search strategy, and according to the selection criteria, 359 were obtained after the duplicate removal. Articles were further identified for full-text screening based on the selection criteria. Consequently, 347 studies were not relevant according to the selection criteria, and 8 studies were excluded after assessment of eligibility due to the non-use of bee venom substances in acupuncture therapy. Finally, 4 articles were included in the systematic review and all were eligible for meta-analysis. Despite an exhaustive search, no unpublished studies fulfilling the inclusion criteria were identified. This absence did not affect the conclusions and also minimized the potential of qualitative publication bias.

Quality assessment

A total of three articles [1,16,17] were reviewed using ROB2; while one study [19] was assessed using the ROBINS-I tool. The three articles evaluated using ROB-2 were deemed to have a low risk of bias; while the quasi-experimental study by Doo et al. was considered to have a moderate risk of bias. In line with Cochrane's recommendations, the Robvis (visualization tool) was used to summarize the risk of bias, as shown in figures 2 and 3.

The included studies characteristics

Table 1 presents the collected features of the included studies. One quasi-experimental research (a prospective open-label self-controlled trial) and three RCTs were among the included trials. Three were carried out in Korea [1,16,19] and one was carried out in France [17]. According to Cho et al. 2018 [1] and Doo et al. 2015 [19], the majority of BVT groups were male with percentages of 58% and 64%, respectively. The BVT group's members' average ages varied from 58.5+16.6 [16] to 64.6$\pm$6.2 [19] years old; while the control group varied from 57.9$\pm$11.6 [16] to 64.6$\pm$6.2 [19] years old. The inclusion criteria, administration doses and protocol, and duration of treatment were varied across studies. The types of bee venom used ranged from dried bee venom [1] as well as Alyostal® [17], with the most common being diluted bee venom with normal saline or distilled water [16,19]. The inclusion criteria for the four studies were different, but most studies included patients with a PD definitive diagnosis, with a negative skin test for bee venom. The participants of each study were given BVT for 8 or 12 weeks [1,19] or up to 11 months [17]. Among the treatments proposed in the studies, the main method of administration of ther-

