Allergic Diseases

Chapter 2

Allergy Caused by Bee Stings

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Abstract

Bees inhabit every continent except Antarctic; thus, bee stings occur in almost all the world. Bee stings can cause symptoms ranging from mild, such as edema and skin rashes, to anaphylactic reactions and death. In this book chapter, aspects related to the epidemiology of bee stings, bee venom compounds, bee venom-induced allergy, and recommended therapy will be discussed.

Keywords: Bee venom; Bee stings; Allergy, Hypersensitivity.

1. Introduction

Hymenoptera stings may cause both local and systemic allergic reactions, and even life-threatening anaphylaxis [1,2]. Apidae family consists of *Apis mellifera* (honeybees) and Bumblebee species (bumblebees) [3,4]. Honeybees (*Apis* species) are social insects that live in well-organized communities and have a fundamental economic role, due to honey production and their role as a pollinator; however, they can cause envenomings in humans [5,6]. Most commercially important bees are derived from Europe, whilst evolutionarily they would originate from African bees [7-9]. European bees were successfully introduced to North America for pollination and honey production in 1960 [10-13].

The bee introduction in Brazil was carried out in 1839. Nevertheless, due to the extremely divergent climate of the original regions, replication was not possible [14,15]. In 1956, African bees (*Apis mellifera scutellata*) were imported to Brazil to crossbreed with European bees for commercial purposes, and the resulted hybrid species thrived in the tropical environment [14]. Accidentally, African queens scaped from the Brazilian experimental hives and initiated the Africanization of other species of honeybees in the Americas. Africanized bees are very aggressive and can attack in large groups even without being threatened [14,16,17]. So far, A. m. mellifera, A. m. ligustica, and A. m. scutellata are the bee species predominantly responsible for human envenomation's [18]. In general, the accidents are usually mild, even injecting a lot of venom. For cooperation purposes, one bee sting may inject 50 to 140 μg of venom, while wasp releases only 3 μg of venom during its sting [18-20].

Bee stings occur in several regions of the planet, and in Brazil there are more than 10,000 cases every year [16,21]. Allergic manifestations, anaphylactic shock, and systemic toxic reactions are the main clinical manifestations of bee envenomings [16,19,22,23]. In general, allergic reactions are characterized by the presence of edematous and erythematous plaques at the sting site [24]. These allergic reactions are characterized to be IgE-dependent and are classified as type I hypersensitivity, which will be detailed Section 4.

Allergic reaction induced by bee venom may progress to an anaphylactic reaction, with bronchoconstriction and anaphylactic shock [14,25]. Systemic allergic reactions can range from generalized urticarial and malaise to edema of the glottis, bronchospasm, anaphylactic shock, drop in blood pressure, collapse, loss of consciousness, urinary and fecal incontinence, and cyanosis. Systemic allergic reactions are characterized by immunological mechanisms and can lead the patient to death in a few hours, due to the release of different cytokines and multiple organ failure [2,16,25,26].

Thus, a unique bee sting can be extremely dangerous for a hypersensitive person, due to the occurrence of anaphylactic shock [27]. The chance to develop an allergic reaction and the chance of life-threatening anaphylaxis are related to many factors, including the severity of

the previous reaction, the range of bee venom allergy, baseline serum tryptase level, presence of mastocytosis, increased basophil activation, age of the victim, and underlying medical conditions [1,28-31].

In this book chapter, aspects related to the epidemiology of bee stings, bee venom compounds, bee venom-induced allergies, and recommended therapy will be discussed. On the other hand, the multiple stings with large amounts of inoculated venom trigging severe toxic envenoming will not be explored in this chapter, since it is resulted by direct action of bee toxins to specific targets and not related to allergy.

2. Epidemiology of Bee Sting Allergies

Systemic allergic reactions to Hymenoptera stings have been reported in 1-4% of the whole population [32]. The prevalence of stings from all flying Hymenoptera bees ranges from 56.6% to 85.5% in an adult life [33-36]. The probability of someone being stung by a bee at least once during their lifetime ranges from 55% to 95%, and the incidence of allergic events can varies [32,37-39]. Generally, after a bee sting, symptoms range from mild local reactions to severe systemic reactions, ranging from 1.2% to 3% of cases [40,41]. The incidence of bee stings, regardless of the species involved, diverges from country to country. Climate, ecological parameters, biodiversity, distribution of species, human population density, economic activities, types of dwellings, among others, are responsible for the differences in the distribution of cases [42]. Allergic reactions and their magnitude generally depend on the victim's sensitivity to the venom, body mass, as well as the number of the stings [14,15,22,42,43].

