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Studies on Bee Venom and Its Medical Uses

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ABSTRACT

Use of honey and other bee products in human treatments traced back thousands of years and healing properties are included in many religious texts including the Veda, Bible and Quran. Apitherapy is the use of honey bee products for medical purposes, this include bee venom, raw honey, royal jelly, pollen, propolis, and beeswax. Whereas bee venom therapy is the use of live bee stings (or injectable venom) to treat various diseases such as arthritis, rheumatoid arthritis, multiple sclerosis (MS), lupus, sciatica, low back pain, and tennis elbow to name a few. It refers to any use of venom to assist the body in healing itself. Bee venom contains at least 18 pharmacologically active components including various enzymes, peptides and amines. Sulfur is believed to be the main element in inducing the release of cortisol from the adrenal glands and in protecting the body from infections. Contact with bee venom produces a complex cascade of reactions in the human body. The bee venom is safe for human treatments, the median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight, i.e. a person weighing 60 kg has a 50% chance of surviving injections totaling 168 mg of bee venom. Assuming each bee injects all its venom and no stings are quickly removed at a maximum of 0.3 mg venom per sting, 560 stings could well be lethal for such a person. For a child weighing 10 kg, as little as 93.33 stings could be fatal. However, most human deaths result from one or few bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth. As compare with other human diseases, accidents and other unusual cases, the bee venom is very safe for human treatments.

Keywords: honey bees, apitherapy, bee venom, bee sting, chemical composition, physical properties, medical uses.

1 INTRODUCTION

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 (Rose, 1994). Use of honey and other bee products can be also traced back thousands of years and healing properties are included in many religious texts including the Veda, Bible and Quran [5], [6]. 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 (MS) [7].

Among the many species of insects, only very few have the capability of defending themselves with a sting and venom injection during stinging. All insects that can sting are members of the order Hymenoptera, which includes ants, wasps and bees. Since the sting is believed to have evolved from the egg-laying apparatus of the ancestral, hymenopteran species, only females can sting. The sting is always at or near the abdominal end, rather than the head. Therefore the pain inflicted by a honeybee, defending its colony, is not caused by a bite, as is frequently said, but by a sting [8]. The larger drone bees, the males, do not have stingers. The female worker bees are the only ones that can sting, and their stinger is a modified ovipositor. The queen bee has a smooth stinger and can, if need be, sting skin-bearing creatures multiple times, but the queen does not leave the hive under normal conditions. Her sting is not for defense of the hive; she only uses it for dispatching rival queens, ideally before they can finish pupating [8].

Bee venom (BV) therapy which utilizes the application of bee venom to treat various diseases has been used since ancient times in traditional medicine [1], [2], [3], [4], [92], [101], [133]. Honey bee venom as a well-known pharmacologically active product of the hive. It is synthesized by the venom glands associated with the sting apparatus of worker and queens, stored in the venom reservoir, and injected through the sting apparatus during the stinging process [9], Its production increases during the first two weeks of the adult worker's life and reaches a maximum when the worker bee becomes involved in hive defense and foraging. It diminishes as the bee gets older [8]. A mature defender or forager contains about 100-150 µg of venom, and it inject 0.15 – 0.30 mg of venom via its stinger [10], a honeybee can inject 0.1 mg of venom via its stinger. The queen bee's production of venom is highest on emergence, probably because it must be prepared for immediate battles with other queens [8]; the young queen contains about 700 µg [11].

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However, BV administration was reported to stimulate the function of immune system [12] and to affect the release of cortisol production which is known as natural anti-inflammatory agent [13]. Melittin which is the major component of BV was found to suppress inflammation by inhibiting phospholipase (PLA) enzymatic activity [14]. This enzyme was abundantly released in severe inflammatory disorders and actively found to cause tissue and organ degradation which will lead to the loss of their functions [15]. Furthermore, melittin was also found to block the production of neutrophil superoxide [16].

A large number of studies have been carried out on the composition of honeybee venom. Much of the basic identification of compounds, their isolation and the study of their pharmacological effects of bee venom was done in the 1950's and 1960's. There are some comprehensive summaries in [17] which cover the morphology of the venom apparatus, the collection of venom, the pharmacological effects of bee venom and allergies to the Hymenoptera venom of bees, wasps and ants. [11] presents a comprehensive account of allergies to honeybee and other Hymenoptera venoms. [18], [19], [20], [21] give a very good overview of its composition, effects, harvesting and use.

2 PHYSICAL CHARACTERISTICES OF VENOM

Honeybee venom is a transparent liquid dries up easily even at room temperature, odourless, ornamental pungent smell, a bitter taste, hydrolytic blend of proteins with basic pH (4.5 to 5.5) that is used by bees for defense [8], [9]. When coming into contact with mucous membranes or eyes, it causes considerable burning and irritation. Bee venom is soluble in water and insoluble in alcohol and ammonium sulfate. When it comes in contact with air it forms grayish-white crystals. Dried venom takes on a light yellow colour and some commercial preparations are brown, thought to be due to oxidation of some of the venom proteins. Bee venom contains a number of very volatile compounds which are easily lost during collection, it is considered a rich source of enzymes, peptides and biogenic amines, it is specific weight 1.1331 [22], [8].

3 THE COMPOSITION OF BEE VENOM

The venoms of most stinging insects including honey bees consisted of enzymes, protein, peptides, and a verity of smaller molecules (Table 1). The pharmacological and biochemical activities of the various stinging insect venoms remarkably convergent. Most venoms induce immediate pain, contain phosphlipases, hyaluronidase, and other enzymatic activities, and are capable of destroying red blood cells [22]. Most hymenopterous venoms also contain low molecular weight peptides that are highly basic and have isoelectric points ranging from pH 9-12 [23], [24], [25], [26], [27], [28], [29], [30], [31].

TABLE 1

Biochemical composition of venom of insects that frequently sting humans. a (as cited by [42]).