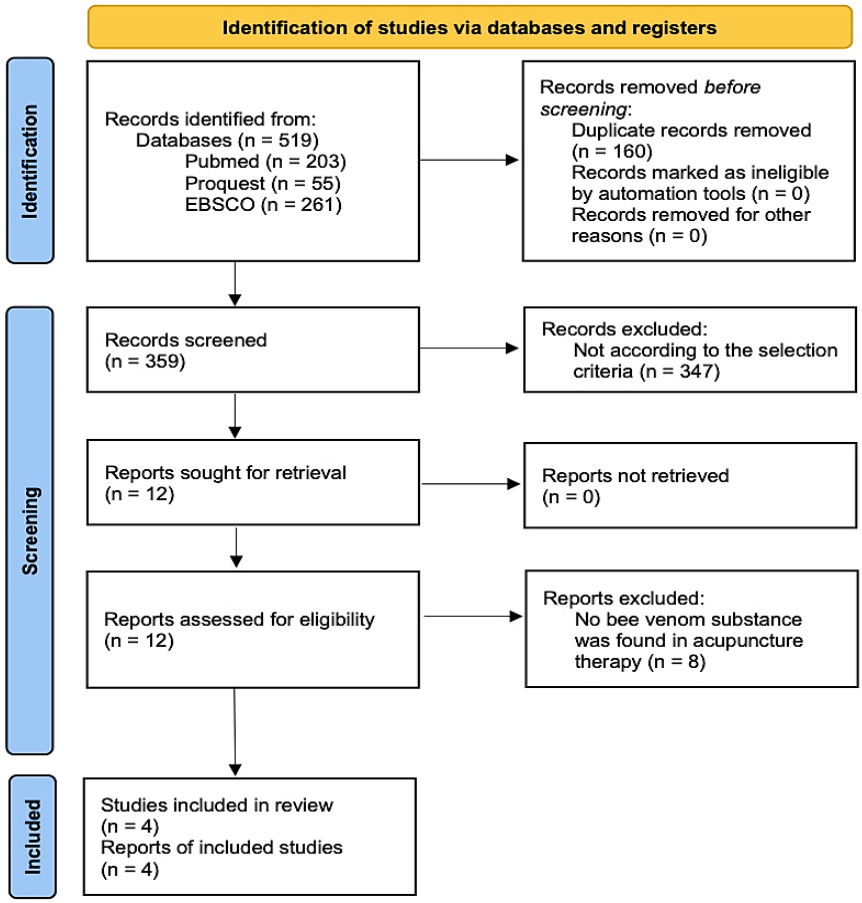

Figure 1. The referenced studies' PRISMA 2020 flow diagram.

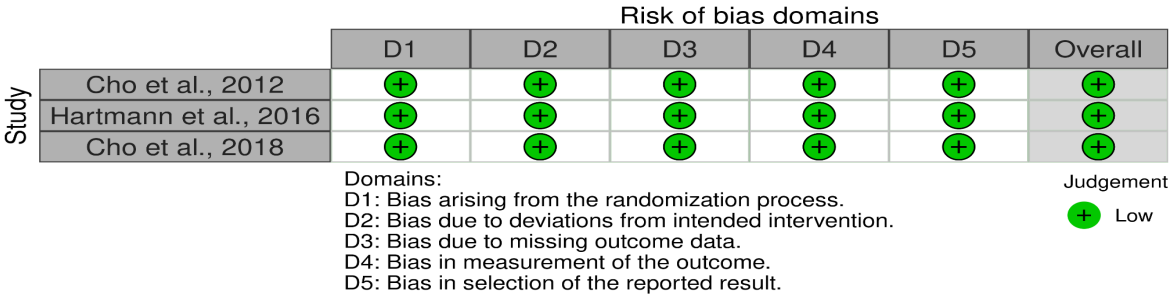

Figure 2. Outcomes of the RoB 2 study quality evaluation in RCT studies

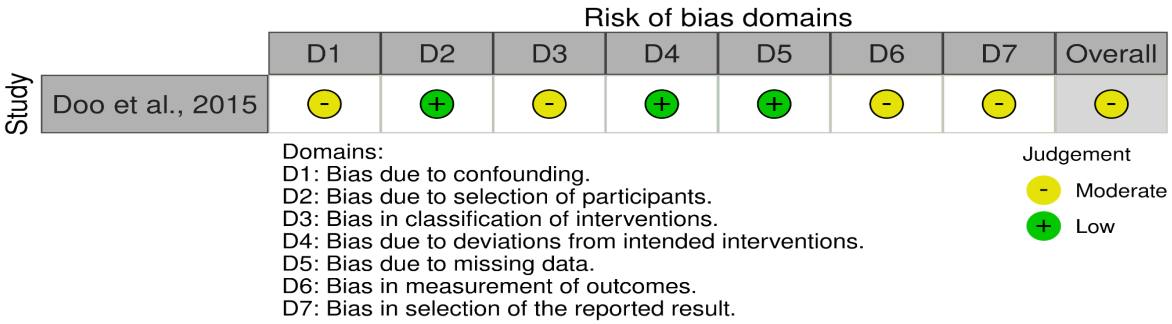

Figure 3. Outcomes of a quasi-experimental research that used ROBINS-I for study quality evaluation.

apy was acupuncture (through 10 different acupoints) [1,16,19] or via injection exclusively [17]. All studies had a comparison control therapy except for Doo et al. whose control was the same group population, after being given conventional treatment (antiparkinsonian medication).

Meta-analysis results

The functional improvements of patients with PD could be assessed using some parameters, and all studies reported the result of UPDRS III. Meanwhile, three studies [1,16,19] depicted the results of UPDRS II, PDQL, BDI, and two [1,19] disclosed results of UPDRS II+III, gait speed, gait number, MXE, and DCL. The forest plots of these results were presented in figure 4.

