USE OF APITOXIN AS AN INTERVENTION IN THE TREATMENT OF DERMATOLOGICAL INFLAMMATION

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José Roberto da Cunha Lima[1], Beatriz Gonçalves Guimarães[2], José Wheslley Rodrigues de Lucena[3], Nathanael Nascimento dos Santos[4], Paulo Miguel Simão Araújo[5], Douglas Soares de Oliveira[6], Wendson de Ribamar Machado Corrêa[7], Katrine Nascimento de Carvalho[8] and Durcilene Alves da Silva[9]

ABSTRACT

Bee venom (BV), produced by the species Apis mellifera, is one of the most recognized and widely studied natural toxins, with increasing use in integrative medicine. This venom contains a variety of chemicals, including peptides such as melittin, apamine, adolapin, and the peptide MCD, as well as enzymes such as phospholipase A2 (PLA2), hyaluronidase, acid phosphomonoesterase, and lysophospholipase. Amines such as histamine, dopamine, and norepinephrine are also present, which contribute to antimicrobial, anti-inflammatory, immunomodulatory, and anticancer properties. Studies suggest that it has promising pharmacological effects, especially in the treatment of inflammation. OBJECTIVE: This study aims to investigate the therapeutic effects of bee venom in the treatment of dermatological inflammations, exploring its potential as a natural alternative with proven anti-inflammatory properties. METHODOLOGY: A systematic review of the literature was carried out, focusing on primary articles and results of randomized controlled trials (RCTs) conducted in vivo and in vitro, published between 2014 and 2024. RESULTS: In mouse models of induced atopic dermatitis (AD), phospholipase A2 (PLA2), a BV-derived compound, has been shown to significantly reduce skin thickness and inflammatory cytokine levels, both in animal and human models, highlighting the importance of confirming its clinical applicability. As a result, therapies can include everything from the topical application of BV to the use of emollients and cosmetics with these compounds, based on their pharmacological properties. CONCLUSION: This review evidenced the potential of bee venom as a promising alternative in the treatment of dermatological inflammation, due to its anti-inflammatory and immunomodulatory properties. Studies in animal models and in vitro suggest that compounds such as melittin and phospholipase A2 (PLA2) inhibit inflammatory mediators and relieve symptoms of atopic dermatitis and acne. In addition, research indicates that BV can block inflammatory signaling pathways, such as NF-κB and MAPK, reinforcing its therapeutic potential in the management of skin inflammation, especially in topical applications.

Keywords: Apitoxin. Dermatological Disease. Inflammation. Bee Venom. Treatment.

[1] Doctorate student in Biotechnology in Health - Federal University of Delta do Parnaíba
[2] Undergraduate student in Biomedicine - Federal University of Delta do Parnaíba
[3] Undergraduate student in Biomedicine - Federal University of Delta do Parnaíba
[4] Undergraduate student in Pharmacy - Uninassau Parnaíba
[5] Graduating in Veterinary Medicine - Uninassau Parnaíba
[6] Undergraduate student in Biomedicine - Federal University of Delta do Parnaíba
[7] Undergraduate student in Biomedicine - Federal University of Delta do Parnaíba
[8] Professional Master in Dentistry in the Area of Collective Health - Faculdade São Leopoldo Mandic
[9] Dr. in Inorganic Chemistry - Federal University of Ceará

INTRODUCTION

The skin is the largest organ in the human body, it performs vital functions as a protective barrier against allergens, toxins and pathogens, as well as regulating body temperature and water and electrolyte homeostasis. When these functions are disrupted, several dermatological diseases can arise, significantly impacting the quality of life of affected individuals (Dinu *et al.,* 2024) .

The damage caused to the skin has as one of the reactions inflammation, a generalized response activated by the innate and adaptive immune systems to maintain the body's balance. Under normal conditions, this response promotes recovery from infections and healing, however, when it does not occur in a controlled way, inflammation can lead to immune disorders. (Lee; Bae, 2016)

It is estimated that there are about 3,000 recognized dermatological diseases. In the United States, approximately 11.8% of the population between the ages of 1 and 74 suffer from at least one skin disease, and 75% of Americans report concerns about conditions that affect visible areas of the body, such as the face and neck. In Canada the prevalence rate is 28.4% and 7.05 million people are disabled in China annually. Among dermatological inflammations, atopic dermatitis is considered one of the diseases commonly found in approximately 20% of children worldwide and in 1% of adults (Liang *et al.,* 2024) (You *et al.,* 2016) .

