


## Main bioactive components and therapeutic properties of bee (*Apis mellifera* L.) venom. Review



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### Abstract:

Honeybee venom (HBV) is a secretion produced by *Apis mellifera* L females and is their specialized defense mechanism for colony protection. Among the chemical components are some bioactive compounds to which various biological properties are attributed. It has been used for therapeutic purposes in a complementary or alternative way to traditional methods for various health conditions; nevertheless, the application of HBV always involves a risk for the individual due to the possibility of unfavorable effects. Currently, research work on HBV is incipient; because of this, the present work presents a review of the works related to the chemical composition, bioactive compounds, and their biological properties.

**Keywords:** Honeybees, Bioactive compounds, Venom.

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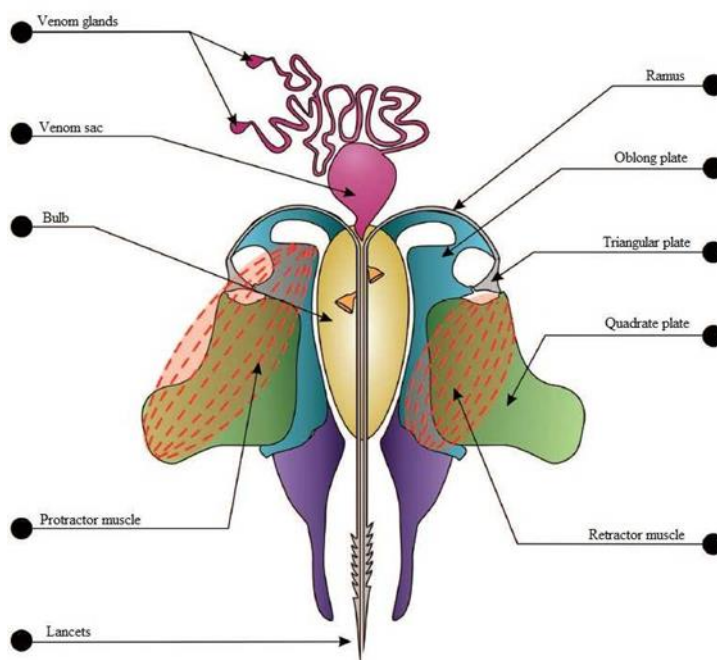
## Introduction

Beekeeping is the livestock activity aimed at raising the bees *Apis mellifera* L. In Mexico, the activity has a social, economic, and ecological impact, because there are more than 43 thousand producers in the country, many of them located in rural areas, who obtain their livelihood through the production and commercialization of honey. In 2021, 64,320 t of honey were produced in the country, which placed Mexico as the ninth largest producer worldwide; however, honey is not the only product that can be obtained from the hive<sup>(1,2)</sup>. It has been reported that up to 15 different products can be obtained from bees, including honeybee venom (HBV)<sup>(3)</sup>. HBV, also known as apitoxin, is a natural substance produced by *A. mellifera* females, which, due to its composition, has been used to treat and combat health problems; nonetheless, its use and application are not adequately regulated, and there is always a latent risk of an exacerbated allergic response on the part of the individual receiving the HBV<sup>(4)</sup>. This review describes the main bioactive components and therapeutic properties identified in HBV, such as the anti-inflammatory, antibacterial, and wound healing effects, and their application against cancer; it also describes the main adverse effects that an organism can present when coming into contact with HBV.

## Honeybee venom

The HBV is produced through two glands located in the abdomen: the venom gland and Dufour's gland, also called the acid and alkaline glands, respectively<sup>(5)</sup>. Only *A. mellifera* females (workers and queen) have the ability to produce venom and possess a stinger, which is located in the last abdominal segment and is associated with the acid and alkaline glands.

In workers, the stinger comes from a modification of the ovipositor organs<sup>(6)</sup> and consists of a dorsal stylet and two lateral lancets with the ability to slide back and forth. The lancets have at their lower end a series of spicules known as barbs, like harpoon points, which are responsible for the stinger not detaching from its aggressor when it is introduced into the skin of the enemy or aggressor, which causes a tear in the abdomen area of the bee causing the loss of this structure along with the venom sac, the muscles and nerve center, allowing the venom to flow easily (Figure 1). This loss of organs and tissues means that the worker dies when it stings, so the use of the stinger is considered a specialized and adaptive mechanism for the protection and defense of the colony against its natural predators or other insects<sup>(7,8)</sup>. The synthesis of venom in workers begins from the moment they emerge from their cells, and after an average of two weeks, the glands are completely full<sup>(9,10)</sup>.