The meta-analysis revealed that only the BDI score was statistically significant (p = 0.01) following bee venom therapy compared to control groups. On the contrary, other outcomes demonstrated non-significant changes (UPDRS II, III, II+III, as well as gait speed and number, PDQL, MXE, along with DCL) following bee venom therapy (p=0.18, 0.24, 0.28, 0.14, 0.30, 0.25, 0.48, 0.97, respectively).

Significant moderate heterogeneity was observed among the studies for gait speed and PDQL (I^2 = 50% and 55%; p = 0.16 and p = 0.11, respectively), and high heterogeneity was observed among the studies for UPDRS II+III (I^2 = 87%, p = 0.005). Therefore, a framework with random effects was used to evaluate the outcomes. The remaining six outcomes were considered to have subtle heterogeneity (0%; p=0.72, 0.46, 0.97, 0.37, 0.46, and 0.93, respectively), hence fixed-effects model was chosen.

Confidence in cumulative evidence

According to Cochrane ROB2 and ROBINS-I, there was a low-to-moderate RoB in the investigated studies, meaning that conceivable bias was unlikely to have a major impact on the outcomes. The results demonstrated that while imprecision was seen in all of the outcomes, there were no discernible indirectness or inconsistencies that might have affected the overall results. Furthermore, the research had a large CI as well as a minimum sample size. Publication bias assessment was restricted due to insufficient data. Consequently, the GRADE evidence profile was developed, and a medium quality of evidence was discovered, as table 2 illustrates.

Discussion

In this analysis, we investigated the potential effect of bee venom therapy as an adjunctive treatment in PD. We reviewed and analyzed a total of four interventional studies comprising of 69 subjects in both groups. The results of meta-analysis demonstrated a significant difference in BDI score (SMD=-0.52, 95%CI= -0.93, -0.11, p=0.01) between bee venom and control groups. Bee venom was shown to effectively reduce the symptoms of PD and have a neuroprotective effect on dopaminergic neurons in mouse models, hence it could improve coordination and locomotor activities [12,14] as mentioned previously. Moreover, it also played a role in reducing depression symptoms. Apamin in bee venom was well-known for its ability to block a specific ion channel that permitted potassium ions to exit neurons selectively. When these brain pathways were blocked, nerves became hyperexcited, thus enhancing learning and offering therapeutic effects for depression and dementia. Following El-Wahab and Eita (2015), volunteers with moderate and severe depression showed no depression at all after 12 months of receiving live bee sting acupuncture [25]. Additionally, Cho *et al.* (2012) [16] stated that acupuncture could ameliorate depression in PD patients, proven by the BDI scores that significantly improved in their study [16].

Following bee venom therapy, no significant changes were observed in UPDRS II, UPDRS III, UPDRS II+III, gait speed, gait number, PDQL, MXE, and DCL (p=0.18, 0.24, 0.28, 0.14, 0.30, 0.25, 0.48, 0.97, respectively). Besides, some outcomes demonstrated high heterogeneity, proven by its I^2 test values of 87%, 50%, and 55%, accounting for UPDRS II+III, gait speed, and PDQL, respectively. The cause of its non-significant dominance was the variation in study designs and bee venom administration, despite some individual studies depicting significant changes in their results [1,16,19]. Compared to Hartman et al. (2016) [17] who had no specific antiparkinsonian medication requirements, Cho et al. (2012, 2018) [1,16] and Doo et al. (2015) [19] ensured participants received stable medication doses for at least a month before the trial. This difference in inclusion criteria raised the possibility that the outcomes were more likely to be affected by the combined action of both conventional medication and the bee venom intervention.