Class of molecules		Honey bees	Yellow jacket	Paper wasps	Hornets	Fire ants	Harvester ants	Bull ants	Bumble bees
Enzymes	Phospholipase A2	10-12%	0	0	0	+	+b	+b	+b
	A1	0	+	+	+				
	B	1%	+	+	+	+	+	0	+
	Hyaluronidase	1-2%	+	+	+	+/-	+	+	+
	Acid Phosphates	1%	0	0		+	+		+
	Alkaline Phosphates	+	0	0			+		
	Lipase	0	+	+			+		
	Esterase	+	+	+			+		
	Protease	0	0	0	0?	0	0		
Peptides	Melittin	40-50%	0	0	0		0		0
	Apamine	3%	(0)	(0)	(0)				
	(MCD)-Peptide	2%	(0)	(0)	(0)				
	Secapin	5%							
	Tertiapin	1%							
	Bombolitins	0							0
	Kinins	0	+	+	+		+		
	Mastoparans	0	+	+	+				
	Chemotactic Peptides	0	+		+				
	Antigen 5 Vespid	0	+	+	+				
	neurotoxins	0	+		+				
	Barbatolysin	0	0	0	0		+		
Small molecules	Histamine	0.7-1.6%	+	+	+		+	+	
	Dopamine	0.1-1%	+	+	+				
	Norepinephrine	0.1-0.2%	+	0			+		
	Acetylcholine	0	0	0	+			0	+
	Putescine	0							+
	Serotonin	0	+	+	+		0	0	
	Tyramine	0	+	+	+				
	Leukotrienes	0.003%	+	+					
	Alkaloids	0	0	0	0	95%	0		

[a] Data from: [17], [110], [111], [22],[112], [113],[37], [38], [115], [36], [116]; [b] Specificity of A1, or A2 unknown.

In contrast to pharmacological similarities of insect venoms, their biochemical structure differ remarkably among the varies taxa. The phospholipases derived from honey bees, yellow jackets, and fire ants have very different molecular weights: 16,000 for bees [32], 30,000 to 37,000 for yellow jackets [33], [34], [35], [36], and 28.000 in the form of tow roughly equal subunits for fire ants [37]. their specific activities are also strikingly different as indicated by the assignments of A2, A1, or B activity (Table 1). This activities refer to the side of hydrolysis of the phospholipids and how many sides can be hydrolyzed by the enzyme (designations for the "activity of the ants is not known and can be either A1 or A2). The amino acid compositions and sequences of the phospholipases are also different as determined by direct analysis [32], [38], [37] and lack of cross-reactivity by antibodies [39], [40], [41]. The venom of honey bees, yellow jacket, paper wasps, true hornets, and harvester ants all contain small, highly basic pain-inducing peptides. These algogenic peptides exhibit almost no structure similarities among the venoms of the different

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insects families. The honey bee peptide, melittin, contains 26 amino acids, seven which form a very hydrophilic end of the molecule and 19 which form a highly hydrophobic end.

As cited by [42], the allergens in bee, wasp, and ant venoms are all proteins (Table 2). These proteins are not generally believed to cause immediate sting pain (melittin, a minor allergen is an exception [43]), but cause, or enhance, toxicity, and all are capable of inducing hypersensitive reactions in some individuals. An evident feature in Table (2) as that all of these allergens except hyaluronidase and possible acid phosphatase are restricted to the members of only one specific family of stinging insects. Modern biochemical analysis has been employed to identify the components in BV. As a result, there are at least 18 pharmacologically active components have been described, including various enzymes, a variety of peptides and amines (i.e melittin, apamin, adolapin and mast-cell-degranulating (MCD) peptide), enzymes (i.e., phospholipase [PL] A2, hyaluronidase) and biologically active amines (i.e., histamine and epinephrine). Besides that, BV also contains nonpeptide components such as lipids, carbohydrates and free amino acids. These BV components were reported to have a wide variety of pharmaceutical properties [44]. The major components of bee venom as summarized from [19], [45], as cited by [8] are lists in (Table 3). The bee venom contains 88% water. The glucose, fructose and phospholipid contents of venom are similar to those in bee's blood [18]. [46] stated that the main component of bee venom responsible for pain in vertebrates is the toxin melittin; histamine and other biogenic amines may also contribute to pain and itching. They also found the melittin comprising 52% of venom peptides. The melittin is a strong anti-inflammatory agent and induces the production of cortisol in the body. Apamin increases cortisol production in the adrenal gland. Apamin is a mild neurotoxin. Adolapin, comprising 2-5% of the peptides, acts as an anti-inflammatory and analgesic because it blocks cyclooxygenase. Phospholipase A2 comprises 10-12% of peptides and it is the most destructive component of apitoxin. It is an enzyme which degrades the phospholipids which cellular membranes are made of. It also causes decreased blood pressure and inhibits blood coagulation. Phospholipase A2 activates arachidonic acid which is metabolized in the cyclooxygenase-cycle to form prostaglandins. Prostaglandins regulate the body's inflammatory response. The toxin from wasps contains phospholipase A1. Hyaluronidase comprising 1-3% of peptides dilates the capillaries causing the spread of inflammation. Histamine comprising 0.5-2% and is involved in the allergic response. Dopamine and noradrenaline which comprise 1-2% increase pulse rate. Protease-inhibitors comprise 2% and act as anti-inflammatory agents and stop bleeding.

Venom from other Apis species is similar, but even the venoms from the various races within each species are slightly different from each other. The toxicity of *Apis cerana* venom has been reported to be twice as high as that of *A. mellifera* [47].

TABLE 2

Known allergens in insect venomsa, as cited by [42].

