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Bee Venom Phonophoresis on Mild to Moderate Localized Plaque Psoriasis on a Knee Joint: a Randomized Controlled Trial

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ABSTRACT

INTRODUCTION. In psoriasis, plaque psoriasis is the most common kind. Patients may experience mild to severe symptoms, and while the sickness is not lethal, it is difficult to cure.

AIM. The purpose of this study is to evaluate the efficacy of bee venom phonophoresis in treating mild to moderate plaque psoriasis of the knee.

MATERIALS AND METHODS. Group A received bee venom phonophoresis in conjunction with conservative care, group B received bee venom topical application in conjunction with conservative care, and group C served as a control in a double-blind randomized controlled experiment including 96 patients with plaque psoriasis. Over the course of three months, every patient underwent a thorough evaluation that included blood tests to measure systemic inflammation (Neutrophil to lymphocyte ratio, C-reactive protein, and erythrocyte sedimentation rate), as well as PASI (Psoriasis Area and Severity Index) and Isokinetic knee proprioceptive.

RESULTS AND DISSCUSION. No statistically significant difference was found between the three groups at baseline measurement; however, a treatment effect was observed after 12 weeks of treatment ($p = 0.001$ and f-value = 50.718). In addition, both groups (A and B) showed a statistically significant interaction between pre- and post-treatment treatment and time; however, this interaction was much more pronounced and noticeable in group A.

CONCLUSION. Phonophoresis with bee venom improves proprioception in the knee joint and decreases N/L ratio, CRP, ESR, and PASI.

REGISTRATION: Clinicaltrials.gov identifier No. NCT06106230; registered 20.10.2023.

KEYWORDS: bee venom, plaque psoriasis, systemic inflammation, knee joint proprioception, phonophoresis

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Применение фонофореза пчелиного яда при бляшечном псориазе легкой и средней степени тяжести: рандомизированное контролируемое исследование

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РЕЗЮМЕ

ВВЕДЕНИЕ. Наиболее распространенным видом псориаза является бляшечный псориаз. Пациенты могут испытывать как легкие, так и тяжелые симптомы, и, хотя болезнь не смертельна, она трудно поддается лечению.

ЦЕЛЬ. Определить влияние фонофореза пчелиного яда на псориаз легкой и средней степени тяжести.

МАТЕРИАЛЫ И МЕТОДЫ. Группа А получала фонофорез пчелиного яда в сочетании с консервативным лечением, группа В — местное применение пчелиного яда в сочетании с консервативным лечением, а группа С служила контролем в двойном слепом рандомизированном контролируемом эксперименте, включавшем 96 пациентов с бляшечным псориазом. В течение трех месяцев каждый пациент проходил тщательное обследование, включавшее анализ крови для измерения системного воспаления (соотношение нейтрофилов и лимфоцитов, С-реактивный белок и скорость оседания эритроцитов), а также PASI (индекс площади и тяжести псориаза) и изокинетическую проприоцепцию колена.

РЕЗУЛЬТАТЫ И ОБСУЖДЕНИЕ. При исходном измерении статистически значимых различий между тремя группами обнаружено не было, однако после 12 недель лечения наблюдался эффект лечения (p = 0,001 и f-значение = 50,718). Кроме того, в обеих группах (А и В) наблюдалось статистически значимое соотношение между показателями до и после лечения и временем; однако это соотношение было более выраженным и заметным в группе А.

ЗАКЛЮЧЕНИЕ. Фонофорез с применением пчелиного яда улучшает проприоцепцию в коленном суставе и снижает соотношение N/L, CRP, ESR и PASI.

РЕГИСТРАЦИЯ: идентификатор Clinicaltrials. gov: No. NCT06106230; зарегистрировано 20.10.2023.