Variation in the study design also appeared to be the cause of the absence of a statistically significant treatment effect across studies. Cho et al. (2012, 2018) [1,16] employed shorter treatment durations (12 and 8 weeks) compared to Doo et al. (2015) [19], who adopted a unique 24-week phased approach within a single intervention group, initially focusing on conventional antiparkinsonian medication for 12 weeks before introducing BVA for the subsequent 12 weeks. In contrast, Hartman et al. (2016) [17] employed a non-acupuncture delivery method, administering bee venom subcutaneously once a month for 11 months. The lack of therapeutic effect could also be attributed to the lower individual dosages and infrequent admin-

Table 1. The Included Studies Characteristics

Author, publication year, country	Study Type and Duration of Treatment	Groups				Inclusion criteria	Evaluation tool	BVA preparation and duration of treatment	Outcome (Compared to the control group):
		Bee venom group		Control group					
		Age (Mean+ SD)	Sex N (%)	Age (Mean+ SD)	Sex N (%)				
Cho et al., 2012, Republic of Korea	Randomized controlled clinical trial 8 weeks	58.5+16.6	13 Male: 5 (38%) Female: 8 (62%)	57.9+11.6	13 Male: 5 (38%) Female: 8 (62%)	• Subjects with IPD who use antiparkinsonian medicine consistently (at least once a month)	• UPDRS • PDQL • BDI • BBS • 30-m walking time • Steps to walk 30 m	• To attain *Deqi*, acupuncture needles were inserted into each point to a depth of 1.0 to 1.5 cm, and the needles were revolved at a frequency of 2 Hz for 10 seconds. Holding the same posture for twenty minutes • To check for a bee venom allergy, a skin test was conducted. The individual was removed from the research after receiving an injection of bee venom (0.1 ml diluted to 0.005% in distilled water) at LI11. • Acupuncture or BVA stimulation at 10 acupuncture sites (bilateral GB 20, LI 11, GB 34, ST36, and LR 3) twice a week for 8 weeks (16 sessions in total).	• The BVA group demonstrated a noteworthy improvement on the BBS, the UPDRS (total score, II and III, separately), and the 30-meter walking time. • On the UPDRS (total score, II, III separately), the BVA group improved noticeably more than the other group. • Significant improvement in UPDRS (III & total) as well as the BDI (acupuncture group). • Eight weeks later, no discernible changes in any of the outcomes
Doo et al., 2015, Republic of Korea	A prospective, open-label, self-controlled trial 12 weeks	64.6 ± 6.2	12 Male: 7 (64%) Female: 4 (36%)	64.6 ± 6.2	12 Male: 7 (64%) Female: 4 (36%)	• Subjects with UK Parkinson's Disease Society Brain Bank diagnosis of idiopathic Parkinson's disease. • A consistent antiparkinsonian dosage (at least four weeks before to the experiment). • Hoehn and Yahr scale (PD stages 1-4). • At least one point is earned in two or more categories (UPDRS part III), such as bradykinesia, stiffness, postural instability, tremor. • MMSE-> 24 (Korean version). MMSE–(Korean version)> 24.	• UPDRS • PDQL • Pace and steps needed to cover a distance of 20 meters • BDI • Computerized dynamic posturography is used to test postural stability	• A pretreatment skin test was performed (allergy) • The therapy was injected into each listed acupuncture needlepoint, with insertion occurring at a depth of 1.0 to 1.5 cm. To get de qi, I rotated at Hz for 10 seconds. After that, the needle was left in this position for fifteen minutes. At LI4, 0.1 ml bee venom that had been mixed to 0.005% in normal saline was administered. • Acupuncture and BVA treatments are administered twice a week for a total of 24 sessions, covering acupuncture points.	• There has been no discernible shift in the UPDRS scores (II+ III, as well as II and III separately). • Following combination therapy, there was a considerable change in the 20-m gait speed. The results of both combination and conventional therapy showed a substantial change in the PDQL score • There was no discernible difference in postural stability (MXE, DCL) and the BDI score.