There have been very few studies of the epidemiology of insect sting allergy. Two studies have shown that the frequency of bee allergic reactions in children scouts varies between 0.4% to 0.8% [44,45]. Amaruddin et al. (2021) evaluated the prevalence of specific IgE (sIgE) and skin prick test (SPT) to *Apis mellifera* (bee-venom) in schoolchildren living in urban city of Makassar in Indonesia [46]. SPT reactivity against bee venom was 14.3%, while the prevalence of sIgE was 26.5%. The study shows that sensitization to bee venom in Indonesian children is quite prevalent. Indeed, in children, bee venom sensitivity is much more common than in adults, occurring in half of the children stung by bees [47]. Indeed, honeybee specific IgE was found in just 3.7% to 16% of all adults [48-51]. Other study conducted, with industrial workers, showed that the prevalence of systemic reactions to insect sting is 3.3% and, from these, only 5% of subjects were sensitized to bee venom [48]. In contrast, beekeepers are more likely to have allergic reactions, especially systemic reactions whose prevalence can reach 38% [32,39,52-57]. In Turkish beekeepers, a large local reaction occurred in 7.3% of the victims and systemic reactions were found in 37.6% of cases [58]. The highest prevalence of allergies in beekeepers means that they are a high-risk group [56]. Definitely, beekeepers are more likely to be stung by bees, besides presenting frequently contact with other antigens associated with

beekeeping, including bee venom, hive dust containing bee parts and parasites, and propolis [59]. A study conducted with beekeepers demonstrated that they can show symptoms of upper respiratory allergy and other allergies [59]. Corroborating with that, risk factors have been associated with bee venom allergy: concurrent asthma or atopic dermatitis, less than ten bee stings per year, and upper respiratory symptoms of allergy when working with hives [32,56].

In South and Central America, bee stings are considered a public health problem due to the high incidence and clinical severity of the cases. However, epidemiological data on the incidence of bee sting cases are scarce and incomplete, probably due to underreporting [2,42,43,60]. In Brazil, bees' sting is an important public health concern, although epidemiological studies at the national level are scarce [2]. Chippaux (2015), in an epidemiological study of envenomation's by terrestrial venomous animals in Brazil between 2001-2012, showed a total number of 1,192,667 envenomation's, where 66,283 (5.6%) could be attributed to bees with the highest case fatality rate (0.33%; 216 deaths) [61]. Asymptomatic and mild stings accounted for 80 to 90% of patients; moderate envenomations, 10 to 18 %; and severe envenomations, 0.8 to 1.3%. Linard et al. (2014) investigated the clinical-epidemiological characteristics of bee sting cases recorded between 2007 and 2012 in the city of Campina Grande, Paraíba state, Brazil [42]. A total of 459 bee sting cases were retrospectively analyzed. The average annual incidence was 19 cases per 100,000 inhabitants. The most frequent clinical manifestations were pain, edema, and itching, characterizing local allergic reactions. Diniz et al. (2016) describe the epidemiological features of honeybee envenomation cases in the state of Ceará, Northeastern Brazil, from 2007 to 2013 [62]. From a total of 1,307 cases were analyzed, local manifestations demonstrated to be more frequent than systemic ones. Most cases were classified as mild and progressed to cure. The high number of honeybee sting cases shows that Ceará may be an important risk area for such injuries.

The incidence of bee stings in Brazil between 2007 and 2020 and the characteristics of cases by outcomes are shown in **Figure 1** and **Table 1**, respectively. During the period, a total of 163,331 bee stings occurred, ranging allergic and toxic reactions, and 564 resulted in deaths. The highest incidence of cases are found in the Southeast regions, probably due to beekeeping activities located in the region and due to the concentration of the Center of Information and Toxicological Assistance as well [2]. The frequency of allergic reactions is not known in Brazil, however, potentially due to high local manifestations and light cases, it is possible that allergic reactions have been manifested with considerable frequency.