**Figure 1:** Morphological structures that make up a worker's stinger<sup>(11)</sup>

In the queen, the stinger is smooth, so she can sting several times without causing the loss of the structure or death; in addition, at the time of emerging, she already has the venom glands completely full; this is because the queen only uses her stinger against another queen, a situation that can occur when two queens emerge at the same time or when the new queen emerges, she must destroy other royal cells in the colony<sup>(7,8,9)</sup>.

### Characteristics and composition of honeybee venom

HBV is a transparent, odorless, bitter-tasting liquid, with a pH of 4.5 to 5.5, soluble in water and insoluble in alcohol, and dries easily even at room temperature, and when in contact with air, it forms grayish-white crystals<sup>(10,11)</sup>. It is composed mainly of water (80 %) and a mixture of peptides, enzymes, biologically active amines, amino acids, carbohydrates, volatile compounds, phospholipids, pheromones, and minerals such as Ca, Mg, and P (Table 1)<sup>(12,13,14)</sup>. The concentration of the components can be influenced by factors such as the method of collection, environment, time of year, species, and age of the bees<sup>(8,12,15,17)</sup>.

**Table 1:** Percentage of the main components that make up bee venom<sup>(14)</sup>

Component	Group	% in dry matter HBV
Melittin	Peptide	50-60
Phospholipase A2	Enzyme	10-12
Complex ethers	Volatile compounds	4-8
P, Ca, Mg	Minerals	3-4
Glucose, fructose	Carbohydrates	2-4
Apamin	Peptide	1-3
Mast cell degranulating peptide	Peptide	1-3
Hyaluronidase	Enzyme	1.5-2
Secapin	Peptide	1-2
Histamine	Biological amine	0.5-2
Dopamine	Biological amine	0.1-1
Adolapin	Peptide	0.1-0.8
Noradrenaline	Biological amine	0.1-0.5

## Melittin

It is the compound with the most reported biological activities and with the highest concentration in the dry matter of HBV. It is a small and linear peptide, formed by 26 amino acids (Figure 2); it is soluble in water, amphipathic, with a weight of 2,840 Da. Melittin only induces mild allergic reactions, but it is the component that causes most of the pain associated with stinging due to its direct and indirect action on primary nociceptor cells<sup>(14,17)</sup>. It is classified as a lytic peptide due to its amphipathic nature, which allows it to bind to the surface of cell membranes, disturbing the integrity of phospholipid bilayers, creating pores that can cause lysis or necrosis of cells. The formation of pores is what allows this molecule to exhibit hemolytic, antimicrobial, antiviral, and antifungal activity; nevertheless, its non-specific cellular lytic activity poses significant risks to healthy cells<sup>(18,19)</sup>.

**Figure 2:** Amino acid composition of melittin<sup>(20)</sup>

*Gli – Ile – Gli – Ala – Val – Leu – Lis – Val – Leu – Tre – Tre – Gli – Leu – Pro – Ala – Leu – Ile – Ser – Trp – Ile – Lis – Arg – Lis – Arg – Gln – Gln – NH<sub>2</sub>*

In studies carried out with cell cultures and animal models, it has been shown that this component has anticancer activity, part of this activity is due to the fact that it inhibits the angiogenesis process, which retards tumor growth; it also alters the cell membrane, causing necrosis in the cell<sup>(14)</sup>. It has also demonstrated *in vitro* antibacterial activity against *Borrelia*

*burgdorferi*, the bacteria that cause Lyme disease<sup>(21)</sup>, and against different strains of *Staphylococcus aureus*, including methicillin-resistant strains<sup>(22)</sup>. In a study carried out with the human immunodeficiency virus (HIV), it was shown that nanoparticles prepared with a melittin solution form small pore-like attack complexes, which can injure or break the protective envelope of HIV-1, attacking a vital part of its structure<sup>(23)</sup>.

In a study carried out with mice, the effect of this peptide was observed in injuries generated in the biceps femoris muscle of the animals; the mice that received the melittin treatment had less production of proinflammatory cytokines, an increase in the expression of biomarkers of muscle regeneration, and a better locomotor activity compared to the positive control, which received diclofenac; therefore, the authors suggest that melittin could serve as part of a treatment for muscle lesions<sup>(24)</sup>.

