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Review Article

General study of honey bee venom *Apis mellifera* : A Review

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Abstract

Apitherapy is the medicinal application of honeybee products, such as Propolis, honey, pollen, beeswax, honey and, in particular bee venom. The aims of this paper were to review bee venom and it's the composition and properties with giving an overview of the medical importance and applications; as well as describe the process of extraction and the safe storage of bee venom. Bee venom is a clear, bitter in taste, watery liquid and odor less, the bee secrete it when they feel threatened it has at least 18 pharmacologically active components including various enzymes, peptides and amines. Bee venom therapy is the therapy which utilizes the application of bee venom to treat various diseases and it has been used since ancient times in traditional medicine to treat kinds of rheumatism, rheumatoid arthritis, suppressing oedema', low back pain and as anti-inflammatory agent. Currently, special collectors gather bee venom for commercial use. as well as the several electrical collecting devices that have been created to collect it. Dried bee venom should be stored preferably frozen and it should always be kept in dark coloured bottles in the dark.

1. Introduction

The honey bee *Apis mellifera* in the animal kingdom is the main species used for pollination of crops in the world Figure 1. Bee venom is one of the most important honeybee products Figure 1 and has a prime role of defense for the bee colony used in the treatment of many human diseases [1]. However, apitherapy is the use of honey bee products for medical purposes, this include bee venom [2]. It is produced by the worker bees, its production increases during the first two weeks of the adult workers life and reaches maximum when it starts to defined the hive and activities of forage. Bee venom is a clear, bitter in taste, watery liquid and odor less has at least 18 pharmacologically active components including various enzymes, peptides and amines [3]. It has been used traditionally in human medicine for thousands of years to treat kinds of rheumatism, rheumatoid arthritis, suppressing oedema', low back pain and as anti-inflammatory agent [2].

The exact origins of apitherapy are difficult to pinpoint and can be traced back to ancient Egypt, Greece and has been practiced in China for 3-5000 years [5]. Bee venom is extracted by electric shock after one to two hours, just one gram of venom could be extracted from twenty bee colonies. Dried bee venom should always be maintained in dark, dark-colored vials and refrigerated or, better yet, frozen [6].

Now it is being practical all over the world. In the USA the history of apitherapy goes back approximately a century, it was practiced by several prominent doctors including Dr. Bodog Beck, who began treating patients in his New York City office in the late 1920s [5]. The use of honey bee venom in apitherapy has recently become a prominent research topic. We hope that by publishing this review, public will become more aware of the benefits of bee venom and how it might be used in the future.

2. Production of honey bee venom

Honeybees have a stinging device through which they can inject venom into the enemy's body Figure 2. Only female bees have stingers, it is always located at or near the end of the abdomen. While, honey bee venom manufacturing starts after two or three days and reaches its

Figure 1: European honey bee *Apis mellifera* (A) and lyophilized bee venom (B) By [4]

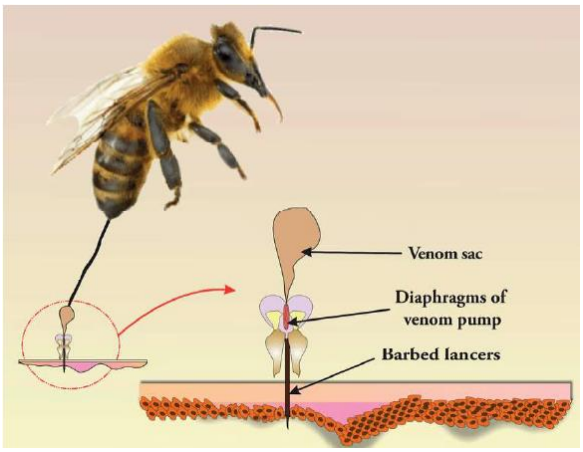

Figure 2: Venom gland of *Apis mellifera* by [11]

maximum production rate between two and three weeks of age, newly born bees do not sting (Zhao, 2015). Less venom is produced by older worker bees. There are roughly 100 µg of dried bee venom in one sting [7]. 1 g The venom of about a million bees is needed to obtain bee venom [8].