Allergen	Percent of Venom				Allergenic importance
	Mol.Wt	Honey bee	Vespid wasps	Fire ants	
Phospholipase A2	15,800	10-12%	-	-	major
Phospholipase A1B	31-37,000	-	10-25	-	major
Phospholipase A1B	28,200	-	-	10-12c	major
Hyaluronidase	40-46,000b	1-2	1.5-5	+/-	Maj/moder
Acid Phosphates	98,000d	1	-	<1	Mod/mod
Antigen 5	22-25,000	-	15-40	-	major
Antigen C	102,000	<1	-	-	moderate
V mac 1	97,000	-	1	-	moderate
V mac 3	39,000	-	<1	-	major
Solenopsis I	35,000	-	-	5-1c	major
Solenopsis III	26,000	-	-	3c	major
Solenopsis IV	14,000	-	-	1-1.5c	major
Melittin	2,800	40-60	-	-	major

[a] Data from: [117], [37], [33], [118], [119], [37], [120], [121], [26], [40], [122], [38], [36]; [b] 40,000 for honey bee, 46,000 for yellow jacket ; [c] percent of venom protein; [d] for honey bee.

TABLE 3

Composition of venom from honeybee worker, as cited by [8].

Class of molecules	Component	% of dry venom[a]	% of dry venom[b]
Enzymes	Phospholipase A2	10-12	10-12
	Hyaluronidase	1-3	1.5-2.0
	Acid Phosphomonoesterase		1.0
	Lysophospholipase		1.0
	□ -glucosidase		0.6
Other proteins and peptides	Melittin	50	40 – 50
	Apamine	1-3	3
	Mast Cell Degranulating Peptide (MCD)	1-2	2
	Secapin	0.5-2.0	0.5
	Procamine	1-2	1.4
	Adolapin		1.0
	Protease inhibitor		0.8
	Tertiapinc	0.1	0.1
	Small peptides (with less than 5 amino acids)	13-15	
Physiologically active amines	Histamine	0.5-2.0	0.6 -1.6
	Dopamine	0.2 – 1.0	0.13 -1.0
	Noradrenaline	0.1 – 0.5	0.1 – 0.7
Amino Acids	□ -aminobutyric acid	0.5	0.4
	□ -amino acids	1	
Sugars	Glucose & fructose	2	
Phospholipids		5	
Volatile compounds		4 - 8	

[a] [19], [b] [45], [c] This peptide may not be present in all venom samples.

4 HONEY BEE VENOM COLLECTION AND ADULT WORKER BEE COLLECTION

4.1 Venom Collection

Early collection methods of bee venom were required

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surgical removal of the venom gland or squeezing each individual bee until a droplet could be collected from the tip of the sting [8], [9]. Since the early 1960's, extraction by the electro-shock method has been continuously improved and is now standard procedure [48], [49], [50]. Different extraction or collection methods result in different compositions of the final products venom collected under water to avoid evaporation of very volatile compounds seems to yield the most potent venom [51]. Venom collected from surgically removed venom sacs showed different protein contents from that collected with the electroshock method [52]. [53] used a cooling system with the standard electro-shock collecting apparatus in order to preserve more of the volatile compounds. This technology had followed various electrical methods involving collecting venom from individual or a limited numbers of bees [54], [132], [55] and, for the first time, allowed the collection of a gram of venom from about 20 colonies in a period of an hour or two [9]. Although similar electrical methods work to an extent with other stinging insects [56], [57], this method appears to be viable method mainly for honey bees [9].The standard electro-shock method cannot be recommended for venom collection from Africanized honeybees or the more defensive races [8]. Colony arousal can become so overwhelming that bees start killing each other and alert other colonies or attack the beekeeper and bystanders. The mass reaction of Africanized honeybees may also result in contamination of the collected venom. Nevertheless, venom is collected by this method in Brazil and Argentina, with only minor modifications. Even European colonies remain disturbed for up to a week after collection and it is said by [58] that colonies from which venom has been collected every three days produce 14% less honey, meanwhile, [50] found no such evidence for reduced productivity, however. [59] found that when using electro-shock treatment, the most efficient collection cycle was three 15-minute stimulations at intervals of three days, repeated after 2 - 3 weeks. As cited by [8] an Argentinean beekeeper found that by modifying the electric stimulus, his collection efficiency greatly increased and the bees remained disturbed for less time.

As cited by [18] the various trap designs stimulate bees by applying a mild electric shock through wires above the collecting tray. The most widely-used designs are modifications of the one first presented by [48]. A review by [60] discusses further developments. The trays are placed either between the bottom board and brood chamber at the hive entrance or in a special box between supers and the hive cover, [132].

As cited by [8] it is unlikely that a bee will eject all the contents of its venom sac, even after repeated stinging. Therefore, typically, only 0.5 to 1.0 jil (0.2 j£l - [8] of venom can be collected per bee, with an average of ten stings per bee [55]. This results in less than 0.1 ijg (0.11 jig – [18] of dry venom per bee. Consequently, at least 1 million stings are required to make one gram of dry bee venom. [19] report that 1 g of venom can be collected from twenty hives over a two hour period. Exact production figure are unavailable, the main venom producer in the USA had produced about 3000 grams of venom over 30 years [60].

4.2 Adult worker bee collection

Instead of collecting bee venom, adult bees may be used to sting the patient directly. This is the way to apply the venom in its freshest, most complete and cheapest form [8]. To collect the bees, a small hole is made in the brood chamber, super or inner cover. To avoid colony disturbance, the hole is opened and a collecting jar placed over it until a sufficient number of bees have come out. Small groups (10-100) of workers can be maintained at home for up to 2 weeks. They should be kept in the dark, in a small box (with one side made of fly-screen) [7], [8] or in a plastic or glass jar and with access to sugar syrup or bee honey (crystallized honey is best) every 3-5 days and pollen paste, and the bees also need water [7], the box or the jar should supply with a piece of wax or some wood sticks for bees to hang on. Care needs to be taken to keep ants away. Alternatively, bees can be collected from frames or from the hive entrance immediately by scraping the bees into the jar or the box or by a suction device or by the hand if the number of bees needed is small.