КЛЮЧЕВЫЕ СЛОВА: пчелиный яд, бляшечный псориаз, системное воспаление, проприоцепция, фонофорез

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List of Abbreviations:
CRP — C-reactive protein, ESR — erythrocyte sedimentation rate, PASI — Psoriasis Area and Severity Index, HIV — Human Immunodeficiency Virus, PUVA — Psoralen and long-wave ultraviolet, B.V. — Bee Venom, ANOVA — analysis of variance

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INTRODUCTION

Psoriasis is an inflammatory skin and joint disorder, primarily associated with systemic dysfunctions. Plaque psoriasis is the most common clinical manifestation. Treatment is challenging, and the initial step is using topical corticosteroids with calcipotriene or coal tar for localized psoriasis [1]. Furthermore, in Egypt polygenic inflammatory immunomodulatory dermatitis known as persistent psoriasis affects 1 % to 3 % of its population. This disease has a negative impact on the physical activity and quality of life for those who suffer from it [2].

Bee venom, widely used animal venom, is primarily used in South America, Eastern Europe, and Asia for medical purposes. It has various therapeutic uses, including treating immune-related disorders, arthralgia, chronic neuralgia, and musculoskeletal ailments. Bee venom can also desensitize individuals to bee stings [3].

Bee venom, rich in active ingredients like enzymes and peptides, has been shown to have strong anti-inflammatory properties, potentially offering potential treatments for inflammatory illnesses and neurological diseases like Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis. [4]. Research on bee venom has shown promising results in combating cancer and viruses, including HIV. Preclinical trials are underway to improve the use of apitoxin and its components as next-generation pharmaceuticals. Comparing the efficacy of different physical therapy modalities in rehabilitation programs is necessary for optimal treatment results [5].

AIM

The purpose of this research was to examine the efficacy of bee venom phonophoresis in treating mild to moderate plaque psoriasis of the knee.

MATERIALS AND METHODS

The randomized, controlled experiment took place from January to April 2024 in the clinic of the Physical Therapy Faculty at Modern University of Technology and Informa-

tion. The study was approved by the Ethical Committee for Human Research of the Faculty of Physical Therapy at Modern University following the 1975 Declaration of Helsinki (Reference number: REC/2111/MTI.PT). Clinical Trials.gov also noted it (No. NCT06106230 registered 20.10.2023).

Participants

El Khanka General Hospital and Om El Masryeen General Hospital were recommended for physical therapy by a dermatologist for male and female patients with mild to moderate localized plaque psoriasis. Consent was obtained from the subjects before to the trial. Participants needed to be 20–50 years old, have symmetrical chronic stable mild–to–moderate plaque psoriasis with lesions measuring around 25 cm^2 on both sides of the body, and have not used a systemic medication for psoriasis in the last three months to be allowed for the study. Patients were not eligible if they had a history of systemic inflammation, a diagnosis of malignant tumors, or were taking systemic corticosteroids, PUVA (a combination of psoralen and long-wave ultraviolet radiation), or had undergone laser phototherapy within the last four weeks.

Participant Characteristics

Each participant was interviewed and examined by a dermatologist. The following information was gathered from participants using a questionnaire: participants' ages, sexes, body mass indexes, percentages of affected body surface areas, intensity levels, erythema, skin thickness and desquamation in the affected areas, ratio of neutrophils to lymphocytes before and after treatment, ESR, C-reactive protein (CRP), PASI scores, isokinetic knee testing at baseline and 12 weeks later. Independent of their involvement in the trial, all patients continued to get their customary care in between their follow-up appointments. This often entailed a dermatologist checking on them no less than once weekly and treating them as needed.

Sample size determination

Data on the N/L ratio from a pilot research that was carried out on eight participants in each group was used to establish the sample size. The necessary number of participants for this study was determined to be N = 96 by the use of the G*POWER statistical program (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany). An effect size of 0.48, $\alpha = 0.05$, and $\beta = 0.2$ were used in the calculation.