## Phospholipase A2

It is the main immunogenic and allergenic component present in HBV; it is an enzyme with a molecular weight of 19 kDa, made up of 134 amino acids. It is the second component with the highest concentration in dry matter of HBV, and the second component in reported biological activities; it is also one of the main allergenic components of HBV, causing high allergic sensitivity<sup>(25)</sup>. Phospholipases are enzymes that hydrolyze free and membrane-associated phospholipids, converting them into fatty acids and other lipophilic substances, leading to tissue injury and cell death by lysis; it also lowers blood pressure and inhibits blood clotting<sup>(8,10)</sup>.

This enzyme induces the synthesis of prostaglandins, which promotes inflammation<sup>(26)</sup>. The injection of phospholipase A2 intraperitoneally and subcutaneously in mice has been shown to help prevent neurodegenerative diseases, such as Parkinson's disease, because it has a neuroprotective effect and contributes to regulating pathological manifestations<sup>(27,28)</sup>. It has been reported that this enzyme can cause lysis and prevent the proliferation of different cancer cell lines, such as human kidney carcinoma (A498), human breast carcinoma (T-47D), human prostate carcinoma (DU145), and human bronchial epithelial cell line (BEAS-2B), in addition to stimulating monocyte-derived dendritic cells, cells with a fundamental role in the immune response<sup>(29)</sup>. Depending on its concentration and exposure time, phospholipase has demonstrated bactericidal (at 2 h) and bacteriostatic (at 12 h) activity against *Trypanosoma brucei*, *Enterobacter cloacae*, *Escherichia coli*, and *Citrobacter freundii*<sup>(30)</sup>.

## Apamin

It is the smallest neurotoxin in HBV; it is a peptide made up of 18 amino acids (Figure 3), present only in HBV<sup>(13,14,18)</sup>. It has neurotoxic action at the central and peripheral level, with nerve cytotoxic and nociceptive effects due to its ability to cross the blood-brain barrier and because it blocks potassium-dependent Ca<sup>2+</sup> channels. In addition, it inhibits neuromuscular transmission through the activation of M2 muscarinic inhibitory receptors in motor nerve endings, an effect that could improve the control of muscle excitability in patients with myotonic diseases, such as Parkinson's disease<sup>(17,31)</sup>.

In studies carried out on animal models, this peptide has been shown to protect dopaminergic neurons<sup>(32)</sup>. Another study demonstrated its anti-inflammatory activity in gouty arthritis<sup>(33)</sup>; its antioxidant, anti-apoptotic, and anti-inflammatory activity in acute kidney injuries has also been demonstrated<sup>(34)</sup>. The results position apamin as a component of interest for research focused on the treatment of Parkinson's disease, gouty arthritis, and problems caused by acute kidney injury.

**Figure 3:** Amino acid composition of apamin<sup>(35)</sup>

*Cis – Asn – Cis – Lis – Ala – Pro – Glu – Tre – Ala – Leu – Cis – Ala – Arg – Arg – Cis – Gln – Gln – His – NH<sub>2</sub>*

## Mast cell degranulating peptide (MCD peptide)

Also known as peptide 401, it is a peptide made up of 22 amino acids (Figure 4). It possesses two antagonistic immune activities. In high amounts, it inhibits mast cell degranulation, inhibiting the release of histamine, acting as a powerful anti-inflammatory agent; however, at low concentrations, it has a powerful degranulating effect on mast cells, which causes the release of histamine, which plays an important role in the inflammatory to allergic processes; there is also release of autacoids, such as arachidonic acid derivatives, and serotonin. It is most responsible for the erythema that appears at the site of the sting. In the central nervous system, it acts as a neurotoxin with the ability to block potassium channels, and in the cardiovascular system, it acts as a hypotensive agent<sup>(17,36,37)</sup>.

**Figure 4:** Amino acid composition of mast cell degranulating peptide<sup>(38)</sup>

*Ile – Lis – Cis – Asn – Cis – Lis – Arg – His – Val – Ile – Lis – Pro – His – Ile – Cis – Arg – Lis – Ile – Cis – Gli – Lis – Asn – NH<sub>2</sub>*

## Secapin

Peptide composed of 25 amino acids (Figure 5), which exhibits antibacterial, antifungal, antifibrinolytic, and anti-elastolytic biological activity<sup>(39,40)</sup>. Its administration in mice causes a hyperalgesic and edematous response, producing inflammation and pain<sup>(41)</sup>.

