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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.

[1] Dr. 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

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Revista ARACÊ
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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; Read; 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; Bucekova; 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

Revista ARACÊ
ISSN: 2358-2472

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.

Revista ARACÊ
ISSN: 2358-2472

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 "Apitoxin") 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)

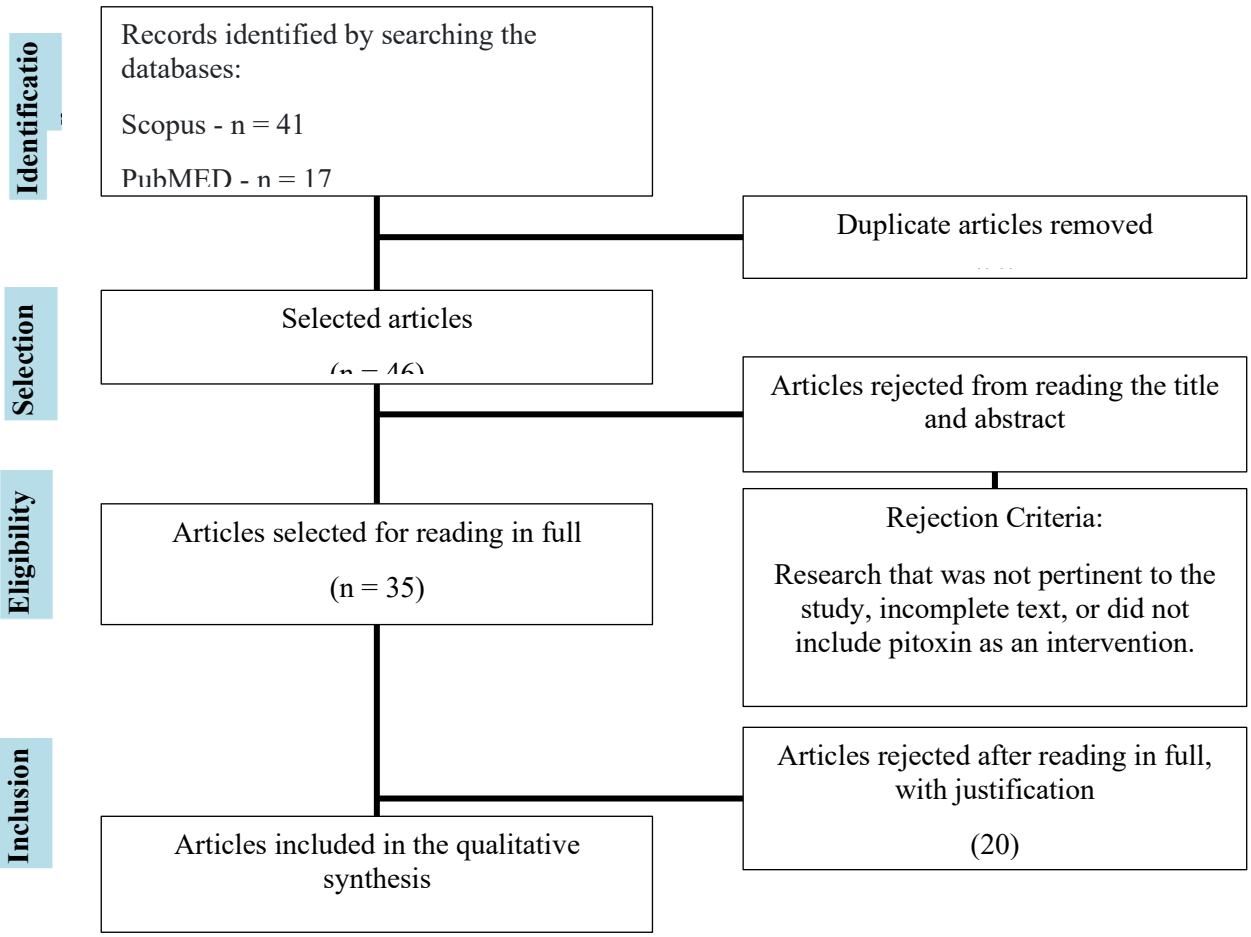
In the third stage, the articles were selected and the inclusion and exclusion criteria were defined. We chose to include primary articles results of randomized clinical trials (RCTs) conducted *in vivo* and *in vitro*; published between 2014 and 2024 with the aim of analyzing both more recent publications 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.