Dermatological inflammations have a different classification, depending on several factors such as cause and manifestation. The most frequently found in addition to atopic dermatitis and psoriasis and acne, which causes thick, scaly plaques and inflammation of the sebaceous glands, respectively. Other inflammations that affect the population are contact dermatitis, caused by exposure to allergens or irritants, and urticaria, an allergic reaction that causes red rashes and itching. These conditions vary in severity and can be triggered by immune, environmental, or infectious factors (Dong; Li; Shi, 2024) (Ashbaugh; Abel; Murase, 2021; Lauritano *et al.,* 2020) .

Currently, there are several drugs used in conventional medicine for skin disorders, but a complexity arises that has several limitations, such as adverse effects or limited penetration, so a new interest arises in discovering molecules that are effective and safe to combat these conditions (Majtan; Bučeková; Jesenak, 2021) .

Bee venom (BV), produced by bees of the species *Apis mellifera*, is one of the most widely recognized natural toxins, currently used in integrative medicine. This venom is composed of a wide variety of chemicals, including peptides such as melittin, apamine, adolapine and the peptide MCD. These components, as well as enzymes such as

phospholipase A2 (PLA2), hyaluronidase, acid phosphomonoesterase, and lysophospholipase, several amines (histamine, dopamine, and norepinephrine) contribute to the biological effects of BV, including antimicrobial, anti-inflammatory, immunomodulatory, and anticancer attributes. (Kim *et al.,* 2017 Cui *et al.,* 2024)

BV has promising pharmacological effects, especially in the treatment of inflammation. Recent studies have shown that by detoxifying bee venom, it is possible to significantly reduce its cytotoxicity and allergenicity while maintaining its potent anti-inflammatory and antioxidant properties. Detoxification involves modifying components of the venom, such as melittin, resulting in a significant reduction in the expression of pro-inflammatory cytokines and the phosphorylation of IκBα, without causing damage to cells (Lee et al., 2021) .

Melittin, the most relevant component of bee venom (representing 50% of its dry weight), has anti-inflammatory and antiarthritic properties, activated by the inhibition of nuclear factor kappa B (NF-κB). Melittine has also demonstrated anticancer, antibacterial, and antiviral activities. Studies report that the PLA2 enzyme, also present in bee venom, contributes to the improvement of skin lesions similar to those of atopic dermatitis (Kim *et al*., 2019).

Due to the significant impact that skin diseases, such as atopic dermatitis, acne and psoriasis, have on the quality of life of individuals, the aim of this study is to investigate the therapeutic effects of apitoxin (Venom produced by the bee *Apis mellifera*) in the treatment of dermatological inflammations, seeking to explore a natural alternative with proven anti-inflammatory properties. It is intended to evaluate its effectiveness in reducing inflammation and in this way, the study aims to contribute to the development of safer and more effective treatments for dermatological conditions.

MATERIAL AND METHODS

The present study is a systematic review of the literature that aims to identify, select, evaluate and synthesize the relevant evidence available in the literature on the subject. To develop the review, the following steps were carried out: 1) elaboration of the research question; 2) literature search; 3) selection of articles and definition of inclusion criteria; 4) data extraction.

The conduct of this review was based on the following research question: "Do apitoxin and its derivatives present in the venom of the bee *Apis mellifera*, have anti-inflammatory properties safe for use in dermatological inflammation?".

From the definition of the problem, inclusion and exclusion criteria were delimited and keywords were defined. In the second stage, there was a search in the literature to locate and select relevant studies. To identify all studies, the following databases were used: *PubMed* and *Scopus,* it is important to emphasize that more searches were carried out in other databases such as *Web of Science*, but the studies found in it had already been selected in the databases mentioned above. The following keywords were used in Portuguese: apitoxin, dermatological disease, inflammation, bee venom, treatment. These descriptors were combined with the Boolean operators "AND" and "OR", to form the search *string*, used in the search strategy in the databases.