Allocation concealment and randomization

Patients were divided into therapy groups using a computer-generated database of random numbers. Using this technique, patients were randomly assigned to one of three groups. Group A underwent conservative care while receiving bee venom phonophoresis. Topical application of bee venom was administered with conservative care to Group B. Only Conservative attention was given to Group C it is recommended to take a bath every day, moisturize your skin, cover the affected regions at night, expose your skin to light but not too much, stay cool, prevent scratching and other psoriasis triggers, and make an effort to lead a healthy lifestyle. To ensure objectivity, the randomization was created by a physical therapist who was not involved in the study protocols. The allocation process was hidden using opaque, sealed envelopes. The sentence structures are fixed in this paraphrase, and it is evident that the treatment groups were chosen randomly.

Outcome measure

Primary Outcome measures:

Neutrophils / Lymphocyte Ratio

The subjects were asked to sit while their veins were dilated. To collect serum and whole blood, a gel separator dry tube with 10 ml of clot activator and two vacuum tubes with 2 ml of K2EDTA (separator tubes contain an additional separating gel and are used for plasma testing) were utilized. The blood samples were let to stand for 30 minutes before being centrifuged at 1250 × g for 15 minutes [6].

C-reactive protein (CRP)

A C-reactive protein (CRP) test measures the level of C-reactive protein in blood [7].

(ESR) erythrocyte sedimentation rate at first 1 hour

A "sed rate" describes it well. This assay provides an indirect measure of protein concentrations in the blood. Blood fills a Westergren-Katz tube to a level of 200 mm. After the tube has been left at room temperature for one hour and is positioned vertically on a rack, the measurement is taken from the top of the red cell sediment to the bottom of the surface meniscus [8].

Secondary Outcome measures

PASI score

In psoriasis trials, is there a standard way to evaluate how severe lesions are and how patients respond to treatment? It produces a score between zero and seventy-two. It is determined by dividing the body into four sections: the head (h), the upper extremities (u), the trunk (t), and the lower extremities (l). Each section accounts for 10 %, 20 %, 30 %, and 40 % of the total body surface area, respectively. Scaling, induration, and erythema are assessed separately in each of these areas, and scores are assigned from 0 (none) to 4 (very severe) [9].

Isokinetic knee proprioceptive test

Knee proprioception was assessed using a dynamometer (System 3 Pro; Biodex Medical Inc., Shirley, NY, USA). The patient's knee and hip will be positioned in a chair at a 90° flexion. The foot was placed in a neutral posture, and a strap restrained the ankle. Straps across the chest, hips, and mid-thighs helped to stabilize the position. Throughout the assessment, patients will be blindfolded and guided by the examiner. The patient will complete the prescribed test three times: active reposition accuracy at a goal angle of 45° and a speed of 15°/s. In a typical test scenario, the patient will move the limb being tested to the goal angle (45°) and hold it there for 10 seconds to help them recall the position before moving it back to the beginning. The patient voluntarily moves the tested limb to the goal position after five seconds of rest, and when they feel the need to stop the device, they push the Hold/Release button. Each of the three trials will be followed by a 30-second break for the patient. By computing the mean angular difference of all trials, which is the difference between the end position (45°) and the patient's perceived end position, we can statistically establish the patient's reposition accuracy deficit [10].

Treatment Procedures

There were primarily two types of therapy procedures.

Therapeutic procedures (preparatory treatment application)

In order to conduct the study, we first collected the patient's medical history, explained the treatment and its goal, and made sure they were comfortable before beginning the procedure. Patients who met the exclusion criteria were not included in the study.

The procedure of bee venom application

Test for allergy

Every subject had a B.V. allergy examination. By a specialist an intradermal or subcutaneous method injected a single clinical dosage of diluted B.V. in normal saline, 0.05 ml (1 g/ml), into the forearm. Participants in this study were those whose assessed injury resulted in a circular skin reaction smaller than 10 mm and erythema smaller than 26.5 mm for 10 to 15 minutes [11].