Hartmann et al., 2016, France	Randomized, double-blind, placebo-controlled, parallel-group single-center trial 11 months	63.3 (8)*	20 Male: 8 (40%) Female: 12 (60%)	60.3 (15)*	20 Male: 12 (60%) Female: 8 (40%)	• Parkinson's Disease Society Brain Bank diagnostic for PD patients. • Ages > 40 years old. • Hoehn and Yahr stages 1,5–3 during off periods. • Had a pathological [123I]-FP-CIT. • An MRI that rules out unusual or secondary types of parkinsonism. • Bee poison skin test result is negative	• UPDRS • Hoehn & Yahr stages. • Schwab & England scores • BREF • MMSE scores • LED • PDQ-39 scores. • Segmental rating scale • ADL subscale	• 0.05 mL of Alyostal®, adjusted in a saline solution with no contaminants contains 0.4% phenol at a concentration of 0.1 µg/mL, is injected intradermally as part of the skin test. • Alyostal® 100 µg administered subcutaneously once a month for 11 months in 1 mL of NaCl 0.9%	• UPDRS III scores decreased in both groups (but differences were non-significant). • The overall UPDRS score (I, II, as well as IV) did not significantly change. • There was a non-significant increase in BREF along with MMS scores in the bee venom group in comparison to the placebo group. • The bee venom group's BREF along with MMS scores increased, albeit not significantly, in comparison to the placebo group. • No significant differences in total PDQ-39 scores. • The bee venom group performed poorer on the ADL subscales. • There was no variation in the progression of temporal or localization scores according to the segmental grading scale.
Cho et al., 2018, Republic of Korea	Double-blind, three-armed randomized controlled clinical trial 12 weeks	64.42 ± 8.24	24 Male: 14 (58%) Female: 10 (42%)	61.33 ± 8.20	24 Male: 8 (33%) Female: 16 (67%)	• Patients on stable antiparkinsonian medication (min. 1 month). • Hoehn and Yahr scale I–IV • Greater than one point on any two or more UPDRS part III elements (tremor, stiffness, postural instability, and bradykinesia). • MMSE (Korean)> 24/30. • Accept the research after reading the complete explanation.	• UPDRS • PIGD score • PDQL • BDI • Number of steps to walk 20 m	• To check for venom allergy, 0.1 mL of bee venom was injected into the LI11 site prior to therapy. • 0.1 mL of diluted bee venom (one milligram of dried powdered bee venom diluted in twenty milliliters of normal saline) was administered after skin testing. • After that, 1.0–1.5 cm acupuncture needles were put into the same locations and spun for 10 seconds at a frequency of 2 Hz. They kept that position for fifteen minutes. • For 12 weeks, BVA and acupuncture were given twice a week at ten different acupuncture sites.	• In both the active and sham treatment groups, there was a significant improvement in the UPDRS (II + III, II, as well as III separately), PDQL, and the number of steps needed to walk 20 meters. • In the group receiving active therapy, the PIGD score increased considerably. • The PIGD score, II, III and the II + III showed significant changes in the active therapy group.

Abbreviations: UPDRS: Unified Parkinson Disease Rating Scale; BDI: Beck Depression Inventory; BREF: Batterie rapide d'évaluation frontale; PIGD: Postural instability and gait disturbance; PDQL: Parkinson's Disease Quality of Life; BBS: Berg Balance Scale; LED: Levodopa-equivalent daily dose; ADL: Activities of daily living; MMSE: Mini-Mental State Examination.