Table 01. Database search strategies

Scopus	(("Apitoxin" OR "Bee Venom" OR "Apitoxina") AND ("Skin Inflammation" OR "Dermatitis" OR "Inflammatory Skin Condition" OR "Dermatological Disease") AND ("Therapy" OR "Intervention" OR "Treatment" OR "Anti-Inflammatory Therapy"))
Pubmed	

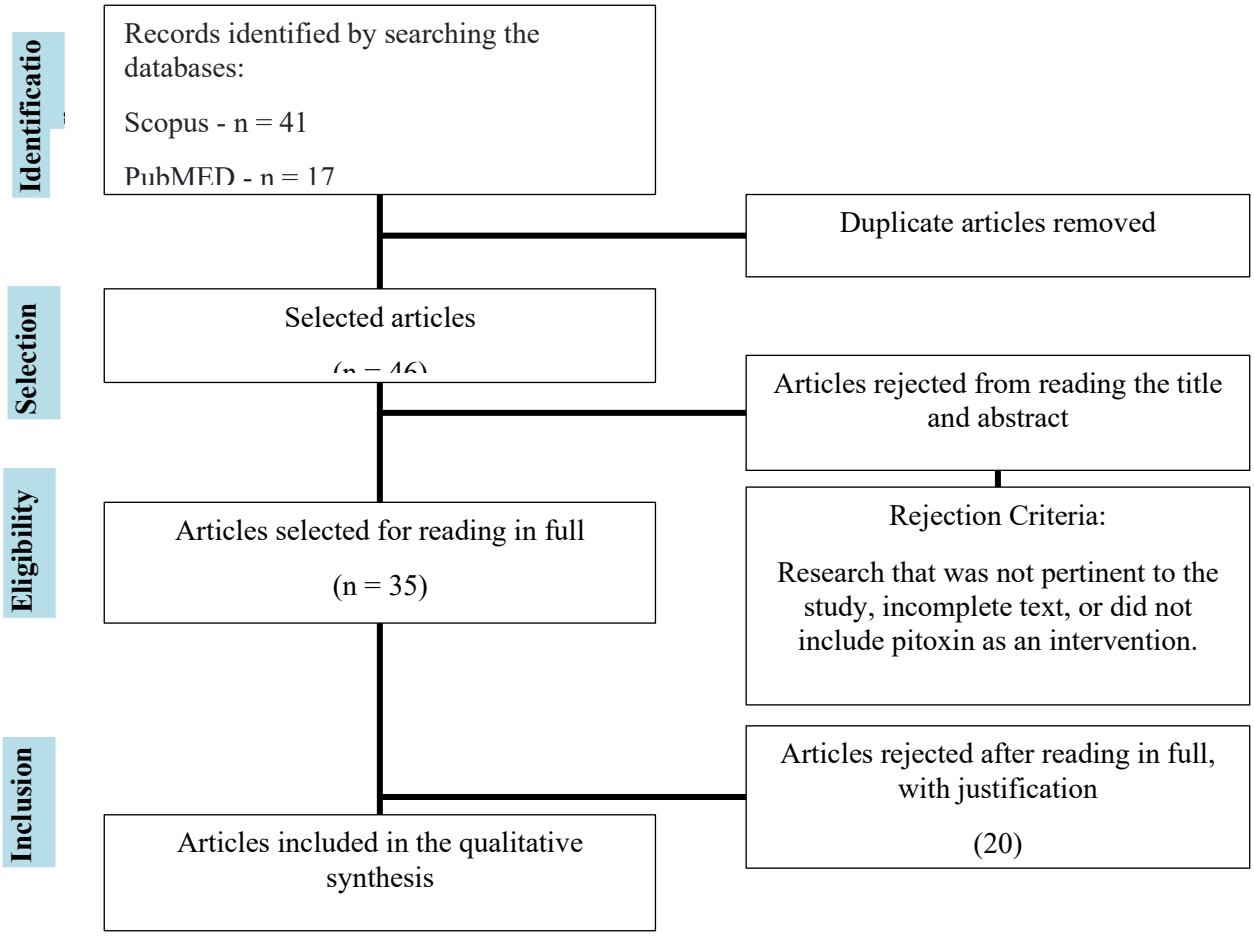
Source: Survey Data, (2024)

In the third stage, the articles were selected and the inclusion and exclusion criteria were defined. We chose to include primary articles results of randomized clinical trials (RCTs) conducted *in vivo* and *in vitro*; published between 2014 and 2024 with the aim of analyzing both more recent publications and previous studies, expanding the understanding of the relationship between the constructs; in Portuguese, English, and Spanish, which are related to apitoxin, skin inflammation and treatment. As exclusion criteria, articles that do not answer the guiding question, that do not deal with apitoxin and/or its derivatives in the treatment of dermatological diseases, theses, theoretical articles, review articles, meta-analysis, editorials, comments on articles, books and book chapters.

