

COSMECEUTICAL APPLICATIONS OF BEE VENOM

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ABSTRACT

God has created & gifted us various creatures on earth which are very useful to mankind. From thousands of years, "Honey Bees" are one among such creatures which are getting used for their medicinal properties and also bee based products. The use of these bee based products is called as "Apitherapy", where the Bee Venom is most importantly used for various treatments. Bee Venom is also known as "Apitoxin", which is composed of 18 pharmacologically active compounds including enzymes, peptides and amines. As a natural ingredient, Bee Venom has raised popularity due to its variety of potential health and skin benefits. It is used cosmetically because it has a potential to 'fool' the skin into thinking that it has been stung by the toxin, resulting in the body to direct blood towards the area thereby stimulating the production of the naturally occurring chemicals collagen and elastin. However, external application of Bee Venom may

cause minor side effects; therefore proper allergy test should be performed by medical professional. The main aim of this review is to summarize about the production of bee venom, extraction method, major components of bee venom, and benefits of venom in skin care.

KEYWORDS: Apitherapy, Bee Venom, Bee Sting, Cosmetic Applications, Honey Bee.

INTRODUCTION

There are many species of insects which have a capability of defending themselves usually by stinging with a sting & injecting their venoms. Honeybees are one of the species of flying

insects and are very close relatives of Wasps and Ants (Order Hymenoptera).^[1] All the varieties of bees live on nectar and pollen. Without honeybees, pollination is not possible, quite difficult & time consuming. The reproduction of plants helps to maintain the equilibrium of the environment and bees are helpful in this process by pollinating flowers. The flowers which give beauty also provide food to bees.^[2]

There are various species of honeybees where they are classified within seven main families, and one of these is the family *Apidae*. *Apidae* has three subfamilies: *Xylocopinae*, *Nomadinae* and *Apinae*. The subfamily *Apinae* comprises of nineteen tribes including *Apini* (honeybees), *Bombini* (bumblebees), & *Meliponini* (stingless bees), where *Meliponini*, the stingless bees found in tropical and southern subtropical areas throughout the globe.^[3]

The tribe *Apini* contains just one genus, *Apis* and is said to be the true honeybees. *Apis andreniformis*, *Apis binghami*, *Apis breviligula*, *Apis cerana*, *Apis dorsata*, *Apis florea*, *Apis koschevnikovi*, *Apis laboriosa*, *Apis mellifera*, *Apis nigrocincta*, *Apis nuluensis* are important species of honeybees.^[3]

Scientific Classification of Bee

Kingdom: Animal	Family: Apidae
Phylum: Arthropoda	Subfamily: Apinae
Class: Insecta	Tribe: Apini
Order: Hymenoptera	Genus: <i>Apis</i>
Suborder: Apocrita	Species: <i>Mellifera</i> , <i>cerana</i> etc.
Superfamily: Apoidea	Binomial name: <i>Apis mellifera</i> , <i>Apis cerana</i> etc. ^[2]

Life Cycle of Honeybees

The life cycle of Honey bees (figure no. 1 represents life cycle of honeybees) is usually of about 3-4 years. They lived in form of a colony which is perennial, & are basically of three types- the queen bee, drones or the males & the worker bee. Queen bee produces eggs, males mate with the queens & usually die upon mating, & the non- producing females are the workers. Queens are responsible to lay eggs single at a time in the cells of comb, where larvae hatch from eggs in 3-4 days, fed by the working bee & develop in cells through various stages. The development from egg to emerging bee varies among queens, workers and drones.^[2]

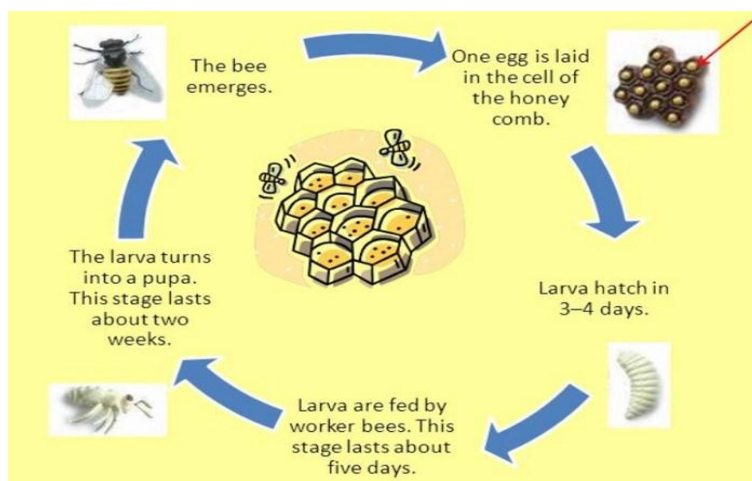


Figure.No.1: Life Cycle of Honeybees.^[4]