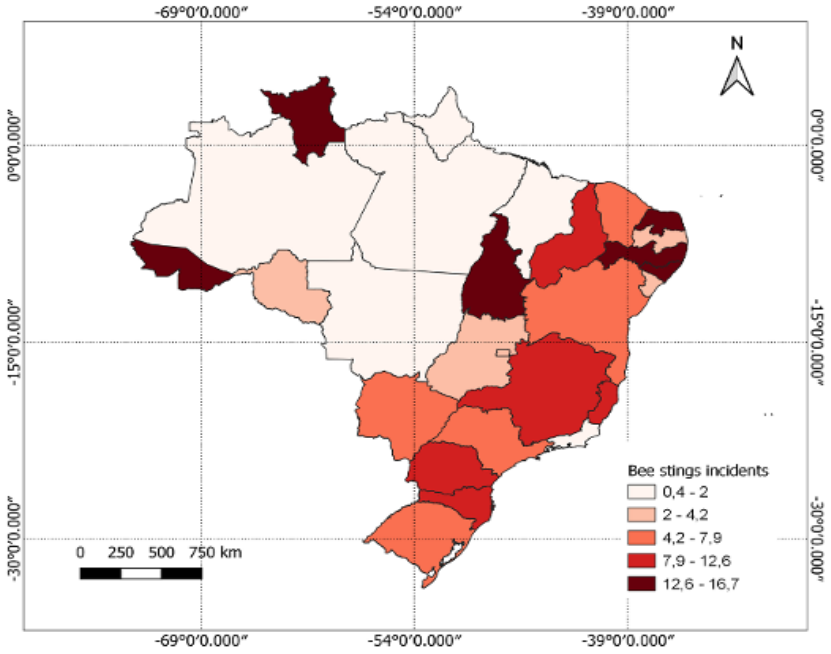

Figure 1: Distribution of incidences (per 100,000 inhabitants) of bee stings in Brazil between 2007 and 2020. The obtained data do not discriminate allergic and toxic reactions.

Table 1: Characteristics of cases by outcomes of accidents by bees in Brazil between 2007 and 2020.

	Total (n=163331)	Cure (n=162767)	Death (n=564)
Gender			
Male	104830/163321 (64.2%)	104349/162757 (64.1%)	481/564 (85.3%)
Age			
0 – 15	42315/163331 (25.9%)	42277/162767 (26.0%)	38/564 (6.7%)
16 – 45	85195/163331 (52.2%)	85074/162767 (52.3%)	121/564 (21.5%)
46 – 60	23708/163331 (14.5%)	23583/162767 (14.5%)	125/564 (22.2%)
≥ 61	12113/163331 (7.4%)	11833/162767 (7.3%)	280/564 (49.6%)
Race			
White	74693/139881 (53.4%)	74435/139371 (53.4%)	258/510 (50.6%)
Black	6055/139881 (4.3%)	6020/139371 (4.3%)	35/510 (6.9%)
Yellow	989/139881 (0.7%)	981/139371 (0.7%)	8/510 (1.6%)
Brown	57550/139881 (41.1%)	57342/139371 (41.1%)	208/510 (40.8%)
Indigenous	594/139881 (0.4%)	593/139371 (0.4%)	1/510 (0.2%)
Education			
Illiterate	1552/127114 (1.2%)	1521/126633 (1.2%)	31/481 (6.4%)
Incomplete elementar school	38080/127114 (30.0%)	37902/126633 (29.9%)	178/481 (37.0%)
Complete elementary school	18461/127114 (14.5%)	18409/126633 (14.5%)	52/481 (10.8%)
High school	24499/127114 (19.3%)	24458/126633 (19.3%)	41/481 (8.5%)
University education	4262/127114(3.4%)	4252/126633 (3.4%)	10/481 (2.1%)
Work related accident	18938/148568 (12.7%)	18794/148059 (12.7%)	144/509 (28.3%)
Occurrence Zone			
Urban	95372/154817 (61.6%)	95190/154276 (61.7%)	182/541 (33.6%)