The extracted data were collected, combined, and summarized to draw logical conclusions from the results of the individual studies. The synthesis considered the strength of the evidence and whether the observed effect is consistent across studies, as well as explanations for possible inconsistencies. After gathering, assessing the quality and extracting the data, the conclusions were made through a narrative approach.

Carried out through a narrative approach.

Figure 01. Search and selection of studies for inclusion in the systematic review



Source: Research Data, (2024).

RESULTS

The present systematic review aimed to investigate the effectiveness of bee venom in the treatment of skin inflammation, that is, in order to provide a comprehensive review of the evidence available in the literature to understand the potential of bee venom as a therapeutic alternative in the management of inflammatory skin conditions. For this, based on the use of the descriptors and databases mentioned above, a total of 69 studies were identified, among which 46 articles were selected for analysis. 23 articles were removed due to duplication in the databases. In addition, 11 papers were rejected due to previous reading of the title and abstract of the text. Thus, a total of 35 articles were selected for full reading and correlation analysis with the proposed theme. Thus, respecting the rejection and inclusion criteria established in the research methodology, 20 studies were rejected. Summatizing 15 articles for the qualitative synthesis of the literature review.

Table 1: Summary of results

Base data	Author/Year	Sample	Intervention	Objective	Denouement	Method	Results
Scopus	Lee; Bae, 2016	Mice (N= 30) (Mean age = 08 months of age).	I use melittin mixed with petroleum jelly.	To analyze the effect of melittin in mice with induced (*P. acnes*).	Effectiveness of the use of melittin in the treatment of acne.	HaCaT (5.0 × 105 cells ml−1) were seeded in complete medium. After 24 hours, the cells were switched to serum-free medium containing the indicated concentrations of melittin (0.1, 0.5, and 1 μg ml−1).	Administration of melittin significantly decreased the expression of several inflammatory cytokines in keratinocytes treated with *P. acnes*. In addition, it exerted anti-inflammatory effects against the live animal model treated with *P. acnes*. These protective effects were mainly due to the suppression of NF-κB and AP-1, which regulate the production of inflammatory cytokines.
PubMed	Han *et al.*, 2017	The experiments were carried out on 39 healthy male guinea pigs of 5 weeks of age	Bee venom gel	Analyze the effects of bee venom as well as evaluate the safety of cutaneous application	Observes skin reaction through phototoxicity and photosensitization of the skin after use of VB	Purified bee venom was collected and diluted in sterile cold water and centrifuged at 10,000×g for 5 minutes at 4°C. The residues in the supernatant were discarded. PBVTM was lyophilized and refrigerated at 4°C for later use. BV gel has been prepared with MFDS-approved materials and formulated. The gel containing 0.06% BV	Erythema and edema were observed after 24, 48, and 72 hours in the positive control group, but not in the negative control and BV gel groups. In summary, Bv has shown great potential in the development of cosmetics.
Scopus	Kim *et al.*, 2019	Cell culture (*in vitro*) and Male mice (7 weeks of age).	Use of melittin and unpurified bee venom.	Observe the effect of purified bee venom and melittin *in vitro and in vivo*.	Effectiveness of the use of melittin in the treatment of atopic dermatitis.	Cultivation of HaCat and THP-1 cells, dilution of bee venom, dissolved in Dulbecco phosphate-buffered saline solution, use of PCR.	From the experiments, it was possible to observe that bee venom relieves atopic dermatitis by inactivating the complement system, especially by inducing CD55.