Revista ARACÊ
ISSN: 2358-2472

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.

Revista ARACÊ
ISSN: 2358-2472

Table 1: Summary of results

Base data	Author/Ye	Sample	Intervention	Goal	Denouement	Method	Findings
Scopu	Lee; Ba 2016	Mice (N= 30) (Mean age 08 months age).	I use melittin mixed with petroleum jelly	To analyze th effect of melittin in mi with induce (*P. acnes*).	Effectiveness the use of melittin in the treatment of acne.	HaCaT (5.0 × 10 cells ml−1) were seeded in complete mediu After 24 hours, t cells were switched to seru free medium containing the indicated concentrations melittin (0.1, 0.5 and 1 μg ml−1)	Administration of melittin significantly decreased the expression of sever inflammatory cytokines in keratinocytes treate with *P. acnes*. In addition, it exerted anti-inflammatory effects against the li animal model treate with *P. acnes*. Thes protective effects we mainly due to the suppression of NF-κ and AP-1, which regulate the production of inflammatory cytokines.
PubMe	Han *al.*, 20	The experiment were carrie out on 39 healthy mal guinea pigs 5 weeks of a	Bee venom g	Analyze the effects of be venom as we as evaluate t safety of cutaneous application	Observes ski reaction throug phototoxicity a photosensitiza n of the skin af 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 t supernatant wer discarded. PBVT was lyophilized and refrigerated 4°C for later use BV gel has bee prepared with MFDS-approve materials and formulated. The gel containing 0.06% BV	Erythema and edem were observed afte 24, 48, and 72 hou in the positive contr group, but not in th negative control an BV gel groups. In summary, Bv has shown great potenti in the development cosmetics.
Scopu	Kim *al.*, 20	Cell culture (*vitro*) and Ma mice (7 weel of age).	Use of melitti and unpurifie bee venom.	Observe the effect of purified bee venom and melittin *in vit and in vivo*	Effectiveness the use of melittin in the treatment of atopic dermatit	Cultivation of HaCat and THP cells, dilution o bee venom, dissolved in Dulbecco phosphate-buffered saline solution, use o PCR. .	From the experimen it was possible to observe that bee venom relieves atop dermatitis by inactivating the complement systen especially by induci CD55.

Revista ARACÊ
ISSN: 2358-2472

PubMe	Kim *al* ., 201	Mice HaCa cells (keratinocyte	Use of melittin component o bee venom	Effect of melittin on ovalbumin-induced atop dermatitis-lik skin lesions	To observe th benefit of melit in lesions simil to induced atop dermatitis	HaCaT cells (CL Eppelheim, Germany) were cultured in modified Dulbec Eagle medium (DMEM) supplemented w 10% fetal bovin serum and 1% antibiotics at 37 in a 5% CO2 humidified incubator. HaCa cells were seede in 1.0 × 106 cell through a comple 3 ml medium in 100 mm CT-treated cell cultu dish. The cells were seeded in 96-well plate at 5 × 103 cells per w and pre-incubate for 24 h. After pr incubation, the cells were treate with melittin (0.1 0.5, 1 and 2 μg ml−1) and 50 n ml−1 each of IL- and IL-13 for 24 48 h.	The results showe that OVA-induced sk thickening and inflammatory infiltration decrease in the melittin-treate group. Melitin prevented OVA-induced filaggrin deficiency and unbalanced inflammatory mediators. In additic melittin inhibited IL 4/IL-13-induced filaggrin downregulation through blocking STAT3 activation i human keratinocyte
PubMe	An *al.* , 201	Female mic and in huma keratinocyte cultures	Bee venom ar melittin	Analyze the efficacy of be venom and melittin are suitable for epicutaneou application	Describe the potential effec of bee venom and melittin i the treatment induced atopi dermatitis *in vi* and *in vitro*	The effects of be venom and melit were studied in a in vivo 1-chloro 2,4-dinitrobenzer (DNCB)-induce AD model in female Balb/c mi and in human keratinocyte cultures, stimulated by TN α/IFN-γ.	Bee venom and melittin exhibited potent anti-atopic activities, demonstrated by th decrease of AD-lik skin lesions induce by DNCB in mice. I vitro studies using human keratinocyte stimulated by TNF α/IFN-γ showed tha bee venom and melittin inhibited increased expressio of chemokines, suc as CCL17 and CCL2 and pro-inflammato cytokines, includin IL-1β, IL-6, and IFN- by blocking NF-κB a STAT signaling pathways.