Rural	56991/154817 (36.8%)	56643/154276 (36.7%)	348/541 (64.3%)
Periurban	2454/154817 (1.6%)	2443/154276 (1.6%)	11/541 (2.0%)
Time elapsed from sting to medical care			
0 – 1 h	67823/143269 (47.3%)	67572/142808 (47.3%)	251/461 (54.4%)
1 – 3 h	32031/143269 (22.4%)	31918/142808 (22.4%)	113/461 (24.5%)
3 – 6 h	10178/143269 (7.1%)	10139/142808 (7.1%)	39/461 (8.5%)
6 – 12 h	4991/143269 (3.5%)	4975/142808 (3.5%)	16/461 (3.5%)
12 - 24 h	11323/143269 (7.9%)	11302/142808 (7.9%)	21/461 (4.6%)
> 24 h	16923/143269 (11.8%)	16902/142808 (11.8%)	21/461 (4.6%)
Location of the bite			
Head	65117/163331 (39.9%)	64858/162767 (39.8%)	259/564 (45.9%)
Arm	17432/163331 (10.7%)	17397/162767 (10.7%)	35/564 (6.2%)
Forearm	6251/163331 (3.8%)	6245/162767 (3.8%)	6/564 (1.1%)
Hand	20634/163331 (12.6%)	20621/162767 (12.7%)	13/564 (2.3%)
Finger	5489/163331 (3.4%)	5487/162767 (3.4%)	2/564 (0.4%)
Trunk	17152/163331 (10.5%)	17005/162767 (10.4%)	147/564 (26.1%)
Thigh	2673/163331 (1.6%)	2668/162767 (1.6%)	5/564 (0.9%)
Leg	5530/163331 (3.4%)	5524/162767 (3.4%)	6/564 (1.1%)
Foot	10037/163331 (6.1%)	10026/162767 (6.2%)	11/564 (2.0%)
Toe	927/163331 (0.6%)	927/162767 (0.6%)	0/564 (0.0%)
Local manifestations	155954/160247 (97.3%)	155472/159736 (97.3%)	482/511 (94.3%)
Pain	142313/155595 (91.5%)	141917/155137 (91.5%)	396/458 (86.5%)
Edema	127733/155333 (82.2%)	127319/154859 (82.2%)	414/474 (87.3%)
Ecchymosis	6791/153441 (4.4%)	6666/152989 (4.4%)	125/452 (27.7%)
Systemic manifestations	12000/155833 (7.7%)	11694/155369 (7.5%)	306/464 (65.9%)
Neuroparalytic	1989/11639 (17.1%)	1923/11359 (16.9%)	66/280 (23.6%)
Hemorrhagic	157/11581 (1.4%)	121/11305 (1.1%)	36/276 (13.0%)
Vacancies	4014/11696 (34.3%)	3954/11420 (34.6%)	60/276 (21.7%)
Myolytic / hemolytic	590/11570 (5.1%)	538/11295 (4.8%)	52/275 (18.9%)
Kidney injury	282/11569 (2.4%)	196/11289 (1.7%)	86/280 (30.7%)
Case Classification			
Light	140705/158899 (88.5%)	140632/158352 (88.8%)	73/547 (13.3%)
Moderate	16731/158899 (10.5%)	16698/158352 (10.5%)	33/547 (6.0%)
Grave	1463/158899 (0.9%)	1022/158352 (0.6%)	441/547 (80.6%)

3. Bee Venom Components

Included in Hymenoptera order [63], bees and wasps have similar components in their venoms, such as phospholipases A2 (PLA2) and B (PLB), hyaluronidase, adrenaline and noradrenaline, dopamine, serotonin and histamine [64]. However, there are compounds unique to bee venoms, such as melittin, mast cell-degranulating peptide (MCD), and apamin [65-69].

These components are involved in bee envenomation, as well as, are capable of triggering allergic reactions from the bee venom [70].

Consisting mostly of water (> 80%), bee venom is a mixture of many other components, such as amino acids, peptides, protein, biogenic amines, phospholipids, pheromones, sugar, and volatile compounds, that are expressed by venom glands, accumulated in the venom reservoir and then released [71-73].

Some components are known to be the main allergens from bee venom, such as PLA2, hyaluronidase, acid phosphatase, melittin, Api m 5, Api m 6, icarapin, and proteases [69]. Besides these, some major royal jelly proteins (MRJP) are also considered allergens [74]. The components present on dried bee venom are summarized on **Figure 2**, and the allergens will be described below.