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PubMed	Kim *et al* ., 2017	Camundongos HaCaT cells (keratinocytes)	Use of melittin, a component of bee venom	Effect of melittin on ovalbumin-induced atopic dermatitis-like skin lesions	To observe the benefit of melittin in lesions similar to induced atopic dermatitis	HaCaT cells (CLS, Eppelheim, Germany) were cultured in modified Dulbecco Eagle medium (DMEM) supplemented with 10% fetal bovine serum and 1% antibiotics at 37 °C in a 5% CO2 humidified incubator. HaCaT cells were seeded in 1.0 × 106 cells through a complete 3 ml medium in a 100 mm CT-treated cell culture dish. The cells were seeded in a 96-well plate at 5.0 × 103 cells per well and pre-incubated for 24 h. After pre-incubation, the cells were treated with melittin (0.1, 0.5, 1 and 2 μg ml−1) and 50 ng ml−1 each of IL-4 and IL-13 for 24 or 48 h.	The results showed that OVA-induced skin thickening and inflammatory infiltration decreased in the melittin-treated group. Melitin prevented OVA-induced filaggrin deficiency and unbalanced inflammatory mediators. In addition, melittin inhibited IL-4/IL-13-induced filaggrin downregulation through blocking STAT3 activation in human keratinocytes.
PubMed	An *et al.* , 2018	Female mice and in human keratinocyte cultures	Bee venom and melittin	Analyze the efficacy of bee venom and melittin are suitable for epicutaneous application	Describe the potential effects of bee venom and melittin in the treatment of induced atopic dermatitis *in vivo* and *in vitro*	The effects of bee venom and melittin were studied in an in vivo 1-chloro-2,4-dinitrobenzene (DNCB)-induced AD model in female Balb/c mice and in human keratinocyte cultures, stimulated by TNF-α/IFN-γ.	Bee venom and melittin exhibited potent anti-atopic activities, demonstrated by the decrease of AD-like skin lesions induced by DNCB in mice. In vitro studies using human keratinocytes stimulated by TNF-α/IFN-γ showed that bee venom and melittin inhibited increased expression of chemokines, such as CCL17 and CCL22, and pro-inflammatory

							cytokines, including IL-1β, IL-6, and IFN-γ, by blocking NF-κB and STAT signaling pathways.
PubMed	Jang S, *et al.*, 2024	2 patients. Mice	Acupuncture and phytotherapy associated with bee venom	To analyze the hypothesis that bee venom acupuncture (VA) is effective for eczema and contact dermatitis.	Suggest that bee venom and herbal medicine may be an alternative treatment for eczema and contact dermatitis.	Both patients with HS and contact dermatitis were treated with BVA BVA treatments for a total of 19 and 16 sessions. On the first day of treatment, a skin test for AVB was performed (0.3 mL of 10% diluted AVB in case 1, 0.2 mL of 10% diluted AVB in case 2). The BVA dose was increased to 2.4 mL (case 1) or 0.9 mL (case 2) on the last day of treatment. Eczema-like contact dermatitis was induced using 2,4-dinitrochlorobenzene (DNCB) as previously described. The six-week-old mice were exposed to 1% DNCB once weekly for 4 weeks. From the second week onwards, the mice were injected with BVA (50 μg/kg diluted in PBS) or saline solution and SWH (200 mg/kg, 3 times/week) was administered orally	This study reports the medical histories and treatment processes of two cases of hand eczema (HE), including contact dermatitis that were cured by bee venom acupuncture (BVA) combined with herbal medicine. This study also confirmed the effect of BVA and SWH co-treatment in a mouse model of eczema-like dermatitis. Bee venom therapy combined with herbal medicine is safe and effective for HS patients.