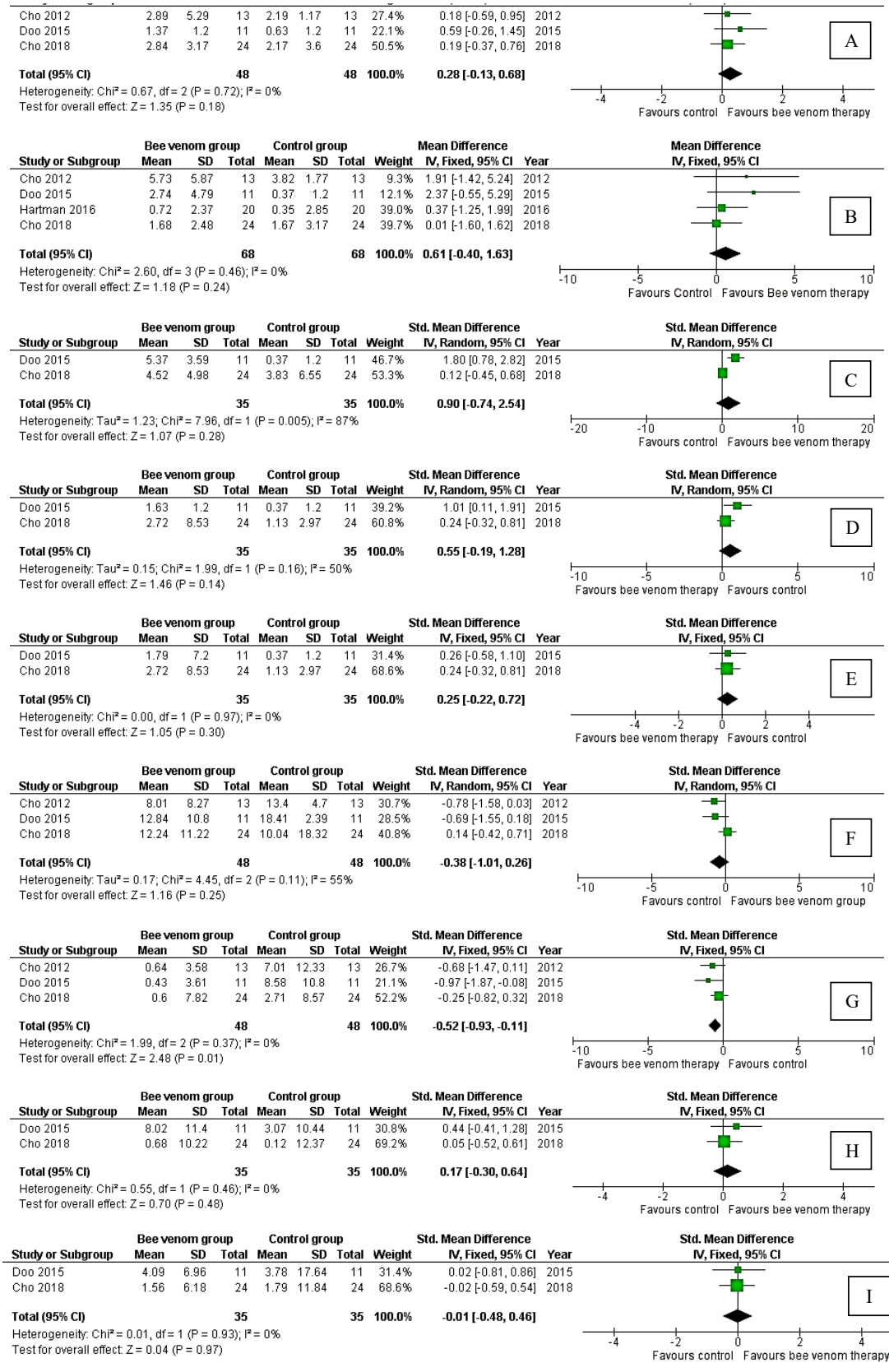

Figure 4. The findings of a meta-analysis of bee venom treatment (a forest plot diagram) for (A) UPDRS II. (B) III, (C) II+III, (D) gait speed, and (E) gait number (F) PDQL; (G) BDI; (H) MXE; and (I) DCL.

Table 2. GRADE evidence profile.