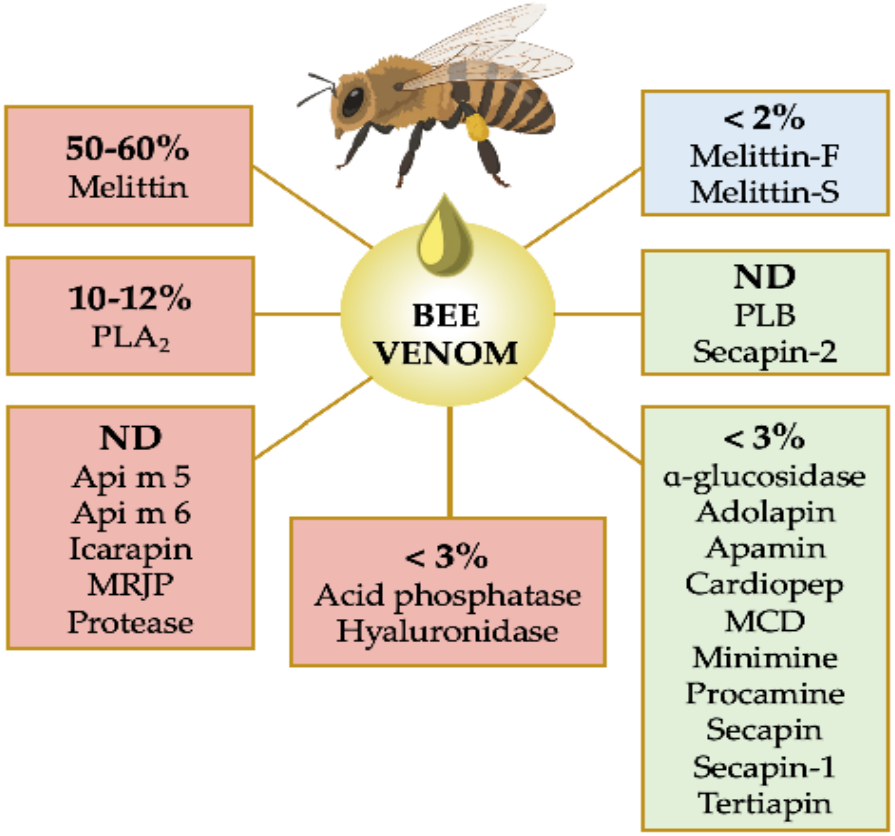

Figure 2: Protein and peptides from bee venom and their potential to induce allergies.

Components proportions in bee venom are represented in the boxes. The components able or not to induce allergy are represented by different colors: in red are the allergens; in green, the non-allergens; and in blue, those that have not yet been determined. For more details, access Pucca et al. (2019) [16]. MRJPs: Major Royal Jelly Proteins; MCD: Mast Cell-Degranulating peptide; ND: not determined; PLA2: phospholipase A2; PLB: phospholipase B. Figure created with BioRender.com.

Acid phosphatase or Api m 3 found in low proportions of bee venom [75]. This could be responsible for the histamine release, as well as, for the papules formation on the skin of individuals allergic to bee venom [76,77].

The MJRPs are family of proteins found only in Apis genus, and are major components of royal jelly, substance used as food for the larvae, and could be used as a medical product, cosmetic of food supplement [78–80]. Isoforms MRJP8 and 9 are also allergens [74].

Api m 5 is a high molecular weight (~100 kDa) that is recognized by IgE [81-83], while Api m 6 present ~7 kDa and is also recognized by IgE [84].

Api m 7 or protease, or specifically, serine protease, is a 39 kDa protein, which has as determinant allergens, its N-terminal peptide, and its serine protease-like domain and CUB (Complement subcomponents Clr/C1s, Uegf, Bmp1) domain, connected by a ligand peptide [85].

Icarapin or Api m 10 is a protein of 204 amino acids, presented in low abundance of bee venom and is instable [86,87]. It has no known functions and functional domains, and has this name, which indicates instability and rapid degradation, due to Greek mythology (Icarus), the genus of the bee (*Apis*) [87].

Hyaluronidase is known as a potent allergen from bee venom. It is also called “spreading factor”, due to its ability to cleave hyaluronic acid, major component of extracellular matrix, facilitating the toxins’ spread [69,88-90].

The second most allergenic and immunogenic component from bee venom is PLA2 or Api m1, and comprise 10-12% of bee venom [69,73]. Only PLA2 is not toxic in venom, but when complexed with melittin, they form the bee hemolytic factor [69,73]. PLA2 have also presented anti-tumor [91], bactericidal and trypanocidal activities [92,93]. In addition, PLB also composes bee venom in a minor proportion, and it is capable of cleaving phospholipid acyl chains at the sn-1 and -2 position [94,95].