Scopus	Cherniack; govorushko, 2018	People with musculoskeletal and neurological diseases associated with depression	Acupuncture with bee venom applied to the tips of acupuncture needles.	To evaluate the efficacy and safety of acupuncture with bee venom in humans.	Treatment of musculoskeletal and neurological diseases, including lumbar disc disease, knee osteoarthritis, rheumatoid arthritis, adhesive capsulitis, lateral epicondylitis, peripheral neuropathies, stroke, and Parkinson's disease.	Review of small studies on the use of acupuncture with bee venom in humans.	Bee venom acupuncture has shown success in treating various musculoskeletal and neurological diseases, but there are significant concerns about safety, including the risk of anaphylaxis.
Scopus	Gazerani, 2021	Humans with Parkinson's Disease	Use of venoms from bees, scorpions, snakes, and lizards as therapeutic options for Parkinson's disease (PD).	To investigate the neuroprotective role of a diverse range of natural products, including venoms, in preclinical PD models and in humans.	Evaluation of the main findings of recent studies that investigated venoms as therapeutic options for PD.	Review of recent studies on the use of venoms in preclinical and human models for PD.	The venoms have shown neuroprotective potential in preclinical models of PD, suggesting that they may be promising therapeutic options for slowing disease progression.
Scopus	Shin; Choi; Bae, 2018	Mice	Application of phospholipase A2 (PLA2) derived from bee venom to treat skin lesions similar to atopic dermatitis induced by 2,4-dinitrochlorobenzene (DNCB) and house dust mite extract (DFE).	To investigate the underlying mechanisms of PLA2 action in atopic dermatitis.	Inhibition of epidermal thickness, serum immunoglobulin E (IgE) and cytokine levels, macrophage and mast cell infiltration into the ear of a DFE and DNCB-induced model of AD.	Application of DNCB and DFE to induce atopic dermatitis in mice, followed by treatment with PLA2. Evaluation of effects through clinical and histological measurements.	Treatment with PLA2 inhibited epidermal thickness, serum IgE and cytokine levels, and macrophage and mast cell infiltration into the ear of mice. These effects were nullified in CD206 mannose receptor-deficient mice exposed to DFE and DNCB.
Scopus	Kim *et al*., 2021	Epithelial cells of A549 airways	Application of bee venom (1.0 μg/mL) to inhibit IL-13-induced AKT phosphorylati	Investigate the effect of bee venom on IL-13-induced mucus metaplasia	Inhibition of MUC5AC production through regulation of SPDEF and FOXA2	In vitro study with A549 cells, using IL-13 to induce mucus metaplasia and bee venom to inhibit AKT	Bee venom inhibited AKT phosphorylation, increased SPDEF expression, and decreased FOXA2 expression, preventing IL-13-induced

			on (10 ng/mL)			phosphorylation	increase in MUC5AC expression
Scopus	Kim *et al*., 2015	Human keratinocytes (HaCaT) and monocytes (THP-1)	Bee Venom Treatment to Investigate Its Anti-inflammatory Properties in Propionibacterium acnes (P. acnes)-induced Skin Inflammation	To investigate the anti-inflammatory properties of bee venom on P. acnes-induced skin inflammation	Inhibition of the secretion of pro-inflammatory cytokines (IFN-γ, IL-1β, IL-8 and TNF-α) and the expression of IL-8 and toll-like receptor 2 (TLR2) in HaCaT and THP-1 cells treated with P. acnes	In vitro study using human keratinocytes (HaCaT) and monocytes (THP-1) treated with P. acnes and bee venom	Bee venom effectively inhibited the secretion of IFN-γ, IL-1β, IL-8 and TNF-α, as well as the expression of IL-8 and TLR2 in HaCaT and THP-1 cells treated with P. acnes
Scopus	Lee *et al*., 2021	Camundongos Balb/c	Topical application of 5% phthalic anhydride (PA) to the dorsal skin and ears to induce atopic dermatitis (AD), followed by treatment with bee venom (BV) three times a week for 4 weeks.	To investigate the anti-inflammatory and anti-DA effects of bee venom in an animal model of PA-induced AD.	Significant reduction in clinical AD score, epidermal thickness, IgE level, and immune cell infiltration into skin tissues.	Topical application of PA to induce AD, followed by treatment with BV. Evaluation of the effects through clinical and histological measurements, in addition to analysis of inflammatory cytokines in the serum.	Treatment with BV significantly reduced the clinical AD score, epidermal thickness, IgE level, and immune cell infiltration into skin tissues. In addition, VB inhibited the expression of iNOS and COX-2, as well as the activation of the MAPK and NF-κB signaling pathway.
Scopus	Jung *et al*., 2017	Mice	Topical application of phospholipase A2 (bvPLA2) derived from bee venom to treat skin lesions similar to atopic dermatitis induced by house dust mite extract (DFE) and 2,4-dinitrochlorobenzene (DNCB).	To determine whether treatment with bvPLA2 exacerbates DFE-induced atopic dermatitis-like allergic inflammations in a murine model.	Significant suppression of increased symptoms of atopic dermatitis, including ear thickness, serum IgE concentration, inflammatory cytokines, and histological changes.	Topical application of bvPLA2 in mice with DFE/DNCB-induced atopic dermatitis. Measurement of epidermal thickness, immune cell infiltration, serum immunoglobulin, and cytokines.	Treatment with bvPLA2 inhibited mast cell infiltration into the ear and significantly suppressed symptoms of atopic dermatitis, including ear thickness, serum IgE concentration, and inflammatory cytokines. Depletion of regulatory T cells abolished the anti-atopic effects of bvPLA2, suggesting that the effects depend on the existence of Tregs.
Scopus	You *et al*., 2016	136 patients with atopic dermatitis	Application of an emollient containing bee venom and silk	To discover the beneficial effect of an emollient containing	Eczema Area and Severity Index (EASI) score, transepiderm	Double-blind, randomized, base-controlled, multicenter study	Patients who applied emollient containing bee venom had significantly lower EASI scores and VAS value compared to