Outcome	Numbers of participants (studies)	Quality Assessment				SMD (95%CI)
		Risk of bias, Inconsistency, Indirectness	Imprecision	Publication bias	The overall quality of the evidence	
UPDRS II	85 (3 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.28 (-0.13, 0.68)
UPDRS III	125 (4 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.61 (-0.40, 1.63)
UPDRS II+III	59 (2 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.90 (-0.74, 2.54)
Gait speed	59 (2 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.55 (-0.19, 1.28)
Gait number	59 (2 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.25 (-0.22, 0.72)
PDQL	85 (3 studies)	Not serious	Serious[a]	NA[b]	Moderate	-0.38 (-1.01, 0.26)
BDI	85 (3 studies)	Not serious	Serious[a]	NA[b]	Moderate	-0.52 (-0.93, -0.11)
MXE	59 (2 studies)	Not serious	Serious[a]	NA[b]	Moderate	0.17 (-0.30, 0.64)
DCL	59 (2 studies)	Not serious	Serious[a]	NA[b]	Moderate	-0.01 (-0.48, 0.46)

UPDRS: Unified Parkinson's Disease Rating Scale; PDQL: Parkinson's Disease Quality of Life Questionnaire; BDI: Beck's Depression Inventory; MXE: Maximum Excursion; DCL: Directional Control, SMD: Standardized Mean Difference; CI: Confidence Interval; NA: Not Applicable.

[a] Since most individual studies had broad confidence intervals, the aggregate CI was also wide.

[b] There was insufficient data to assess publication bias because there were less than ten research.

istration of BVT (only once per month) compared to the other studies, which could result in subtherapeutic drug levels, hence limiting its potential efficacy [5].

Doo et al. (2015) [19] observed improvements in sleep quality and quantity among some participants receiving bee venom therapy. However, these positive effects appeared subjective and limited to individual cases, hindering their incorporation into overall assessments and might contribute to a less significant impact. Moreover, while open-ended questions regarding patients' quality of life could offer rich qualitative insights into patient responses to the treatment, such findings posed a challenge to be analyzed quantitatively.

In an 11-month research Hartmann et al. (2016) [17] gave 100 µg of Alyostal® thrice a month in 1 mL of NaCl 0.9%. Alyostal® was a pharmaceutical preparation containing whole bee venom from *Apis mellifera*, which had been studied for its potential effects in treating motor symptoms of PD. Alyostal® and normal bee venom differed in their composition and potential therapeutic applications. Alyostal®, bee venom in its totality, has concluded a randomized phase II trial to assess its effectiveness and any side effects in individuals with PD who exhibit motor symptoms [26]. Alyostal® had been specifically studied for its effects on PD; while normal bee venom contained various active compounds (including melittin) and had potential therapeutic applications for inflammation and central nervous system diseases [7].

The course of treatment differed depending on the condition, and bee venom could be used in a variety of therapeutic ways, such as BVA or known as apitherapy, injections, or direct bee stings. Using a syringe to administer bee venom was advised over receiving stings directly from honeybees. Due to the increased bioactivity brought about by the mechanical stimulation of acupuncture, BVA was utilized in the majority of trials [27]. However, no standard guidelines had been found regarding the duration, dosage, and administration of bee venom.

Heterogeneity and publication bias analysis

There were small differences in treatment effects between studies for most outcomes, shown in each I^2 test for heterogeneity. From a clinical perspective, the heterogeneity in some results could be due to differences in the regimen and administration of bee venom, duration of treatment, and baseline Hoehn-Yahr Parkinson scale of participants. From a methodological perspective, the difference in study designs, namely three RCTs and one prospective open-label, self-controlled trial could result in considerable heterogeneity. Lastly, from a statistical perspective, variation in reporting data could contribute to increased heterogeneity. Two studies [16,19] supplied data in the form of median as well as interquartile range values; whereas two additional papers [1,17] reported in mean and standard deviation. Nevertheless, all studies were computed using SMD in the meta-analysis, decreasing the statistical heterogeneity, despite the different reporting findings.

Strengths and limitation

This review was the first report regarding the effectiveness of BVT through acupuncture and injection in improving PD symptoms. Non-motor symptoms, such as assessing quality of life and depression that could occur in PD patients were also explored. Despite this novelty, there was a limitation in the review, as the

meta-analysis was restricted by the small number of articles. Consequently, it was unable to ascertain the presence of publication bias and there was high heterogeneity in the study characteristics.