Lastly, the major and most important component of bee venoms is melittin, that comprises 50-60% of venom and, although it is the most toxic component and responsible for causing a lot of pain, melittin causes less severe allergic reactions [65,96,97]. Melittin is a small peptide (almost 3 kDa) that also causes hemolysis due to its lytic action, destroying membrane phospholipids from blood cells [65,98]. There are low proportions of melittin isoforms in venom, such as melittin-F and S [99,100]. In addition, melittin has been shown to increase PLA2 activity by up to 5-fold [101] and there are other studies evidencing its anticancer, anti-inflammatory, antimicrobial, and antiviral actions [98,102-105].

4. Mechanisms of Bee Sting Allergy

The immune system plays a crucial role in maintaining health and protecting the human body against pathogens. Nevertheless, the same immune system can lead to exaggerated and inflammatory responses that result in adverse outcomes known as hypersensitivity reactions.

The so-called allergy is characterized as a type I hypersensitivity response, which is also known as an immediate reaction involving *immunoglobulin E* (IgE). This results in mast cell degranulation and release of histamine and other inflammatory mediators [106]. Like other allergies, bee stings can result in the activation of a IgE-mediated hypersensitivity reaction (**Figure 3**).

Bee stings can cause five classes of reactions including normal local reactions, large local reactions, systemic anaphylactic reactions, systemic toxic reactions, and unusual reactions. Large local and systemic anaphylactic reactions are the most frequent. Systemic toxic reactions have no relation to allergies, since it will result in a envenoming picture.

Systemic anaphylactic reactions generally are IgE mediated, and the detection of venom specific IgE antibodies are considered important in diagnosis of bee venom allergy [107]. The clinical symptoms of systemic anaphylaxis are not always characteristic; however, it can frequently trigger urticaria, airway obstruction, vomiting, nausea, diarrhea, restlessness, unconsciousness, cardiac arrhythmia, or cardiac arrest [108].

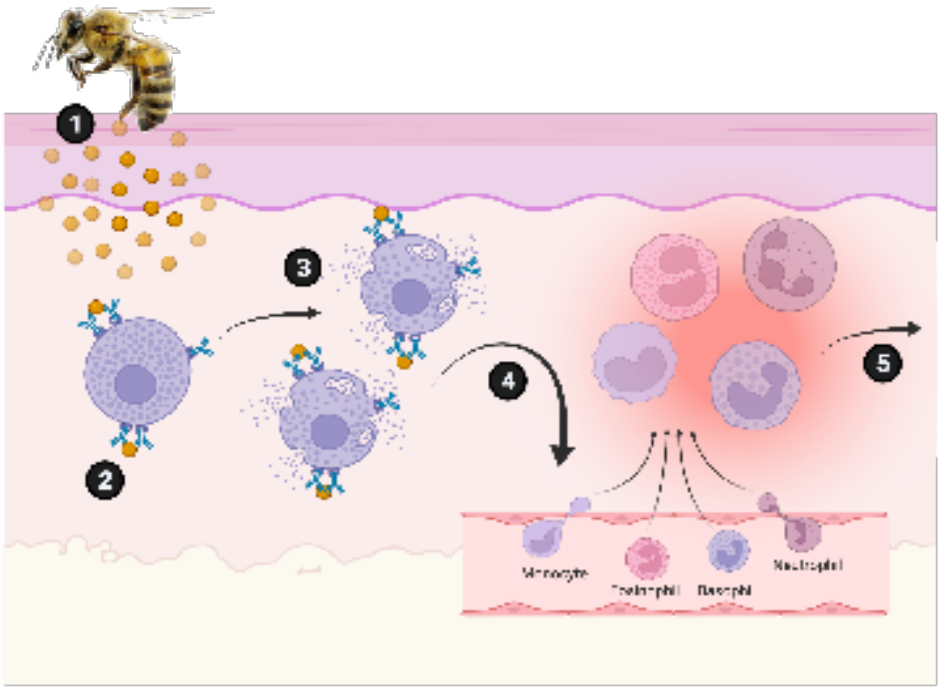

Figure 3: Mechanism of hypersensitivity I reaction induced by bee venom.
(1) A bee sting releases venom. (2) If the victim had been triggered by previous experience to recognize the bee venom, he/she will present IgE venom-specific antibodies, which prime mast cells surfaces. (3) During a further exposure to the venom, bee derived toxins stimulate mast cells to release pro-inflammatory compounds (e.g., histamine), (4) resulting in vasodilatation. (5) The biologically active compounds may case local reaction to systemic anaphylaxis. Figure created with BioRender.com.