**Figure 5:** Amino acid composition of secapin<sup>(42)</sup>

*Tir – Ile – Ile – Asp – Val – Pro – Pro – Arg – Cis – Pro – Pro – Gli – Ser – Lis – Fen  
– Ile – Lis – Asn – Arg – Cis – Arg – Val – Ile – Val – Pro*

## Adolapin

Peptide made up of 103 amino acids; it is the only component that has been shown to possess antinociceptive effects, in addition to a strong anti-inflammatory, antipyretic, and inhibitory activity of phospholipase A2. Its properties are due to the fact that it inhibits the synthesis of prostaglandins by inhibiting cyclooxygenase<sup>(10,17)</sup>.

## Hyaluronidase

Hyaluronidases are enzymes widely distributed in nature, normally involved in pathological activities, such as the diffusion of toxins, inflammation, allergies, etc., and physiological activities, such as fertilization, wound healing, embryogenesis, and angiogenesis. The enzyme found in bee venom belongs to the EC group 3.2.1.35. It is the major allergen present in the venom of honeybees, wasps, hornets, and scorpions, because it stimulates the systemic anaphylactic response mediated by IgE.

It is an enzyme with a molecular weight ranging from 33 to 100 kDa, made up of 349 amino acids, and is active at pH 4 to 6. It is considered a propagation factor because it hydrolyzes the hyaluronic acid of the interstitium, causes dilation and an increase in the permeability of blood vessels, increasing blood circulation, which facilitates the diffusion of the other components of HBV, causing the spread of inflammation and the entry of pathogens found at the site of the injury<sup>(8,26,43,44)</sup>.

### **Biological amines**

They are the main neurotransmitters present in HBV; they include histamine, dopamine, 5-hydroxytryptamine, adrenaline, and noradrenaline. These components have inflammatory, vasoactive properties, in addition to being associated with pain. The histamine present in the HBV has the ability to increase capillary permeability, favoring the inflammatory response, promotes smooth and skeletal muscle contraction, and is the first mediator of the inflammatory cascade in anaphylactic shock<sup>(45,46)</sup>. Catecholamines (noradrenaline and dopamine) increase cardiac output, which helps to improve the distribution of HBV<sup>(17)</sup>.

### **Other components**

The presence of carbohydrates, proteins, volatile compounds, amines, and hormones, among others, has been reported. Some authors consider the presence of carbohydrates in the HBV as contamination caused by pollen and nectar at the time of collection<sup>(15)</sup>. The presence of the major royal jelly proteins PMJR8 and PMJR9 has been detected, and in addition to the fact that they have a nutritional function, their glycosylation has the potential to cause IgE sensitization in patients hypersensitive to HBV. The presence of more than 20 volatile compounds has been identified, including isopentyl acetate and (Z)-11-eicosen-1-ol, pheromones that serve bees to warn other members of the colony of danger and stimulate stinging<sup>(16,17)</sup>.

### **Therapeutic effect**

In traditional and alternative medicine, HBV has been used for several years for various therapeutic purposes in a complementary or alternative way to conventional medical methods. Its application to reduce pain and swelling in persistent inflammatory problems, such as rheumatoid arthritis or multiple sclerosis, and its use for bursitis, tendonitis, shingles, and gout, among others, stand out<sup>(47,48)</sup>. Its use is due to its chemical composition, made up of a wide variety of pharmacologically active molecules. The techniques used for its application vary from creams, liniment, unguents, ointments, and subcutaneous injections into acupuncture points (diluted HBV), or through the direct sting of the live bee<sup>(6,27)</sup>.



### **Anti-inflammatory effect**

The best-known use of HBV is for the control of pain, edema, and inflammation in arthritis, where it acts with an antinociceptive effect. Studies carried out with animals and that used a model of induced arthritis have shown that the use of HBV reduces the presence of inflammatory mediators, the clinical signs of arthritis (localized swelling), and does not cause liver damage<sup>(49)</sup>. In another study, it was reported that the use of HBV produces an anti-inflammatory effect, in addition to presenting an effective response in the repair and regeneration of tissues in joints<sup>(50)</sup>. Kwon *et al*<sup>(51)</sup> conclude in their study that the application of the HBV at specific acupuncture points produces an analgesic effect on pain caused by arthritis significantly greater compared to the application at distant points. In an experiment conducted directly with patients in which the HBV was applied to acupuncture points over a period of 8 weeks, patients reported a decrease in joint tenderness and inflammation, and morning stiffness<sup>(52)</sup>.