Revista ARACÊ
ISSN: 2358-2472

PubMe	Jang S, *et al.*, 2024	2 patients. Mice	Acupuncture a phytotherapy associated wi bee venom	To analyze th hypothesis th bee venom acupuncture (VA) is effective fo eczema and contact dermatitis.	Suggest that b venom and herbal medicir may be an alternative treatment for eczema and contact dermatitis.	Both patients wi HS and contac dermatitis were treated with BV BVA treatments a total of 19 and sessions. On th first day of treatment, a ski test for AVB wa performed (0.3 n of 10% diluted AVB in case 1, 0 mL of 10% dilute AVB in case 2) The BVA dose w increased to 2.4 mL (case 1) or 0 mL (case 2) on t last day of treatment. Eczema-like contact dermatit was induced usi 2,4-dinitrochloroben ne (DNCB) as previously described. The s week-old mice were exposed t 1% DNCB once weekly for 4 weeks. From th second week onwards, the mi were injected wi BVA (50 μg/kg diluted in PBS) saline solution a SWH (200 mg/k 3 times/week) w administered ora	This study reports th medical histories ar treatment processe of two cases of han eczema (HE), including contact dermatitis that wer cured by bee venor acupuncture (BVA combined with herb medicine. This stud also confirmed the effect of BVA and SWH co-treatment a mouse model of eczema-like dermatitis. Bee venc therapy combined w herbal medicine is safe and effective f HS patients.
Scopu	Cherniac govorushk 2018	People with musculoskele l and neurologica diseases associated w depression	Acupuncture with bee veno applied to the tips of acupuncture needles.	To evaluate t efficacy and safety of acupuncture with bee venom in humans.	Treatment of musculoskelet and neurologic diseases, including lumb disc disease, knee osteoarthritis rheumatoid arthritis, adhesive capsulitis, later epicondylitis, peripheral neuropathies stroke, and	Review of smal studies on the us of acupuncture with bee venom humans.	Bee venom acupuncture has shown success in treating various musculoskeletal an neurological disease but there are significant concern about safety, includi the risk of anaphylaxis.

Revista ARACÊ
ISSN: 2358-2472

					Parkinson's disease.		
Scopu	Gazeran 2021	Humans wit Parkinson's Disease	Use of venom from bees, scorpions, snakes, and lizards as therapeutic options for Parkinson's disease (PD)	To investigat the neuroprotecti role of a diverse rang of natural products, including venoms, in preclinical P models and humans.	Evaluation of t main findings recent studie that investigate venoms as therapeutic options for PD	Review of recer studies on the us of venoms in preclinical and human models f PD.	The venoms have shown neuroprotecti potential in preclinic models of PD, suggesting that the may be promising therapeutic options t slowing disease progression.
Scopu	Shin; Cho Bae, 201	Mice	Application o phospholipas A2 (PLA2) derived from b venom to trea skin lesions similar to atop dermatitis induced by 2,4 dinitrochlorobe ene (DNCB) a house dust mi extract (DFE)	To investigat the underlyin mechanisms PLA2 action atopic dermatitis.	Inhibition of epidermal thickness, seru immunoglobul E (IgE) and cytokine level macrophage a mast cell infiltration int the ear of a DF and DNCB-induced model AD.	Application of DNCB and DFE induce atopic dermatitis in mic followed by treatment with PLA2. Evaluatio of effects throug clinical and histological measurements	Treatment with PLA inhibited epiderma thickness, serum Ig and cytokine levels and macrophage ar mast cell infiltration into the ear of mice These effects were nullified in CD206 mannose receptor deficient mice exposed to DFE an DNCB.
Scopu	Kim *et al* 2021	Airway Epithelial Ce A549	Application o bee venom (1 µg/mL) to inhil IL-13-induce AKT phosphorylatio (10 ng/mL)	Investigate th effect of bee venom on IL 13-induced mucus metaplasia	Inhibition of MUC5AC production through regulation of SPDEF and FOXA2	In vitro study wit A549 cells, usin IL-13 to induce mucus metaplas and bee venom inhibit AKT phosphorylatio	Bee venom inhibite AKT phosphorylatio increased SPDEF expression, and decreased FOXA2 expression, preventi IL-13-induced increase in MUC5A expression
Scopu	Kim *et al* 2015	Human keratinocyte (HaCaT) an monocytes (THP-1)	Bee Venom Treatment to Investigate It Anti-inflammatory Properties in Propionibacter m acnes (P. acnes)-induce Skin Inflammation	To investigat the anti-inflammator properties o bee venom o P. acnes-induced skin inflammatio	Inhibition of th secretion of pr inflammatory cytokines (IFN- IL-1β, IL-8 an TNF-α) and th expression of I 8 and toll-like receptor 2 (TLR2) in HaC and THP-1 cel treated with F acnes	In vitro study usi human keratinocytes (HaCaT) and monocytes (THP 1) treated with P acnes and bee venom	Bee venom effective inhibited the secreti of IFN-γ, IL-1β, IL- and TNF-α, as well the expression of IL and TLR2 in HaCa and THP-1 cells treated with P. acne
Scopu	Lee *et al* 2021	Balb/c mice	Topical application of 5 phthalic anhydride (PA to the dorsal sl and ears to induce atopic dermatitis (AD followed by treatment wit	To investigat the anti-inflammator and anti-DA effects of be venom in a animal mode of PA-induce AD.	Significant reduction in clinical AD sco epidermal thickness, IgE level, and immune cell infiltration int skin tissues.	Topical applicati of PA to induce AD, followed by treatment with B Evaluation of th effects through clinical and histological measurements, addition to analys	Treatment with BV significantly reduce the clinical AD scor epidermal thickness IgE level, and immu cell infiltration into sl tissues. In addition VB inhibited the expression of iNOS and COX-2, as well