A bee typically injects only a tiny amount of the 0.15–0.3 mg of venom contained in a full venom sac when it stings Crane, [9] While, when it stings an animal with skin as tough as ours will it lose its sting - and with it the whole sting apparatus, including the venom sac, muscles and the nerve centre. The loss of such a considerable portion of its body is almost always fatal to the bee [10].

Many factors affecting honey bee venom production and its quality such as honey bee race, age of bees, colony strength, season of collection, feeding supply, its defense behavior and method of collection [12].

Honeybee venom is produced by two glands associated with the sting apparatus of worker bees. Its production increases-during the first two weeks. of the adult workers life and reaches maximum when the worker bee becomes involved in hive defense and foraging activities. The queen bee's production of venom is highest on emergence. While, drones do not have [1].

3. The Composition of honey Bee Venom

Numerous research have been conducted to determine the structure of bee venom Figure 4 and Table 1. It has been noted that the venom composition of the various bee races varies rather little [13]. found that the venom of Apis cerana is twice as poisonous as that of A. mellifera.

88% of the venom from honeybees is water. It has been reported that bee venom contains smaller quantities of low molecular compounds are different in nature: at least 18 pharmacologically active substances are present, including different enzymes such as histamine, peptides, formic acid hydrochloride, phosphoric acid, acetate, sulfur, calcium, magnesium, biologically active amines (e.g.,histamine and epinephrine) and nonpeptide components (including lipids, carbohydrates and free amino acids [6, 14, 15] mentioned that bee venom is a complex mixture of enzymes, peptides, and amines, includes melittin Figure 5. phospholipase A2, and apamin, as well as other constituents such as hyaluronidase, mast cell degranulating peptide, and secapin.

İzol, et al. [3] states that the odorless, colorless, and bitter nature of bee venom might vary depending on the bee race, plant flora, and time of collection. It is composed of 88% water, 12% polypeptides, bioactive amino acids, peptides, enzymes, carbohydrates, and minerals. Phospholipase A, hyaluronidase, phosphatase, mast cell degranulation peptide, pamin, cardiopeptin, tertiapin, norepinephrine, dopamine, adolapin, glucose, fructose, Mg, Ca, and P are among the ingredients found in this mixture.

Bee venom have some physiologically active amines, such as catecholamines like histamine which is considered one of the major components in the inflammatory response by increasing the permeability of capillaries. In a similar manner, the catecholamines dopamine and nor-adrenaline increase heartbeat, thereby enhancing venom circulation and thus, its distribution. However, like histamine, the effects of these two catecholamines are largely overshadowed by those of other components of venom. Serotonin can act as an irritant and can contribute to the pain caused by the venom [16].

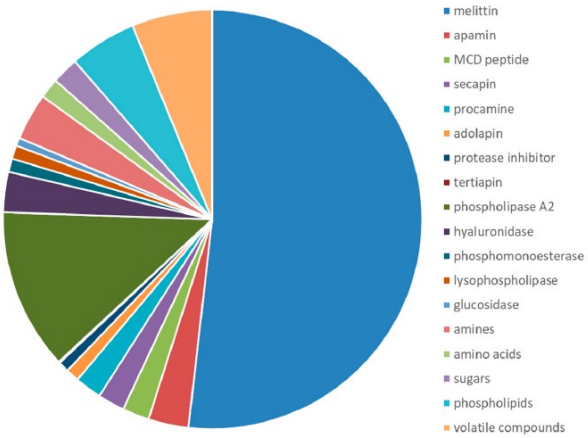

Figure 3: Composition of dry honey bee venom by [4]