Bee venom gel preparation

Vacsera, the Egyptian Organization for Biological Products & Vaccines, supplied the bee venom solution (100 mg/mL) that was properly produced and stored. The mixture was a sterile standard saline solution with a 1:1 vol/vol concentration ratio, and a crude form of B.V. (Bee Venom) dissolved. Next, the prior mixture was dissolved in 10 % propylene glycol at the Faculty of Pharmacy, Modern University, Cairo, Egypt laboratory, and then 0.01 % butylparaben was added. The resulting combination was combined with the matrix to create bee venom gel. The B.V. gel had a pH of 7.53 and seemed uniform and translucent. No phase separation, discoloration, or disagreeable smell was present. Stratification was not seen after centrifugation for 30 minutes at 2.500 rpm and 25°C [12].

Bee venom phonophoresis application

The attendees were made to feel at ease and laid down to rest. Their garments were undressed up to the knees, and the bee venom gel for phonophoresis application was ready. At each session, the participants were given 0.8–2 mg of B.V. gel. A 2 cm diameter applicator was used to apply a thin mist of sterile saline to the psoriatic knee. With a power density of 0.5 W/cm and a pulsed duty cycle of 40 % [4 ms on, 6 ms off], the movement was executed over the lesion. The psoriatic knee treatments lasted for 10 minutes per session. Three 20-minute sessions per week were scheduled for twelve consecutive weeks.

Statistical analysis

So that we could compare the subjects' traits across categories, we ran an analysis of variance (ANOVA). For the purpose of comparing the gender distribution across the three categories, the chi-square test was utilized. The data was checked for normal distribution using the Shapiro-Wilk test. To ensure that the groups' variances were similar, the Levene's test was employed. Isokinetic proprioception knee testing, Psoriasis Area and Severity Index, erythrocyte sedimentation rate, C-reactive protein, N.L. ratio, and other outcomes were examined using a mixed-design MANOVA that included both within-group and between-group variables. The Bonferroni adjustment was used in post hoc tests to compare multiple groups. The statistical tests were carried out using a pre-established p-value less than 0.05. We used SPSS, a statistical application created by IBM SPSS in Chicago, IL, USA, specifically version 25 for Windows, to conduct the analysis.

RESULTS AND DISCUSSION

As a treatment for mild to moderate localized plaque psoriasis of the knee, the study looked at the effectiveness of bee venom phonophoresis. A total of one hundred participants were assessed to determine their eligibility for the study. After two people were taken out for different reasons, there were 98 people left behind who were randomly divided into three groups. A 12-week intervention was administered to each group separately. Group A underwent Bee venom phonophoresis with Conservative treatment tailored to their specific situations. Group B underwent topical administration of Bee venom and received Conservative care tailored to their conditions. Group C control participants received conservative care exclusively based on their particular conditions. The participants underwent assessments following the 12-week intervention period to measure the study's outcomes. These assessments included laboratory tests to evaluate systemic inflammation (such as N/L ratio, CRP, and ESR), a PASI assessment to determine the severity and grade of psoriatic lesions, and an Isokinetic machine proprioceptive test to evaluate knee proprioception. A certified physical therapist oversaw the randomization process without involvement in the study's methods. During the trial, one person withdrew from Group A and Group B due to skin irritation and was referred to a dermatologist for treatment. The trial analysis encompassed 32 participants in each group who completed the entire intervention (Fig. 1).

Participants characteristics

Groups A, B, and C's participant characteristics are displayed in Table 1. When comparing the three groups according to age, weight, body mass index (BMI), number of years with psoriasis, and BSA percentage, there was no statistically significant difference ($p > 0.05$). Groups' sex distributions were not significantly different from one another ($p > 0.05$).

Effect of treatment on N.L. ratio, CRP, ESR, PASI and Isokinetic test

Mixed MANOVA revealed a significant interaction of treatment and time ($f = 58.85$, $p = 0.001$). There was a significant main effect of time ($f = 278.979$, $p = 0.001$). Treatment had a significant main effect ($f = 50.718$, $p = 0.001$).