5 THE ALLERGIC FOR HONEY BEE VENOM

A bee sting is strictly a sting from a bee (honey bee, bumblebee, sweat bee, etc.). In the vernacular it can mean a sting of a bee, wasp, hornet, or yellow jacket. The stings of most of these species can be quite painful, and are therefore an object of dread for many people [42]. The bee stings differ from insect bites (horse-fly and ants), and the venom or toxin of stinging insects is quite different. Therefore, the body's reaction to a bee sting may differ significantly from one species to another. The most aggressive stinging insects are wasps (Family: Vespidae; Order: Hymenoptera) including bald-faced hornets and other yellow jackets but not hornets in general (e.g., the European hornet is gentle) [42]. All of these insects aggressively defend their nests. In people who are allergic to bee stings, a sting may trigger a dangerous anaphylactic reaction that is potentially deadly.

5.1 Allergic Reactions to Insect Stings

As cited by [42] allergy is a general term that descriers a verity of human symptoms and reactions to diversity of materials including pollen, animal dander, foods, drugs, dust mites (house dust), stinging insects and others. Stinging insect allergy refers to sting-induce systemic reactions of the body that occur at body locations distant from the sting site. Allergic reactions do not include immediate pain caused by the sting itself or to the burning, redness, itching and swelling that might occur around the sting site. Such reactions including very large local swelling are referred to as "local reactions" [8]. [61] stated that most stings cause localized swelling, redness, and acute pain that may throb or burn. This is reaction to the insects venom. Whoever, some people are highly allergic to insect venom, and if they are stung, a very severe reaction can occur. People who are highly allergic to insect stings can experience anaphylactic shock, which can lead to unconsciousness and, in extreme

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circumstances, death. Anaphylactic shock can cause symptoms such as bluish skin, coughing, difficulty breathing, dizziness, hives, nausea, severely swollen eyes, lips or tongue, stomach cramps, and wheezing.

As cited by [8] although, bee venom is safe for human treatment; it should only be used under the supervision of a qualified health care professional. Most experts recommend having an emergency sting kit available in case of allergic reaction. This kit should include a syringe and a dose of epinephrine and antihistamine tablets. The kit can get by prescription from the doctor, be sure you read the directions on the package before you get your test sting. It is also advisable that a test sting be performed before undergoing a treatment [7]. Those who are sensitive to the test sting can be de-sensitized to bee venom in order to undergo apitherapy. It is estimated that 1% of the population is allergic to bee stings. Only a small percentage of those allergic to a honeybee sting will suffer anaphylactic shock [7]. A severe reaction just after a few stings is rare, but the danger grows with the number of stings. A person who is having a severe reaction to a bee sting may develop hives on the skin and swelling around the eyes, lips, throat, and tongue. The person may vomit, slur words, show signs of mental confusion and even struggle to breathe. This is usually followed by the loss of consciousness. If any of these signs are present, immediately consult with an emergency medical professional.

In theory any stinging insect species can cause allergic reaction in humans. This because an insect sting introduces venom-which essentially is a blend of foreign proteins- into the body where it contacts the immune system and can induce production of allergy- causing antibodies [42]. An allergic reaction typically occurs after the second or subsequent stinging event by the same or a closely related species. The first sting, (or stings), induces the production of the allergy causing antibody, immunoglobulin E (IgE), by the body resulting in the sensitization of the individual to the venom. Later when the now hipper sensitive individual is stung again, the venom causes an IgE-mediate allergic reaction.

Normal and allergic reaction to stings can vary enormously from individual to individual (Table 4, as cited by [42]. Normal reactions are those that virtually everybody experiences and are characterized mainly by pain and burning that typically are in tense for a few minutes and then decrees over time. After the intense pain decreases a redness and swelling are oven observed and this can last several hours to a day or more. Like normal (non-allergic) reactions, large local reaction is nothing to be feared. Though they are thought to be immunologically based reactions [62], [63], [64], [65], [66], they rarely progress to systemic reaction [63], [65], [66], 67], [68]. Moreover, the frequency of individual who experience large local reaction later having systemic reactions is no greater than that of people not experiences large local [63], [65], [66].

TABLE 4

Normal and allergic reaction to insect stings, as cited by [42].

Case of allergic	Symptoms
Normal, non-allergic reaction at the time of the sting	Pain, sometimes sharp and piercing
	Burning, or itching burn
	Readiness (erythema) around the sting site
	A wide area (wheal) immediately surrounding the sting puncture mark
	Swelling (edema)
	Tenderness to touch
Normal, non-allergic reaction hours or days after sting	Itching
	Residual readiness
	A small brown or red damage spot at the puncture site
	Swelling at the sting site
Large local reaction	Massive swelling (angioedema)around the sting site
	Extending over an area of 10 cm or more and frequently increasing insize 24 to 72 hours, sometimes lasting up to a week in duration
Cutaneous allergic reaction	Urticaria (hives, nettle rash) anywhere on the skin
	Angiodema (massive swelling) remote from the sting site
	Generalized pruritis (itching) of the skin
	Generalized erythema (redness) of the skin remote from the sting site
Non life-threatening systemic allergic reaction	Allergic rhinitis or conjunctivitis
	Minor respiratory symptoms
	Abdominal cramps
	Severe gastrointestinal up set
	Weakness
	Fear or other subjective feeling
life-threatening systemic allergic reaction	shock
	Unconsciousness
	Hypotension or fainting
	Respiratory distress (difficulty in breathing)
	Laryngeal blockage (massive swelling in the throat)

5.2 Allergy Test

As cited by [7], [8] stinging the patient with live bees should be done under medical care and by prescription from a doctor. It also will need to have a bee sting kit (epinephrine and antihistamine) available, this kit you can get it by prescription from your doctor. Be sure you read the directions on the package before you get your test sting [7]. The allergy test should be done by giving the person who will receive the bee venom for healing with only one sting by a live bee, either direct sting or just scrape it on his/her skin. The stinger should be remove immediately after stung, just leave it for about 10 seconds, it is often done on the knee, because it is far away from the heart and wait for the body reaction [7]. If no allergic reaction develops 15-20 minutes after stung, the bee stings is continued, but in case allergic reaction happened, the person shouldn't use bee stings for treating and should avoid exposure to honey bees stings.