			protein or an identical vehicle, except for bee venom, for 4 weeks	bee venom in the treatment of patients with atopic dermatitis	al water loss, and pruritus visual analogue scale (VAS) score		patients who applied emollient without bee venom
Scopus	Tender *et al.*, 2024	Ratos Wistar	Application of melittin to induce toxicity, followed by treatment with mini-αA-crystalline gel (MAC) and its modified version (MAC-GRD).	To compare the skin permeation, anti-inflammatory and analgesic activities of the natural peptide MAC and its modified version (MAC-GRD).	Improvement in skin permeability and anti-inflammatory, analgesic, and antioxidant activities of MAC-GRD compared to MAC and 1% hydrocortisone cream.	Study of ex-vivo skin permeation using a vertical-type Franz's diffusion apparatus and in vivo preclinical experiments in Wistar rats.	MAC-GRD gel demonstrated greater skin permeability and superior anti-inflammatory, analgesic, and antioxidant activities compared to MAC gel and 1% hydrocortisone cream.

Source: survey data, 2024.

The studies in this review are generally characterized as studies of variable dates, but occurring mainly in the years 2017 and 2018. Among the studies selected for the review, most were conducted in experimental models with mice, indicating a predominance of animal model research to evaluate the effect and efficacy of BV. For example, Lee and Bae (2016) evaluated the effect of melittin in topical preparations, while Shin, Choi and Bae (2018) investigated the application of phospholipase A2 (PLA2), derived from BV to treat skin lesions that simulate inflammatory conditions, such as atopic dermatitis induced by environmental chemical agents, being an experimental model widely used to evaluate immunological and anti-inflammatory properties.

In addition to the *in vivo model,* a considerable additional portion used cell culture, i.e., *in vitro model*. For example, Kim *et al* (2019) used both the in vivo model and cell culture in order to explore the activity of melittin and unpurified venom. In addition, Kim *et al.* (2021) focused on the use of the venom in airway epithelial cells (A549), which demonstrated its potential to inhibit AKT phosphorylation, induced by IL-13. A relevant point of such a methodology is the provision of the detailed molecular mechanism that is involved in the therapeutic properties of BV, which allows an accurate analysis of cellular responses of different concentrations and composition of the venom.

In addition, some studies have applied alternative methodology such as clinical trials, which explore the use of venom in alternative medical applications, such as acupuncture, as indicated by Cherniack and Govorushko (2018), as well as topical formulations for patients with chronic inflammatory conditions, as demonstrated by You *et al.* (2016); even

by people with neurological conditions, such as Parkinson's disease, as demonstrated by Gazerani (2021). Three studies complement the experimental models previously mentioned, in addition to being able to expand the understanding of the effects of BV in diversified therapeutic environments.

DISCUSSION

The analyzed research shows patterns regarding the widespread use of animal models, especially Wistar mice and rats, to explore the therapeutic effects of bee venom including substances present in its composition such as melittin. For example, studies such as those by Bae *et al.* (2018) and Jung *et al.* (2017) tested in mice the effectiveness of phospholipase A2 (PLA2), a compound derived from VA, in reducing the symptoms of atopic dermatitis (AD), noting a considerable decrease in skin thickness and levels of inflammatory cytokines.

On the other hand, Tender *et al.* (2024) conducted studies in Wistar rats, showing that the application of melittin, followed by treatment with mini-αA-crystalline gel (MAC-GRD), led to superior skin permeability and more effective anti-inflammatory activities compared to conventional treatment with 1% hydrocortisone.

For Kim *et al.* (2019) and Kim *et al.* (2017) in vivo studies with mice and HaCaT cell cultures were used to examine the effects of melittin. In both cases, there is evidence that melittin blocks inflammatory mediators such as NF-κB and AP-1, decreasing the production of cytokines that favor inflammation. The research by Kim *et al.* (2017) also highlights the protection against the downregulation of filaggrin, essential for the preservation of the skin barrier, indicating that melittin may be advantageous in preventing problems in the epidermis.