Within group comparison

There was a significant decrease in N.L. ratio, CRP, ESR, PASI and Isokinetic test at post-treatment compared with pre-treatment ($p < 0.001$) (Table 2).

Between-group comparison

Before therapy, there was no statistically significant difference in any of the groups.

After treatment, group A's N.L. ratio was significantly lower than groups B and C ($p < 0.001$). After the treatment, group B's N.L. ratio was significantly lower than group C's

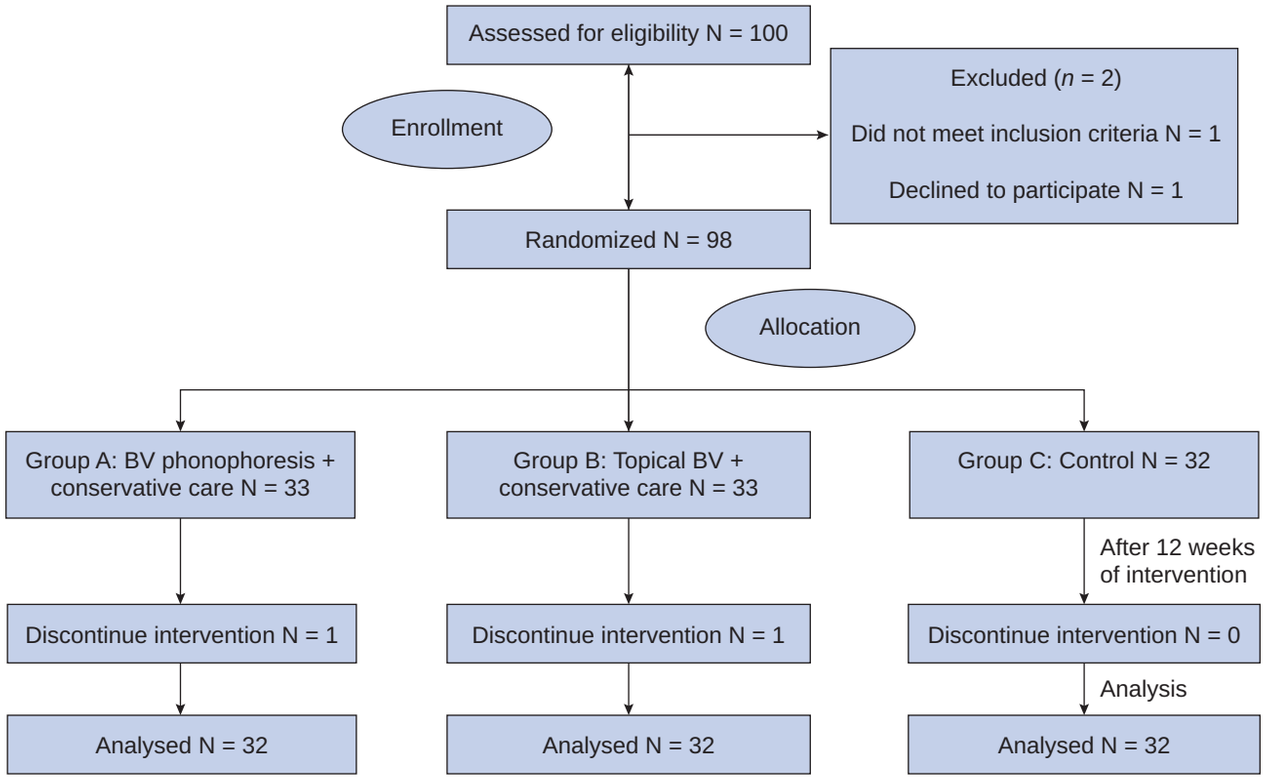

Fig. 1. Flow chart diagram

Table 1. Demographic data of the participants in three groups

	Group A Mean ± SD	Group B Mean ± SD	Group C Mean ± SD	*p*-value
Age (years)	30.34 ± 5.35	30.88 ± 5.12	29.53 ± 5.49	0.931
Weight (kg)	67.47 ± 8.48	69.81 ± 8.70	67.31 ± 8.05	0.445
Height (cm)	166.6 ± 8.51	165.88 ± 9.02	166.84 ± 8.23	0.405
BMI (kg/m^2)	24.5 ± 3.48	25.3 ± 2.9	24.06 ± 2.88	0.378
BSA %	6.51 ± 1.90	6.74 ± 2.03	6.65 ± 1.96	0.496
Duration of psoriasis(years)	11.65 ± 93	11.65 ± 94	11.656 ± 9487	0.844
Sex, *n* (%)				
Females	18 (55.26%)	15 (46.87%)	14 (43.75%)	0.582
Males	14 (44.57%)	17 (53.12%)	18 (56.25%)	

Note: *S.D. — standard deviation; p-value — level of significance*

($p < 0.001$) .After therapy, group A had significantly lower levels of CRP, ESR, PASI, and Isokinetic test compared to groups B and C ($p < 0.001$ and $p < 0.001$, respectively). After the treatment, group B had significantly lower levels of CRP, ESR, PASI, and Isokinetic test compared to group C ($p < 0.001$) (Table 2)**.**

For mild to moderate localized plaque psoriasis on the knee joint, this study sought to assess the efficacy of bee venom phonophoresis. Bee venom phonophoresis as a treatment for localized plaque psoriasis of the knee requires further investigation. Consistent with previous research, our findings suggest that phonophoresis using B.V. may improve PASI and isokinetic proprioceptive testing for the knee joint in addition to reducing systemic inflammation.