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6 MEDICAL USES OF BEE VENOM

While apitherapy encompasses use or consumption of bee products, in the Anglosphere the term is most commonly associated with bee venom therapy and not the consumption of honey or other bee products. Due to its anticoagulant and anti-inflammatory properties BV was mainly used to treat many inflammatory disorders such as arthritis, bursitis, tendinitis, dissolving scar tissue (e.g. keloids), Herpes zoster, joint disease, and rheumatoid arthritis [2], [69], [1], [3], [70], [71], [72], [73], [8], [74], , Lyme disease [75], Multiple Sclerosis and osteoarthritis [76], [77]. Furthermore, research in various animal experimental models with inflammatory diseases demonstrated that BV administration was successfully effective in suppressing the inflammation. [78], [71], [72], [79], [80], [78], [81]. Interestingly, BV administration through acupuncture point (acupoint) was proven successful for producing a strong therapeutic effect as compared injection to non-acupoint area [78].

Testimonials and observations indicating the effectiveness of bee venom are common throughout Western and Asian cultures [82], [83], [84], [85], [86] discovered that daily injection of 1 mg/kg of bee venom into rats reduced formaldehyde-induced arthritis in the foot pad. In another rat model in which Mycobacterium was the inducer of inflammation, intraperitonal injection of 1 mg of bee venom inhibited the arthritic effect whom given daily [9]. [87] stated that bee venom is a method for treating arthritis.

When a bee stings, it doesn't normally inject all of the 0.15 to 0.3 mg of venom held in a full venom sac [10], [18], only 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. These nerves and muscles however keep injecting venom for a while, or until the venom sac is empty. The loss of such a considerable portion of its body is almost always fatal to the bee [8]. Used in small doses however, bee venom can be of benefit in treating a large number of ailments. This therapeutic value was already known to many ancient civilizations. Today, the only uses of bee venom are in human and veterinary medicine [8].

Bee venom contains 18 different compounds that all possess pharmaceutical properties. [88] reported that bee venom, its peptides melittin, and apamin, but not venom phospholipase suppress edema, probably through an immunosuppressive. The immunosuppressive effect of bee venom in rats was confirmed when high dose of bee venom were injected daily [71]. Whole bee venom and the peptide melitin experimentally lowered the cycle adenosine monophosphate (cAMP), an intra-cellular mediator, in mouse skin and whole venom and phospholipase caused a dramatic increase in prostaglandin E levels in that tissue [89], [90]. Bee venom, particularly the peptide apimen, also exerts an anti-complement activity in rats [91]. In humans, bee venom inhibits superoxide production by human neutrophils, thereby acting as anti-inflammatory activities of bee venom. [8] stated that the most abundant active component of the venom is melittin, which has many useful properties, including powerful anti-inflammatory, anti-bacterial and anti-viral actions. However, bee venom is a complex mix of a variety of peptides and proteins, some of which have strong neurotoxic and immunogenic effects. There is no standardized practice for the administration of bee venom. Some purport that the location of the sting is important, with the sting acting as a sort of acupuncture in combination with the effects of the venom, while others report the location is not important. The number of stings also varies widely from a few to hundreds and they may be administered either by live bees or by injection. This treatment can cause pain, and even result in death if the subject has an allergy to bee venom, which can produce anaphylactic shock [8].

As cited by [8] the apamine, melittin, phospholipase, and hyaluronidase in bee venom have the ability to block or inhibit the nervous system, stimulate the heart and stimulate the adrenal glands. The other compounds that comprise bee venom include formic acid, hydrochloric acid, ortho-phosphoric acid, mineral substances and volatile organic acids. Also present are some antibiotics, phospholipase A, as well as two amino acids rich in sulfur methionine and cystine. Sulfur is believed to be the main element in inducing the release of cortisol from the adrenal glands and in protecting the body from infections. The mechanism by which all the components of bee venom might work together to alleviate symptoms is unknown. Contact with bee venom produces a complex cascade of reactions in the human body. Homeopaths theorize that bee sting therapy stresses the body's immune system, thus getting it to come back stronger. The active portion of the venom is a complex mixture of proteins, which causes local inflammation and acts as an anticoagulant. The main component of bee venom responsible for pain in vertebrates is the toxin melittin; histamine and other biogenic amines may also contribute to pain and itching [93].

As cited by [8] the list of benefits to human beings as well as to animals is very long. Most of the reports of cures are of individual cases, though several unrelated patients have experienced the improvement or cure of similar ailments. Bee venom treatments are often accompanied by changes in life style, nutrition or other which may account for part, if not most of the benefits from treatments. The diseases and problems which have been reported by patients or doctors as improved or healed with bee venom therapy are listed in (Table 5). [8] stated that this does not constituent an endorsement or recommendation for the treatments. On the other hand stinging should never be tried unless there is immediate access to emergency treatment in case of an allergic reaction.

[94] stated that bee venom has long been used in traditional medicine for the treatment of various kinds of rheumatism. Although venoms of the different honeybee species differ slightly, there have been reports of successful rheumatism treatment with *Apis dorsata* venom by and with *A. cerana* venom.

TABLE 5

List of diseases and health problems improved or healed according to anecdotal reports, as cited [8].

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Humans		
Arthritis, many types[a]	Multiple sclerosis[a]	Premenstrual syndrome[a]
Epilepsy[a]	Bursitis[a]	Ligament injuries[a]
Mastis[a]	Some types of cancer[a]	Sore throat[a]
Chronic pain[a]	Migraine[b]	General immuno-stimulant
Decreases blood viscosity and coagulability[b]	Dilates capillaries and arteries[b]	Decreases blood cholesterol level[b]
Neruoses[b]	Rhinosinusitis[c]	Endoarteriosis[d]
Therosclerosis[d]	Polyneuritis[e]	Radicultitis[ef]
Infectious spondylitis[e]	Neuralgia[e]	Endoarthritis[e]
Infect. Polyarthritis[e]	Malaria[e]	Intercostal myalgia[f]
Myositis[f]	Tropical ulcers[f]	Slowly healing wounds[f]
Thrombophiletritis[f]	Cancer, temporary[f]	Keratoconjunctivitis[g]
Iritis[g]	Iridocytis[g]	Asthma[h]
Animals		
Arthritis		

[a] [76], [77], [107], [b] [123], [c] [124], [e] [125], [g] [126], [h] [127].