Future directions

Due to the promising evidence regarding BVT's efficacy in alleviating PD symptoms, the establishment of standardized guidelines for its application, comprising treatment duration, dosage levels, and administration routes was required. Future studies employing a different methodologically homogeneous dataset that could validate these findings must also be carried out. In addition, large-scale RCTs or network meta-analysis were needed to directly compare the various approaches.

Conclusion

In conclusion, a systematic review and meta-analysis were conducted to assess the therapeutic effects of bee venom as an adjuvant therapy in PD, which aimed to reduce symptoms and improve patient's quality of life. In addition, the results showed that BVT had a significant effect in improving BDI. Although findings obtained were not significant, the results were considered favorable for BVT.

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Ethical statement

No ethical approval was required as this review did not comprise human participants or laboratory animals.

Conflict of Interests

There have been no conflicts of interest from all authors.

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Supplementary Files

Table 1. PICOTS-SD

PICO elements	Operational Definition
Patients	Subjects with idiopathic Parkinson's Disease (PD), with or without anti-parkinsonian medication. No limitations for gender and races.
Intervention	Bee venom therapy, administered either through acupuncture or subcutaneous injection
Comparator	Conventional anti-parkinsonian medication or placebo (sham acupuncture)
Outcomes	• Unified Parkinson's Disease Rating Scale (UPDRS) II, III, and II+III • Parkinson's Disease Quality of Life Questionnaire (PDQL) • Beck's Depression Inventory (BDI) • Gait speed • Gait number • Maximum Excursion (MXE) • Directional Control (DCL)
Time	Not restricted
Setting	Subjects visiting medical facility
Study Design	Interventional study (randomized controlled trial (RCT), quasi-experimental study, multiple-arm study)

Notes. PICOTS-SD: participant, intervention, comparator, outcomes, time, setting, study design.

Table 2.A. Search Terms and Strategy: PubMed/MEDLINE

Search Number	Query	Filter	Results
1	((Parkinson Disease[MeSH Terms]) OR (Parkinson Disease[Title/Abstract]))	Randomized Controlled Trial, Full Text	4,777
2	(Acupuncture Therapy[MeSH Terms])) OR (Acupuncture Therapy[Title/Abstract]))	Randomized Controlled Trial, Clinical Trial, Full Text	3,268
3	((((((Apitherapy[MeSH Terms]) OR (Apitherapy [Title/Abstract])) OR (Bee Venom[MeSH Terms])) OR (Bee Venom[Title/Abstract])) OR	Randomized Controlled Trial, Clinical Trial, Full Text	90
4	#2 OR #3	Randomized Controlled Trial, Clinical Trial, Full Text	3,344
5	#1 AND #4	Randomized Controlled Trial, Clinical Trial, Full Text	203

Table 2.B. Search Terms and Strategy: ProQuest

Search Number	Query	Filter	Results
1	((“Parkinson Disease”) OR “Idiopathic Parkinson Disease”)	Scholarly Journals, Full text, Article type	18,753
2	((“Acupuncture”) OR “Acupuncture Therapy”)	Scholarly Journals, Full text, Article type	30,552
3	((“Apitherapy”) OR “Bee Venom”)	Scholarly Journals, Full text, Article type	3,951
4	#2 OR #3	Scholarly Journals, Full text, Article type, Humans	4,258
5	#1 AND #4	Scholarly Journals, Full text, Article type	55

Table 2.C. Search Terms and Strategy: EBSCOhost

Search Number	Query	Filter	Results
1	((“Parkinson Disease”) OR “Idiopathic Parkinson Disease”)	Research articles, Open access	11,751
2	((“Acupuncture”) OR “Acupuncture Therapy”)	Research articles, Open access	8,583
3	((“Apitherapy”) OR “Bee Venom”)	Research articles, Open access	3,211
4	#2 OR #3	Research articles, Open access	7,468
5	#1 AND #4	Research articles, Open access	261

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