Psoriasis is a prevalent, persistent, and recurring inflammatory skin disease characterized by red and scaly patches. In addition, Şenel E. suggested that bee venom therapy could be an alternate treatment for psoriasis vulgaris on the knee joint, as it follows a similar pathway to rheumatoid arthritis [13]. According to Watanabe's findings, bee honey possesses anti-inflammatory, antibacterial, antiviral, and

Table 2. Mean NL ratio, C-reactive protein, ESR, PASI and Isokinetic proprioception test of the groups A, B and C at pre& post

	Group A	Group B	Group C	*p*-value		
	mean ± SD	mean ± SD	mean ± SD	A vs. B	A vs. C	B vs. C
NL ratio						
Pre	2.84 ± 0.34	2.88 ± 0.34	2.80 ± 0.31	1	1	1
post	1.56 ± 0.17	2.18 ± 0.50	2.77 ± 0.29	0.001	0.001	0.001
MD(95%CI)	1.28(1.14 : 1.42)	0.70(0.56: 0.83)	0.02(-0.10:0.16)			
% of change	45%	24.3%	1.02%			
	p = 0.001	***p = 0.001***	***p = 0.161***			
C-reactive protein						
Pre	7.61 ± 1.5	7.05 ± 1.63	6.98 ± 1.60	0.487	0.352	1
Post	1.27 ± 0.89a, b	4.46 ± 1.59a, b	6.58 ± 1.43a, b	0.001	0.001	0.001
MD(95%CI)	6.3(5.76: 6.92)	2.58(2.0: 3.16)	0.39(-0.18: 0.97)			
% of change	83.3%	36.7%	5.7%			
	p = 0.001	***p = 0.001***	***p = 0.077***			
ESR						
Pre	21.37 ± 0.89	21.04 ± 0.62	21.12±0.60	0.197	0.493	1
Post	9.37 ± 1.56a, b	18.67 ± 3.33a, b	20.87±0.70a, b	0.001	0.001	0.001
MD(95%CI)	14.1(13.3: 14.9)	2.36(1.57: 3.16)	0.24(-0.54:1.04)			
% of change	56.1%	11.26%	1.1%			
	p = 0.001	***p = 0.001***	***p = 0.272***			
PASI						
Pre	6.29 ± 1.43	7.20 ± 1.3	7.12 ± 1.4	0.131	0.06	0.812
Post	2.93 ± 0.80a, b	6.15 ± 2.08a, b	7.11 ± 1.4a, b	0.001	0.001	0.001
MD(95%CI)	3.35(2.88: 3.82)	1.04(0.57: 1.51)	-0.02(-0.49:0.44)			
% of change	53.41%	14.58%	0.14%			
	p = 0.001	***p = 0.001***	***p = 0.715***			
Isokinetic proprioception knee						
Pre	4.87 ± 1.04	5.13 ± 1.02	4.87 ± 1.02	0.951	1	0.933
Post	2.91 ± 0.77a, b	4.70 ± 1.06a, b	4.69 ± 1.10a, b	0.001	0.001	0.001
MD(95%CI)	1.96(1.64: 2.27)	0.43(0.11: 0.74)	0.17(-0.14: 0.49)			
% of change	40.2%	8.3%	3.6%			
	p = 0.001	***p = 0.001***	***p = 0.061***			