[95] conducted study to investigate bee venom and hyaluronic acid in the intra-articular treatment of osteoarthritis in an experimental rabbit model. They found that a significant difference was observed in the HA group ($P < 0.05$). The MRI evaluation of at any time in group BVI (b) was found to be different. No significant differences were seen between the groups, biochemically. Histopathologically, cellularity, and orthochromasia was evident with Safranin-O in the BVI (b) and BVII (a); adhesions were seen in the BVII (a) group and clustering of chondrocyte in the HA (b) group were found to be different. Consequently, intra-articular application of HA and BV for experimental model of osteoarthritis has no significant influence upon recovery after therapy.

The first step in treatment following a bee sting is removal of the stinger itself. The stinger should be removed as quickly as possible without regard to method: studies have shown the amount of venom delivered does not differ whether the sting is pinched or scraped off and even a delay of a few seconds leads to more venom being injected [96]. Once the stinger is removed, pain and swelling should be reduced with a cold compress [97]. Many traditional remedies have been suggested for bee stings including damp pastes of tobacco, salt, baking soda, papain, toothpaste, clay, garlic, urine, onions, aspirin or even application of coppercoins [98]. [97] concluded that ice alone is better treatment for bee and wasp stings than aspirin.

The sting may be painful for a few hours, swelling and itching may persist for a week. The area should not be scratched as it will only increase the itching and swelling. If a reaction persists for over a week or covers an area greater than 7-10 cm (3 or 4 inches), medical attention should be sought. Doctors often recommend a tetanus immunization. For about 2 percent of people, anaphylactic shock from certain proteins in the venom can be life-threatening and requires emergency treatment [110]. If the victim is allergic to bee stings, the victim must be treated to prevent shock. People known to be highly allergic may carry around epinephrine in the form of a self-injectable EpiPen for the treatment of an anaphylactic shock.

For patients who experience severe or life threatening reactions to insect stings, researchers have developed a series of allergy injections composed of increasing concentrations of naturally occurring venom which provide excellent and usually life-long protections against future insect stings [99].

7 TECHNIQUE

Bee venom therapy is practiced by healthcare providers and apitherapists who follow certain treatment protocols. The therapy starts with the determination of whether the patient is allergic to the venom by administering a small amount of venom intradermally. If no allergic reaction develops, the therapy is continued with the administration of one or two injections. The therapy is carried out every other day by gradually increasing the number of bee stings or injections. The length of treatment is determined by the condition that is being treated.

Traditionally, live bees that were stimulated to sting the affected area, trigger points or acupuncture points were used in bee venom therapy. Depending on the disease that is being treated, bee venom can be used in a cream, liniment, ointment or injection form. However, bee venom is thought to be most effective when it comes directly from a live bee during the late spring to early fall season. This season provides the bee with a good pollen source, allowing the bee to provide more potent venom. While venom from a live bee is the most potent source of venom, the injectable form of venom is most commonly used. A qualified health professional typically injects a venom solution prepared from pure bee venom intradermally, just between the skin layers, or subcutaneously, under the skin, to imitate the effect of a bee sting.

8 SCIENTIFIC EVIDENCE

Over 1700 scientific publications on the composition and various effects of bee venom in animals and humans have been published. An overwhelming proportion comes from Eastern Europe and Asia [8]. Most of them concentrate on demonstrating the site specific, physiological effects of individual components such as membrane destruction, toxicity, or the stimulation or blocking of enzyme reactions, the physiological effects of isolated venom compounds and the substances responsible for most of the allergic reactions. It has contributed little to verifying the increasing claims of different therapeutic values attributed to honeybee venom. A study with whole bee venom on dogs [12], and rats [100] showed that melittin and apamine produce increased plasma cortisol. Together with various other arguments, this suggests that many of the curative effects of bee venom may work through stimulation of the body's enzyme and immune system, in a way similar to the common drug cortisone. Cortisone has been used in the treatment of many ailments, but it is also known to have strong, undesirable side-effects. Melittin also

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appears to have toxic side effects as do some of the other individual compounds in venom. When whole venom is applied however, no side-effects have been shown, other than in allergic patients [84]. The anti-inflammatory effects of bee venom are perhaps the best studied and the various mechanisms have been repeatedly described in scientific literature [102]. The neurotoxic venom compounds have shown a potential benefit for epileptic patients [103]. The protective value of bee venom and melittin against the lethal or damaging effects of x-rays has been investigated [104], [134]. Recently, after long efforts by the American Apitherapy Society and its members, some interest has been shown by national institutions in several Western European countries and the USA for clinical and large scale tests of bee venom therapy.

As cited by [8] a good summary of the scientific studies, with further references can be found in [20], [11]. Summaries of some of the major specific effects of the various venom compounds that are shorter and more easily understood, can be found in [60], [19], [18], [105]. The American Apitherapy Society keeps records of scientific as well as anecdotal information on the use of bee venom. It is also probably the best source of information on any subject related to apitherapy.

9 VENOM PRODUCTS

No uses for venom, other than medical ones are known [8]. The only legally accepted medical use of bee venom in Western European and North American countries is for desensitizing people who are hypersensitive (allergic) to bee venom. Since the early 1980's, pure bee venom has been used for desensitization. The use of whole body extracts has been largely discontinued after a double-blind test proved the higher efficiency of pure venom [106]. In Eastern Europe and in many Asian countries bee venom has been used in official medical treatment of a large variety of ailments for a considerable length of time.