Class of Molecules	Components	% of Dry BV
Enzymes	Phospolipase A_2	10–12
	Hyaluronidase	1–3
	Acid phosphomonoesterase	1
	Lysophopholipase	1
	α-glucosidase	0.6
Proteins and peptides	Melittin	40–50
	Apamin	1–3
	Mast cell degranulating peptide	1–2
	Secapin	0.5–2
	Procamine	1–2
	Adolapin	1.0
	Protease inhibitor	0.8
	Tertiapin	0.1
	Other small peptides (<5 amino acids)	13–15
Physiologically active amines	Histamine	0.5–2.0
	Dopamine	0.2–1.0
	Noradrenalin	0.1–0.7
Amino acids	Aminobutyric acid	0.5
	α-amino acids	1
Sugars	Glucose and fructose	2
Phospholipids		5
Volatile compounds		4–8

Figure 4: Composition of dry bee venom expressed as type of molecule, components, and weight percentages According to [4]

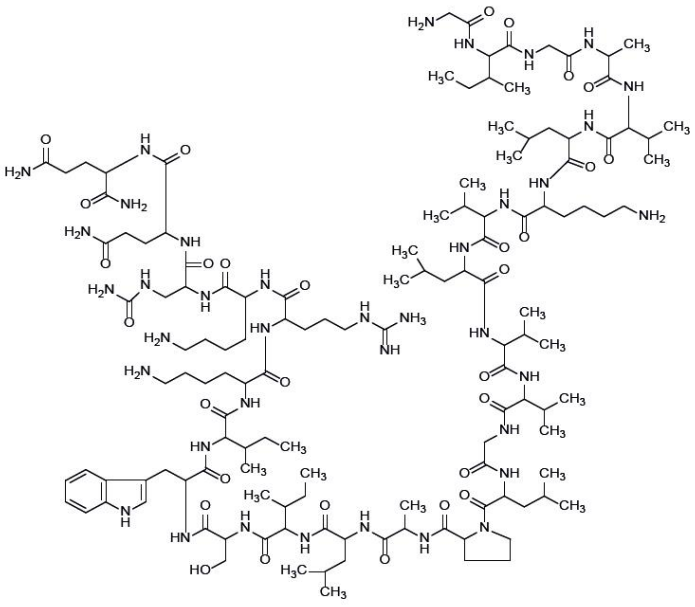

Figure 5: Chemical structure of melittin by [3]

Figure 6: Bee venom collector devices

Figure 7: Bee venom collected using a glass surface According [3]

4. Extraction of honey bee venom

When a bee stings a creature, the bee's sting remains embedded in that creature's skin. This causes a portion of the bee's nerve center, muscles, and intestines to tear at the same moment. The bee dies since most of its body has been lost [17]. The using this procedure to extract bee venom kills bees. Currently, special collectors gather bee venom for commercial use. Devices and publications are described by many researchers [3, 18–20]. Additionally, they covered the process of venom collection and gave a brief description of the properties to the honey bee venom of Apis mellifera, as well as the several electrical collecting devices that have been created to collect it Figure 6.

The most popular technique for gathering bee venom involves using a glass surface and very small wires that are powered by electricity which is called the collecting frame Figure 7 and 8 which can be placed inside or outside at the hive's entrance, is one of the device's main components.

This approach stimulates and disturbs the bees, causing them to release their venom on the glass for a predetermined amount of time when a current is supplied. As a result, the bees retain their poisonous stings [7, 21]. A honey bee venom obtained from an electric shock device unit will drying on glass plate, the whole bee venom is scratch with a sharp knife and quickly packe in opaque glass vials and kept at – 5°C till use [22]. Today, bee venom collector devices are sold by many famous companies.