Note: *S.D. — standard deviation; p — value, level of significance, a — significant difference with pre-treatment; b — considerable difference between pre and post*

antioxidant properties due to its elevated acidity, hydrogen peroxide concentration, and osmotic action. The literature has thoroughly investigated several treatment options for the venom of this order [14].

Chen J. and Lariviere W.R. highlighted the need for an alternative method of applying B.V. for arthritis treatment, as traditional methods like direct bee stings and invasive injections caused pain, inflammation, and poor patient compliance, making this a critical issue [15].

The study reveals that bee venom phonophoresis can modulate the immune response, potentially affecting the ratio of neutrophils to eosinophils, which are involved in allergic reactions, knee joint plaque psoriasis, and parasite infections.

Othman E.M. et al. confirmed that bee venom phonophoresis, a non-invasive treatment method, effectively reduces pain and inflammation associated with systemic inflammation after indirect inguinal hernioplasty, as evidenced by significant differences in VAS, CRP, hip joint range of motion, and ESR [16].

Additionally, Hegazi A.G. observed that oral propolis and topical application of bee venom could serve as a new and effective treatment for chronic localized plaque psoriasis on the knee joint, with few adverse side effects. When used independently or in combination with propolis, intradermal bee venom yields superior outcomes compared to oral or topical propolis [17]. The study by Eltaher found that bee venom injection caused temporary side effects like erythema, moderate swelling, and minor pain at the injection site, but after six months, no recurrence of psoriatic lesions was observed, suggesting B.V. as a safe and beneficial therapy [18].

Hozzein W.N. highlighted the anti-inflammatory properties of bee venom, which can aid in tissue healing by increasing the inflammatory response in the psoriatic knee joint, thereby reducing erythema and itching [19].

Furthermore, Park H.J. and Jeong J.K. discovered that the reduction of Cox-2 expression, which is involved in the formation of prostaglandins (P.G.), which support the inflammatory process, could account for the pharmacological action of bee venom on inflammation. Additionally, bee venom may work by causing IL-10, which Asafova N.N. et al. employed as a novel psoriasis treatment, and decreasing IL-6, which increases inflammatory circumstances [20–22].

The study suggests that venom phonophoresis, along with its active peptides Adolapin and Protease, can have anti-inflammatory effects through various pathways. Adolapin, a physiologically active peptide, inhibits proteases like chymotrypsin, trypsin, plasmin, and thrombin, reducing inflammation and enhancing immune cell function, indicating its direct control over immune cell properties.

Tsai L.C. hypothesizes low molecular weight B.V. could cause pain inhibitory system neurotransmitters, allowing bee venom phonophoresis penetration. Mast cell degranulation peptide has anti-inflammatory properties in animal models [23]. Phonophoresis improves B.V. penetration into the skin during and after cavitation therapy, disrupting stratum corneum lipids and reducing discomfort. It promotes skin permeability, allowing topical B.V. to penetrate the dermis, especially with low molecular weight gels [24].