Revista ARACÊ
ISSN: 2358-2472

			bee venom (B three times a week for 4 weeks.			of inflammatory cytokines in the serum.	the activation of th MAPK and NF-κB signaling pathway
Scopu	Jung *et a* 2017	Mice	Topical application o phospholipas A2 (bvPLA2) derived from b venom to trea skin lesions similar to atop dermatitis induced by house dust mi extract (DFE and 2,4-dinitrochlorobe ene (DNCB)	To determin whether treatment wi bvPLA2 exacerbates DFE-induce atopic dermatitis-lik allergic inflammation in a murine model.	Significant suppression c increased symptoms of atopic dermatit including ear thickness, seru IgE concentration inflammatory cytokines, an histological changes.	Topical applicati of bvPLA2 in mic with DFE/DNCB induced atopic dermatitis. Measurement c epidermal thickness, immu cell infiltration, serum immunoglobulir and cytokines.	Treatment with bvPLA2 inhibited ma cell infiltration into th ear and significantl suppressed symptor of atopic dermatitis including ear thickness, serum Ig concentration, and inflammatory cytokines. Depletion regulatory T cells abolished the anti-atopic effects of bvPLA2, suggestin that the effects depend on the existence of Tregs
Scopu	You *et al* 2016	136 patients with atopic dermatitis	Application of emollient containing be venom and si protein or an identical vehic except for be venom, for 4 weeks	To discover t beneficial effe of an emollie containing be venom in th treatment o patients witl atopic dermatitis	Eczema Area and Severity Index (EASI) score, transepiderma water loss, an pruritus visua analogue scal (VAS) score	Double-blind, randomized, bas controlled, multicenter stud	Patients who applie emollient containin bee venom had significantly lower EASI scores and VA value compared to patients who applie emollient without be venom
Scopu	Tender e *al*., 202	Wistar Rats	Application o melittin to indu toxicity, follow by treatment w mini-αA-crystalline ge (MAC) and its modified versi (MAC-GRD)	To compare the skin permeation anti-inflammator and analges activities of th natural pepti MAC and its modified version (MA GRD).	Improvement skin permeabil and anti-inflammatory analgesic, an antioxidant activities of MAC-GRD compared to MAC and 1% hydrocortison cream.	Study of ex-vivo skin permeation using a vertical type Franz's diffusion apparat and in vivo preclinical experiments in Wistar rats.	MAC-GRD gel demonstrated great skin permeability ar superior anti-inflammatory, analgesic, and antioxidant activitie compared to MAC g and 1% hydrocortisone crea

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

Revista ARACÊ
ISSN: 2358-2472

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

Revista ARACÊ
ISSN: 2358-2472

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-

Revista ARACÊ
ISSN: 2358-2472

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.

Revista ARACÊ
ISSN: 2358-2472

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