Unlike preclinical studies, there is research that seeks to apply these results to human models. You *et al.* (2016) conducted a clinical study with 136 patients, analyzing an emollient that contained BV. The research revealed a remarkable advance in clinical AD scores, with a decrease in the EASI score and the visual analogue scale (VAS) of pruritus. This underscores the clinical efficacy of BV-derived compounds in the treatment of inflammatory conditions. This shift from animal to human models is crucial to confirm the clinical applicability of the findings.

Therapies can vary greatly, ranging from the topical application of BV to the use of products such as emollients, specifically made with these compounds based on their pharmacological properties and studies. For example, Jung *et al.* (2017) focused on the topical use of melittin, while You *et al.* (2016) analyzed the impacts of an EBV-enhanced

emollient. The variety of therapeutic methods reflects the constant search for treatment techniques that are both efficient and safe, reducing possible adverse effects.

The purposes of these studies are consistent in evaluating the anti-inflammatory and anti-allergic effects of BV. For example, Jung *et al.* (2017) reported a reduction in skin lesions and inflammatory cell infiltration, whereas You *et al.* (2016) noted a significant improvement in the clinical symptoms of patients. These findings underline the promising possibility of these compounds in the control of chronic inflammatory conditions. The action processes addressed in the surveys also offer valuable insights into the effectiveness of treatments. Inhibition of NF-kappa B and STAT signaling pathways is often cited as a crucial process in modulating the inflammatory response. Tender *et al.* (2024) proved that melittin has the ability to block the production of pro-inflammatory chemokines and cytokines, indicating a solid mechanism that underpins the observed anti-inflammatory effects. These results highlight the therapeutic efficacy of melittin and BV in the treatment of inflammatory diseases, laying a robust foundation for future clinical research.

Bee venom, in addition to being used as an intervention in the treatment of atopic dermatitis, studies have also shown a great effectiveness of this substance in the treatment of acne, as described by Lee; Bee (2016). The researchers investigated the anti-inflammatory effects of melittin treatment on heat-inactivated HaCaT cells exposed to *Propionibacterium acnes* . The results showed that treatment with melittin reduced the increase in phosphorylation of IKK, IκB, NF-κB, and p38, caused by *P. acnes* in HaCaT cells. Thus, the data indicate that melittin inhibits the production of inflammatory cytokines induced by *P. acnes* by blocking NF-κB and p38 MAPK signaling in these cells.

In addition to the applicability of bee venom in dermatological inflammations, research has suggested its use in the composition of cosmetics according to the results obtained by . Due to its anti-inflammatory, antibacterial, and healing properties, purified bee venom can help reduce inflammation and fight infection-causing bacteria on the skin. In this way, the use of VB in cosmetics has shown great potential based on its supposed anti-aging and regenerative properties. The venom, composed of melittin, apamine, and phospholipase A2, is promoted as an active ingredient that can stimulate collagen and elastin production, helping to improve skin firmness and elasticity. Han *et al* (2017)

FINAL CONSIDERATIONS

The present review showed that bee venom has been shown to be a promising alternative in the treatment of dermatological inflammations, due to its anti-inflammatory and immunomodulatory properties. Studies in animal models and in vitro have shown that

compounds such as melittin and phospholipase A2 (PLA2) have the ability to inhibit inflammatory mediators and reduce symptoms of conditions such as atopic dermatitis and acne. In addition, research indicates that BV may be effective in blocking crucial signaling pathways, such as NF-κB and MAPK, which are involved in exacerbated inflammatory responses. These findings reinforce the therapeutic potential of BV in the management of skin inflammation, especially in topical applications.

However, despite the promising results, there is still a need for additional studies, especially in human models, to confirm the clinical efficacy and long-term safety of BV. Although preliminary studies in humans, such as those by You *et al.* (2016), have demonstrated significant improvements in chronic inflammatory conditions, it is essential to ensure that risks, such as cytotoxicity and allergic reactions, are minimized. Thus, the continuity of clinical research and the search for methods that detoxify the venom without compromising its efficacy are fundamental steps for the validation of BV as a viable and safe option in the treatment of dermatological inflammation.

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