A study by Park H.J. examined the long-term effectiveness of Bee venom Application (B.V.) acupuncture and physiotherapy in treating adhesive capsulitis. It suggested that melittin, a component of B.V., may be a major causative factor. The study included 42 patients who received B.V. 2 and 21 who received B.V. 1, while the remaining 18 patients received regular saline injections and physiotherapy without intervention [25].

Additionally, Dadar M. clarified that substances with anti-inflammatory qualities, such as melittin and adolapin, are found in bee venom. Joint inflammation contributes to pain, stiffness, and decreased mobility in patients with plaque psoriasis knee. Bee venom may relieve these symptoms by reducing inflammation and enhancing joint proprioception and movement [26].

Once more, Jang S. attested to bee venom's analgesic (pain-relieving) properties. Patients with psoriatic arthritis frequently suffer pain in the afflicted joints, which can restrict their range of motion. Because bee venom inhibits the development of rheumatoid synovial cells, it can improve position sense and lessen joint pain while facilitating movement [27]. Nam K.W. et al. discovered bee venom's pharmacological activity in psoriatic arthritis by reducing 1L-1 β levels, possibly due to its ability to inhibit the synthesis of pro-inflammatory cytokines [28].

Interestingly, no systemic side effects were found in any of the study's patients, in contrast to most psoriasis treatments. This finding suggests that the novel treatment is a safe treatment option that may benefit patients with liver or renal impairment.

Other research, in contrast to ours, refutes the study's hypothesis. According to Altan L.A. et al., numerous in vitro research types using 1-MHz continuous U.S. at spatial peak doses equal to or greater than 1 W/cm2 reported cellular damage due to cavitation. It is also known that high-intensity U.S. treatments might cause discomfort and a hot feeling [29]. Regretfully, Kołaczek A. et al. reported that there could be adverse effects from using B.V. It has been shown that individuals who are highly susceptible to bee venom are at a higher risk of developing a systemic allergic reaction when administered B.V [30]. According to Shim W.H. et al., there were moderate side effects along with temporary skin reactions such rash, edema, and itching. Each research subject had a bee venom allergy test to guard against these adverse effects [31].

The current study has limitations, including limited sample size and no follow-up for Treatment group. To determine the long-term efficacy of bee venom phonophoresis on localized plaque psoriasis, more research with a larger sample size, more observation time is required, in addition to diversity in the participants and their implications on the rate of recovery. Also using different parameters of ultrasound (intensity, frequency, and duration of treatment) or with other physical therapy modalities, such as iontophoresis instead of phonophoresis and different concentrations of bee venom gel.

These are the reasons, from the researchers' point of view, that led to this study's results:

- Ultrasound topical application can enhance anti-inflammatory cytokine production and decrease pro-inflammatory cytokine levels, regulating immune reaction and indirectly impacting ESR levels by modifying overall inflammatory response.
- Phonophoresis enhances B.V. penetration into the skin, altering stratum corneum's lipids. Topical B.V. penetrates deeper into dermis due to low molecular weight and concentration gradient.

- Topical bee venom phonophoresis has been shown to influence ESR through its anti-inflammatory and immune-modulatory effects; more research is needed to establish a direct link and fully understand the clinical implications.
- Bee venom, when applied topically, can increase skin permeability, stimulate pain-inhibiting mechanisms, and control immune system activity, potentially reducing psoriasis-related autoimmune reactions.
- Bee venom contains peptides with antimicrobial properties, which may help prevent secondary infections in psoriatic skin lesions antimicrobial properties.

CONCLUSION

Researchers found that bee venom phonophoresis improved proprioception in knee joints and reduced the severity of mild to severe localized plaque psoriasis by lowering CRP, ESR, and N.L. ratios.

ADDITIONAL INFORMATION

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