The use of pure venom injections and well placed bee stings is increasing in Western countries as an alternative to heavy (and sometimes ineffective) drug use, which is often associated with numerous side-effects. This is particularly so for arthritis and other rheumatoid inflammations. Application methods for venom include natural bee stings, subcutaneous injections, electrophoresis, ointments, inhalations and tablets [94].

Bee venom may be sold as whole bee extract, pure liquid venom or an injectable solution, but in either form the market is extremely limited. Most venom is sold in a dry crystalline form. Depending on the disease that is being treated, bee venom can be used in a cream, liniment, ointment or injection form. Bee venom solutions are also used in Europe and China with electroporesis or ultrasonophoresis.

For injections, the venom can be mixed at the time of injection with injectable fluids, such as distilled (sterile) water, saline solutions and certain oils, or it may be taken from prepared ampoules. Ampoules with set doses of ready-to-inject venom should only be prepared by certified pharmaceutical laboratories, because of the need to maintain stringent aseptic conditions and to measure the dosages very precisely [8].

There are creams available which include bee venom (e.g. Forapin and Apicosan in Germany, Apivene in France and Immenin in Austria) which are used for external application on arthritic joints [107], [94]. Bee venom therapy can also be delivered in the form of Bee Venom Balm although this may be less potent than using live bee stings [8].

Tablets can be impregnated with quantities of bee venom, but [94] recommended the removal of toxic proteins, such as Melittin and the use of colours to indicate different dosages. The tablets should be placed under the tongue, but no indication is given to the effect or usefulness of such a preparation.

Some specialized laboratories may be able to separate and purify different venom compounds and sell them to scientific and pharmaceutical laboratories. Phospholipase A2 and highly active peptides are among some of the proteins purified from bee venom for scientific suppliers or laboratories [105]. Entry to this limited market requires a highly sophisticated laboratory and very well-trained technicians and chemists.

Ointments can be prepared by thoroughly homogenizing bee venom with white Vaseline, petrolatum or melted animal fat, and salicylic acid, in the ratio of 1:10:1. The salicylic acid softens the skin, increases its permeability and is a treatment for rheumatism even on its own. The ointment may contain a small amount of silicate crystals to act as an abrasive [94]. Other preparations consist of mixing bee venom with sterile, injectable fluids and packaging them in single dosages in glass vials or syringes. In some packages the dry venom is kept separate from the fluid and the two are mixed when the vial is broken [8].

Though not directly related, bee sting emergency kits can be sold in some countries, particularly to people who are allergic. They also should be at hand for any beekeeper working with honey bees or Africanized honeybees and at training centres, police and fire departments, in areas with Africanized honeybees. In the USA, they are now available only against a prescription. Such a kit (e.g. Anakit by Hollister Stier, USA, as cited by [8]) should contain at least: One syringe with a premeasured content of epinephrine (adrenaline) or atropine, for immediate intramuscular injection - usually 0. 3 m1 of a diluted solution of epinephrine (1:1000) in saline solution. There are special, easy-to-use, syringes available from bee supply houses or through pharmacies, which can even be used through clothing (Epipen by Centre Laboratories, USA); anti-histamine tablets; tourniquet and instructions about when, where and how to use the syringe and anti-histamine tablets; when not to use epinephrine, and where to seek medical help.

Epinephrine injections should be given only in extreme emergencies when no other medical help is available. The sting emergency kit has a limited shelf-life and should be kept refrigerated when not in use.

10 BUYING AND STORAGE THE BEE VENOM

As cited by [8] the best way to buy bee venom is in the crystallized form, since it is more stable, impurities are easier to detect and adulteration is less likely. The colour

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of both crystals and powder should be a very light yellow. Liquid venom should be clear and colourless. Darker venom is slightly oxidized and may have lost some of its effectiveness. As with all other products where immediate testing is not possible or is very expensive, the producer should be one who is well-known and who can be trusted to produce a high quality product. The producer as well as the buyer should have adequate storage facilities.

Even dried bee venom should be stored refrigerated or preferably frozen and it should always be kept in dark bottles in the dark. All producers and buyers should closely observe these conditions. Dried bee venom can be kept frozen for several months, but should not be kept refrigerated for more than a few weeks. Liquid venom and diluted venom can be stored for similar periods if maintained in well sealed, dark glass containers [8].

11 QUALITY CONTROL OF BEE VENOM

As cited by [8] there are no official quality standards, since bee venom is not recognized as an official drug or as a food. Purity analysis may be carried out by quantitative analyses of some of its more stable or more easily measured components such as melittin, dopamine, histamine, noradrenaline or those for which contamination is suspected. A nematode, Panagrellus redivivus was reported to react selectively and specifically to bee venom and a quantitative analysis of the venom in pharmaceutical preparations was developed by [108] using this organism. [51] describes a method for testing the biological activity of bee venom by measuring electric pulses from muscles of excised honeybee abdomens in response to the volatile materials from bee venom. [109] described standardization and quality control methods for purity and effectiveness of Hymenoptera venom, including honeybee venom.

12 SAFTY OF BEE VENOM

The median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight, i.e. a person weighing 60 kg has a 50% chance of surviving injections totaling 168 mg of bee venom [10]. Assuming each bee injects all its venom and no stings are quickly removed at a maximum of 0.3 mg venom per sting, 560 stings could well be lethal for such a person. For a child weighing 10 kg, as little as 93.33 stings could be fatal. Therefore, quick removal of the stings is important. However, most human deaths result from one or few bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth.

Table (6) shows the number of honey bee stings that can cause death 50% of individuals exposed to bee stings on the basis of body weight as cited by [8]. In case of a child weighing 10 kg, about 93.33 or 186.67stings could well be lethal for such a child assuming each bee injects 0.30 or 0.15 mg venoms, for a person weighing 60 kg, about 560 or 1120 stings could well be lethal for such a person assuming each bee injects 0.30 or 0.15 mg venoms (Table 6).