5. Treatment for Bee Allergies

Generally, treatment for people who have been stung by bees does not require medical and hospital intervention, but if necessary, corticosteroids and antihistamines are used [22]. However, when it comes to individuals who are allergic to bee venoms, the treatment is different and more delicate.

Allergic people to bee venoms are hypersensitive and, if a single bee stings them, anaphylaxis can occur, requiring immediate medical attention, and, if this care does not occur within one hour, the person may die [109].

Treatment for allergic individuals is still somewhat controversial regarding the first action to be taken, although the intramuscular administration of adrenaline is the preferred first care [24,110-112], besides to administration of intravenous fluids for resuscitation, bronchodilators, and oxygen therapy [110,113,114]. The act of removing the stingers first is important if it is done within 60 seconds after the sting, due to the fast ejection time of the stinger venom [24,111].

Another first care is intramuscular adrenaline injection and then removal of the bee stinger [110]. This neurotransmitter acts as an agonist of α and β adrenergic receptors, acting as a bronchodilator, relieving and preventing situations of airway edema, hypotension and shock, besides to interfering with cardiac contractions, by increasing their strength and speed [112]. Furthermore, among the adrenergic effects linked to β2 receptors is the inhibition of the release of prostaglandin D2, histamine and leukotrienes, due to the increased production of cAMP by mast cells [115].

Secondary treatment for hypersensitive victims is considered optional and it is characterized by the administration of glucocorticoids, which can prevent the prolonged symptoms of anaphylaxis and airway edema, as well as the administration of H1 and H2 receptor antihistamines, which are effective for cutaneous symptoms [110,113].

Additionally, it is possible to carry out a preventive treatment for these individuals, called “Venom Immunotherapy” (VIT), capable of reducing the risk of systemic reactions after a bee sting [116]. This immunotherapy is nothing more than the administration of small amounts of bee venom for a certain period, changing your immune response from the Th2 type to the Th1 type, that is, non-allergic response [117,118].

There are two protocols to perform VIT: i) conventional VIT: consists in the venom injection once a week, for 3-4 months, until reach the maintenance dose; and ii) rush VIT: consists in the venom injection for 3-4 days, until reach the maintenance dose. After these protocols, venom injection will be administrated once a month, during 5 years [118,119].

Goldberg and Confino-Cohen (2010) observed that both protocols can work, but the maintenance dose was the main factor in inducing immunity in patients, and when increased, patients who had mild to moderate allergic systemic reactions no longer had that [118].

6. Risks of Therapies Using Bee Venom

Bee venom therapy (BVT) has been used as alternative medicine for the treatment

of several diseases (*e.g*., arthritis, pain, musculoskeletal conditions, and cancer) [120]. Nevertheless, although promising, the adverse/toxic effects of some bee venom-derived compounds need additional studies. Indeed, the immune response from a person submitted to the BVT can range from a usual skin reaction to anaphylaxis [121].

Adamic et al. (2009) showed that the incidence of systematic reactions in patients who received venom and inhaled-allergen subcutaneous immunotherapy was 13.60%, on the other hand, the prevalence of systemic reactions in patients that received VIT was 28.72% [122]. Thus, systemic reactions are not rare, being the VIT (with bee venom extract) the most prominent risk factor for systemic reactions.

Although bee venom has been conducted as alternative therapy against certain pathologies, it can cause both local (*i.e*., skin rashes, swelling and pruritus) and systemic (*i.e*., headaches, pain in some extremity and nasopharyngitis) adverse effects, suggesting that broad-spectrum clinical studies must be performed to prove the efficacy and validation of BVT [123].

7. Conclusion

Clinical manifestations after bee sting may vary from only local inflammatory reactions to allergic manifestations and anaphylactic shock, when the victim was previously sensitized. Bee venom allergic people have higher levels of bee venom specific IgE and sensitized mast cells, resulting in a quick hypersensitivity type I response. The healthcare system should be aware of the potential risk of allergic reactions in patients stung by bees, especially when the victim is a beekeeper, presenting an increased risk of severe anaphylaxis. VIT have been demonstrated efficacy to treat patients presenting allergy to bee venom, while BVT still needs additional studies to be validated. At last, an improved collection of epidemiological data related to bee stings is still required since bee stings' reports are very scarce worldwide.

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