The anti-inflammatory effect of HBV has also been analyzed in spinal cord injuries in animal models. In a study conducted with Wistar rats subjected to spinal cord injury, researchers reported improved locomotor performance and a decrease in injury size when the HBV was applied to specific acupuncture points<sup>(53)</sup>.

In atopic dermatitis or eczema, the use of a moisturizing emollient is one of the main treatments; in a study carried out with 136 patients who were offered an emollient containing HBV among its ingredients, a decrease in the area where eczema occurs and a decrease in pain according to the visual analog scale were reported; improvements in patients were mainly attributed to the anti-inflammatory activity of the HBV<sup>(54)</sup>.

### **Anti-cancer application**

Among the strategies used to control or cure cancer is the research of new drugs from natural sources, such as plants or toxins from animals<sup>(55)</sup>. HBV has been shown to have a potential effect against different types of cancer because it inhibits the proliferation of cancer cells through several cytotoxic mechanisms, such as the induction of apoptosis, necrosis, effects on the inhibition of growth and proliferation of malignant cells, and alterations in the cell cycle. It has also been observed that it can decrease the number of metastatic cells, most likely due to the stimulation of the immune cellular response in lymph nodes<sup>(19)</sup>.

Pancreatic cancer is one of the most aggressive and deadly types of cancer in people. In a study conducted with pancreatic cancer cell lines, HBV suppressed cell proliferation through

cell cycle arrest, promoting apoptosis and inhibiting cancer cell migration; the results suggest an antitumor effect of HBV against pancreatic cancer<sup>(56)</sup>.

Glioblastoma is one of the most common malignant brain tumors; it has a poor prognosis, with the possibility of resistance to therapy and a wide possibility of metastasis. A study conducted with cell lines evaluated the effect of HBV on the expression and activity of the matrix metalloprotein-2 because an increase in its expression and activity has been reported in many types of cancer. The results obtained showed that HBV inhibits the viability of glioblastoma cells through the induction of apoptosis, in addition to reducing the expression of metalloproteins, suggesting that it may cause an inhibition in tumor metastasis<sup>(57)</sup>.

Breast cancer is the most common malignant cancer in women around the world. For its treatment and control, *in vitro* studies have been carried out with breast cancer cell lines, where the components present in the HBV have demonstrated a cytotoxic effect on cell lines, in addition to apoptotic effects, controlling metastasis and decreasing the viability of cancer cells<sup>(58)</sup>.

### **Antibacterial effect**

Antibiotic resistance presented by the bacteria that cause infectious diseases has led to the search for new alternatives to control them. In different studies, HBV has been shown to have an antibacterial effect, positioning it as an option in research for the development of new drugs against pathogenic bacteria. In *in vitro* studies, HBV was shown to be effective against the causative agent of Lyme disease, the bacteria *Borrelia burgdorferi*<sup>(21)</sup>. A similar response was obtained when analyzing the effect of HBV against methicillin-resistant bacteria *Staphylococcus aureus*, where a synergistic effect was also observed in combination with oxacillin, an antibiotic used to control *S. aureus*<sup>(22)</sup>. Its effect against different strains of the bacteria *Salmonella enterica* and *Listeria monocytogenes* makes HBV a potential alternative for the control of foodborne pathogens<sup>(59)</sup>.

In another study, a significant effect on cell wall deformation was demonstrated in the bacteria *Escherichia coli*, *Pseudomonas putida*, and *Pseudomonas fluorescens*, and the researchers concluded that the mechanism of action of HBV against bacteria is cell wall destruction, membrane permeability change, cell content leakage, inactivation of metabolic activity, and cell death<sup>(60)</sup>.

### **Effects on wound healing**

Wound healing involves a tissue repair process involving different molecular and cellular factors, starting with an inflammatory response, re-epithelialization, and ending with a permanent scar. The anti-inflammatory, antimicrobial, analgesic, and antioxidant properties present in HBV give it great potential to aid in healing processes. In a study with Wistar rats, the authors tested the effect of 0.1 g of HBV diluted in 10 mL of saline solution on wounds made in the oral mucosa of the rodents. The researchers concluded that HBV stimulated the proliferation of epithelial cells, increasing re-epithelialization, improving wound closure, and decreasing inflammation in the injured area<sup>(61)</sup>. In another study also conducted with Wistar rats, chitosan films with HBV were used, where the healing of wounds induced in the rodents was satisfactory and rapid compared to the rats that did not receive treatment<sup>(62)</sup>.