TABLE 6

The number of honey bee stings that can cause death 50% of individuals exposed to bee stings on the basis of body weight (the median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight. and the bees secretes 0.15 – 0.30 mg), as cited by [42].

Body weight (Kg)	The (LD50) for an adult human is 2.8 mg of venom per kg of body weight	Number of honey bee stings needed for LD50 for humans in case honey bee worker secretes	
		0.3 mg venom	0.15 mg venom
10	28	93.33	186.67
20	56	186.67	373.33
30	84	280	560
40	112	373.33	746.67
50	140	466.67	933.33
60	168	560	1120
70	196	653.33	1306.67
80	224	746.67	1493.33
90	252	840	1680
100	280	933.33	1866.67
110	308	1026.67	2053.33
120	336	1120	2240

It is theoretically estimation depending on the bee worker secretes (0.15 – 0.30 mg venom) and, the median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight [10].

On the other hand the bee venom is very safe for human treatments as compare with other human diseases, accidents and other unusual cases. Table (7) shows the statistics of the rates of death to humans caused by diseases, accidents and other unusual cases in the United States in 1986 as cited by [42], out of 2086440 death in the year 1986 in the USA 977700 cases died by heart diseases acts as (46.86%) from the total death. The total number of death caused by cancer was 641400 (30.74%), by the smoking 150000 cases (7.19%), by asthma 3880 cases (0.186%), by allergy to penicillin 300 cases (0.014%), by insect bites (not honey bees) 24 cases (0.0012%), meanwhile by honey bees stings 17 cases (0.0008%).

Although, bee venom is safe for human treatment, it should only be used under the supervision of a qualified health care professional. Most experts recommend having an emergency sting kit available in case of allergic reaction. This kit should include a syringe and a dose of epinephrine and antihistamine tablets. It is also advisable that a test sting be performed before undergoing a treatment. There may be some discomfort associated with the administration of bee venom. This may include pain, itching, swelling, inflammation and redness at the injection site. More severe reactions may also occur.

TABLE 7

Statistics of the rates of death to humans caused by diseases, accidents and other unusual cases in the United States in 1986 (as cited by [42]).

Cause of death	the	Death	the percentage

	number of deaths/ year	rate per 1,000,000/ year	of the death of the total deaths
Heart disease	977700	4096	46.8597
Cancer	641400	1933	30.7414
Smoking	150000	750	7.189
Abuse Alekhalaat	100000	500	4.7929
Car accident	45601	192	2.1856
Suicide	29453	123	1.4116
Murder	19628	83	0.9407
Radon Gas	13000	54	0.6231
Foot vehicle	7641	32	0.3662
Drowning	4407	18.4	0.2112
House fires	3964	16.6	0.1900
Asthma	3880	16.2	0.1860
Poisoning	3621	15.1	0.1735
incidents of firearms	1649	6.9	0.0790
Freezing	1010	4.2	0.0484
Incidents of electricity	802	3.4	0.0384
Slip and silence while walking	404	1.7	0.0194
Allergy to penicillin	300	1.5	0.0144
Hunger and thirst	195	0.82	0.0093
Silent during Horseback riding	108	0.45	0.0052
Biting animals (dogs, etc.)	101	0.42	0.0048
Lightning	85	0.36	0.0041
During a collision sport	42	0.18	0.0020
Stress overload	28	0.17	0.0013
Insect bites (not honeybees)	24	0.07	0.0012
Honey bee sting	17	0.12	0.0008
Total deaths	2086440	8739	100%

[a] [128], [b] [129], [c] [130], [d] [131], [e] [42].

13 CONCLUSION

Use of honey and other bee products in human treatments traced back thousands of years and healing properties are included in many religious texts including the Veda, Bible and Quran. Apitherapy is the use of honey bee products for medical purposes, this include bee venom, raw honey, royal jelly, pollen, propolis, and beeswax. Whereas bee venom therapy is the use of live bee stings (or injectable venom) to treat various diseases such as arthritis, rheumatoid arthritis, multiple sclerosis (MS), lupus, sciatica, low back pain, and tennis elbow to name a few. It refers to any use of venom to assist the body in healing itself. The bee venom contains 88% water. The glucose, fructose and phospholipid contents of venom are similar to those in bee's blood. At least 18 pharmacologically active components have been described, including various enzymes, peptides and amines. The main component of bee venom responsible for pain in vertebrates is the toxin melittin; histamine and other biogenic amines may also contribute to pain and itching. Melittin comprising 52% of venom peptides. The melittin is a strong anti-inflammatory agent and induces the production of cortisol in the body. Apamin increases cortisol production in the adrenal gland. Apamin is a mild neurotoxin. Adolapin, comprising 2-5% of the peptides, acts as an anti-inflammatory and analgesic because it blocks cyclooxygenase. Phospholipase A2 comprises 10-12% of peptides and it is the most destructive component of apitoxin. It is an enzyme which degrades the phospholipids which cellular membranes are made of. It also causes decreased blood pressure and inhibits blood coagulation. Phospholipase A2 activates arachidonic acid which is metabolized in the cyclooxygenase-cycle to form prostaglandins. Prostaglandins regulate the body's inflammatory response. Venom from other Apis species is similar, but even the venoms from the various races within each species are slightly different from each other. The toxicity of *Apis cerana* venom has been reported to be twice as high as that of *A. mellifera*. The bee venom is safe for human treatments, the median lethal dose (LD50) for an adult human is 2.8 mg of venom per kg of body weight, i.e. a person weighing 60 kg has a 50% chance of surviving injections totaling 168 mg of bee venom. Assuming each bee injects all its venom and no stings are quickly removed at a maximum of 0.3 mg venom per sting, 600 stings could well be lethal for such a person. For a child weighing 10 kg, as little as 90 stings could be fatal. Therefore, quick removal of the stings is important. However, most human deaths result from one or few bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth. As compare with other human diseases, accidents and other unusual cases, the bee venom is very safe for human treatments.

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