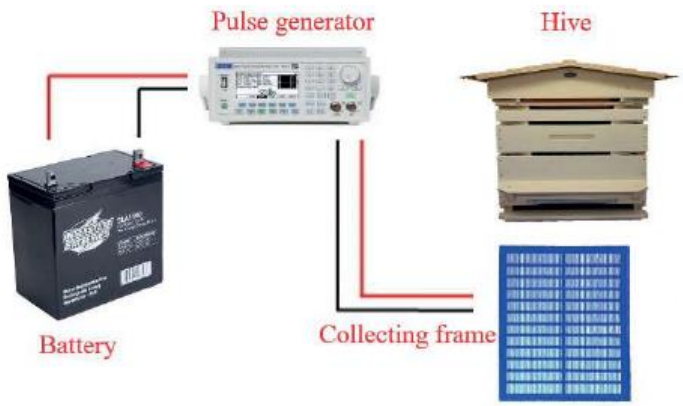

Figure 8: The collecting frame According [11]

Figure 9: Bee venom collecting and the impact of bee venom and its components as antimicrobial agents According [11]

Figure 10: Types of bee venom Product Packaging

5. Therapeutic Values

The ancient origins of bee venom treatment for apitherapy can be traced back to ancient China, India, Egypt, Babylon and Greece [7] and has been practiced in China for 3-5000 years [5]. Use of honey bee venom can be also traced back thousands of years and healing properties are included in many religious texts [23].

Now it is being practical all over the world. In the USA the history of apitherapy goes back about 100 years, it was practiced by several prominent doctors including Dr. Bodog Beck, who started treating people in his New York City office in the late 1920's. Dr. Beck's book "Bee Venom Therapy" has been classic for 60 years. The last surviving student of Dr. Beck is Middlebury, Vermont beekeeper named Charles Marz, who was known by the many as the "King of bee venom therapy". He had been practicing apithirapy for over 60 years with remarkable results, and most of his experience had been with treating arthritis, but his success was with multiple sclerosis [5]. Because of two compounds found in bee venom that have been identified and isolated phospholipase A2 (PLA2) and melittin. Despite the fact that melittin and PLA2 are the two main ingredients in *Apis mellifera* venom and that numerous research have documented their antitumoral effects [24] Figure 9.

Many inflammatory disorders, including arthritis, bursitis, tendinitis, keloids, Herpes zoster, joint disease, rheumatoid arthritis, Lyme disease, osteoarthritis, and multiple sclerosis, were treated with bee venom primarily because of its anticoagulant and anti-inflammatory properties Lubke and [25, 26] and rheumatoid arthritis [27].

Furthermore, this intricate blend of natural ingredients has been discovered to possess an array of medicinal attributes, such as anti-inflammatory, anti-apoptotic, and analgesic actions [28].

Despite this, because of its medicinal and antiviral and antimicrobial properties thus can be used as complementary antibacterial agents [29]. Bee venom has been proposed as a possible COVID-19 treatment [30]. It has also been noted that bee venom and its constituent parts have the ability to treat a variety of illnesses and can be used as a drug delivery system [31].

İzol, et al. [3] states that Antidiabetic, anticancer, antibacterial, antiviral, antioxidant, anti-inflammatory, antimutagenic, anti-arthritis, radioprotective, and neuroprotective properties are all present in bee venom. Its benefits include radiation protection, nervous system regulation, stimulation of smooth muscle, improvement of blood circulation, and wound healing. Pain in the skeleton, muscles, and nervous system is lessened by acupuncture treatments containing bee venom. However, It has been used in clinical settings to treat a range of disorders lead to adverse reactions, such as skin reactions [32].

6. Storage

Dried bee venom should always be kept in dark, opaque vials and refrigerated, or better yet, frozen. Dried bee venom should not be refrigerated for longer than a few weeks, but it can be frozen for several months. Both diluted and liquid venom can be kept in well-scaled, dark glass containers for comparable lengths of time Figure 10, [33].

The venom is stored in tightly sealed containers in a freezer at -20°C. It can be stored in this manner for at least five years, retaining its

healing properties. Dates, locations of hives, and even weather conditions and other factors that may be of interest should be recorded. Some companies recommend the following: storage conditions for bee venom. Short-term storage: 3 weeks at 25-30°C; medium-term storage: 3 months at 4°C; long-term storage: up to 5 years at -20°C [11].

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