Despite the positive responses, most authors recommend further research on the use of HBV to evaluate its efficacy *in vivo*, and safe and effective administration, before recommending its direct use.

### **Adverse effects of HBV**

It has been scientifically proven that the components present in the HBV can offer health benefits to organisms; however, there are also reports of how its use can cause unfavorable effects in individuals. Allergy to HBV is dangerous and can be deadly; depending on the number of stings the individual receives, clinical manifestations can range from mild to severe. Variables such as age, weight, diseases present in the individual and how quickly medical attention is obtained also affect the response.

The main effects observed locally at the site where the stinger injured the skin are: pain, swelling, pruritus, erythema, and urticaria<sup>(63)</sup>. The reactions can decrease and disappear after a long time of contact with HBV, a situation that occurs mainly in people who work directly with insects, such as beekeepers; nonetheless, in individuals who overreact to a bee's sting and who also do not have continuous contact with the insect, one option to prevent moderate to severe systemic reactions is venom immunotherapy. This treatment is used to improve quality of life, as opposed to having the fear of a severe reaction or premature death caused by a bee attack. Immunotherapy should always be performed by a health professional with experience in the area<sup>(64,65)</sup>.

In some cases, HBV can cause serious medical, immunological, and neurological complications, and even death. A common complication is anaphylaxis<sup>(66)</sup>. Anaphylaxis occurs when the body is hypersensitive to HBV and is not dependent on the amount of venom. It results from the release of inflammatory mediators, such as histamine, and occurs after re-exposure to the antigen, such as proteins present in HBV, which act as specific antigens and trigger early or late manifestations of hypersensitivity. Anaphylactic shock can be divided into four categories: mucocutaneous, respiratory, cardiovascular, and gastrointestinal reactions. Signs and symptoms that may occur most often in anaphylaxis caused by HBV may include skin problems such as erythema, pruritus, hives, or angioedema; the respiratory system such as laryngeal edema and bronchospasm; the cardiovascular system such as myocardial depression, hypotension; and the gastrointestinal system with nausea, vomiting, and incontinence<sup>(45,67)</sup>.

Other types of reported complications, which are not so common, are: immune thrombocytopenia<sup>(68)</sup>, lymphedema<sup>(69)</sup>, Guillain-Barré syndrome<sup>(70)</sup>, optic neuropathy<sup>(71)</sup>, pontine and thalamic infarction<sup>(72)</sup>, acute kidney injury<sup>(73)</sup>, Wolff-Parkinson-White syndrome<sup>(74)</sup>, Kounis syndrome<sup>(75)</sup>, pemphigus foliaceus<sup>(76)</sup>, to name a few. These complications are mainly due to the immunostimulatory action and the presence of multiple protein allergens with enzymatic activity and IgE inducers present in the HBV<sup>(18)</sup>.

According to Ali<sup>(6)</sup>, the LD<sub>50</sub>% of the HBV is 2.8 mg per kilogram of weight. If it is considered that a bee can inject 0.3 mg of venom, 560 bees would be needed to reach the LD<sub>50</sub>% in an adult person with an average weight of 60 kg; however, the sensitivity to the components in each organism can vary. The incidence of death due to bee stings is approximately 0.03-0.48/1'000,000 individuals per year, and several risk factors are associated, such as sex (men are three times more at risk than women), age (people over 40 yr of age are at greater risk, probably due to the greater presence of cardiovascular diseases), and the place of the body where the bee stung (the neck and head are the areas of greatest problem)<sup>(64)</sup>. Honeybees are social insects, therefore, the possibility of mass attacks occurring when they are attacked is high. The most recommended way to avoid problems is prevention, focusing mainly on minimizing exposure to attacks by avoiding places where the presence of these insects is known<sup>(8)</sup>.

Studies are currently being conducted on people to evaluate the dose and effectiveness of drugs that counteract the different effects caused by bee stings. Although the study groups have been small and tests and analyses are still ongoing, the responses to the drugs are promising<sup>(17,77)</sup>.

## Conclusions

HBV is a defense mechanism that helps bees care for and protect their colony; the components that make it up are a source of resources that can help against some pathologies; nevertheless, it is always necessary to consider that each organism may respond differently to the use of HBV and that reactions can range from moderate to lethal, so it is necessary to carry out more studies on the use of HBV and its compounds in order to make better use of them, and above all to avoid the possible adverse effects of its use on organisms. The use of HBV, either directly or indirectly, should always be done with caution and under the recommendation and support of a health professional with experience in the area.

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