Bee Venom

Bee Venom is a complex mixture of proteins and amino acids, enzymes, sugars and lipids. Melittin, a polypeptide is a major component of venom, and in humans it has the effect of stimulating the adrenal cortex (part of the adrenal gland) to release cortisol, a hormone associated with reducing inflammations and healing responses.^[5] Following figure no. 2 represents bee venom sting apparatus and venom gland. The sting of bees ideally consists of three parts: a stylus and two barbed slides (or lancets), one on other side of the stylus. The bee does not shove the sting in but it is drawn in by the barbed slides. The slides move on the other hand and down the stylus so when the barb of one slide has caught and retracts it pulls the stylus and the other barbed slide into the wound. When another barb has caught it also retracts up the stylus pulling the sting further in. This process is repeated until the sting is fully in and even continues after the sting and its mechanism is detached from the abdomen of the bee.^[6]

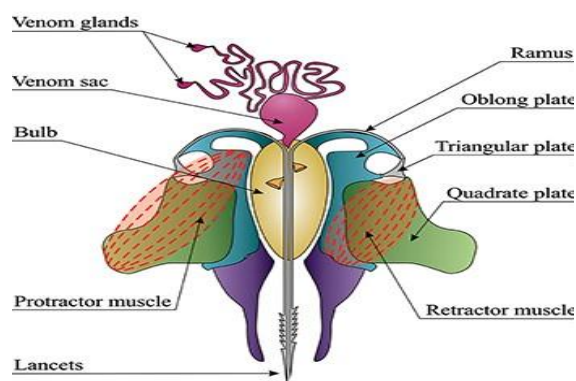


Figure no. 2: Bee Venom Sting apparatus & Venom Gland.^[7]

Bee venom has been widely used in medicine in treatment of various diseases, & also as a cosmetic ingredient. Bee venom has a wide spectrum of biological activity. It exhibit antibacterial, anti-inflammatory effects so it can be used as an ingredient of anti-acne products. Among all the species of honey bees the venom produced by *Apis mellifera* is the well-known natural toxins.^[8]

Physical Properties of Bee Venom

Color - Transparent liquid, dried venom color is light yellow or brown. This is because oxidation of some of the proteins of venom.

Odor - Odorless, or honey like

Smell - Ornamental pungent

Taste - Aromatic, bitter, acidic and hot

PH - 4.4-5.5

Specific Gravity - 1.13

Solubility - Soluble in water, about 10 % are insoluble, water solutions are unstable, insoluble in ethanol.^[9,10]



Figure No. 3 Bee Venom Drop.^[6]



Figure No. 4 Dried Bee Venom.^[6]

The Venom (figure no. 3.Venom drop & figure no. 4. Dried Venom) which is collected, dries quickly in ordinary room temperature, turning into a yellow-brownish powder crystalline mass. Bee Venom is relatively stable and is destroyed by sun light & high temperatures, whereas stable at low temperature. It is easily destroyed by oxidizing substances: for e.g. potassium permanganate, potassium sulfate; halogen elements-chlorine & bromine- where it is destroyed very quickly; the effect of iodine is much slower. Alcohol possesses a strong and quick destructive effect on the venom. In contact with tincture of iodine, the alcohol is more destructive than the dissolved iodine.^[11]

Composition of Bee Venom

Bee Venom is an odorless, transparent liquid which contains a hydrolytic mixture of proteins along with acids with a pH of (4.5-5.5) where bees often use this as a defensive tool. A single drop of Bee Venom consists of about 88% of water & about 0.1µg of dry venom. The dry venom is a complex blend of some peptides, enzymes, & some low molecular weight biologically active amines for e.g. histamine, epinephrine and also some minerals. Following table no. 1 represents major compounds of Bee Venom.^[12,13]

Table no. 1: Major Compounds of Bee Venom.

Major Compounds of Bee Venom	Description
Melittin	It is the main component of Bee Venom which is a 26- residue peptide, accounting 40-60% of Venom's composition. The peptide has carboxyl-terminal region which is hydrophilic in nature & is responsible for lytic action. The amino- terminal region is hydrophobic in nature with no lytic activity. ^[14, 15]
Apamin	It is an 18- amino acid peptide which contains two disulfide bridges. Apamin is the smallest neurotoxin in the Bee Venom. It constitutes about 2-3% dry weight of Bee Venom. ^[16]
Adolapin	It is a polypeptide with 103 amino acids residue. It constitutes about 1% dry weight of Bee Venom. ^[17]
Mast-Cell Degranulating (MCD) Peptide	The MCD peptide is also known as Peptide 401, which is a Bee Venom Polypeptide containing 22 amino acids which is similar to apamin structure where both of them contains two disulfide bonds. It constitutes about 2-3% dry weight of Bee Venom. The mast cell degranulating peptide echoes the biological action in histamine release from mast cells. ^[18]
Phospholipase A2 (PLA2)	PLA2 is single polypeptide chain of about 128 amino acids containing about four sulfide bridges. It is the most fatal enzyme in the Bee Venom. Bee Venom PLA2 is about 12-15% of Bee Venom's dry weight & very alkaline in nature. ^[19]
Hyaluronidase	Hyaluronidase is responsible to break down hyaluronic acid in tissues. It allows the active component of Bee Venom to effectively diffuse into the victim's tissue, responsible to affect the structural integrity and thereby increase the blood flow in that area. These actions combine together & increase the spreading of venom. It constitutes about 1.5-2% of dry weight of Bee Venom. ^[20, 21]

Production of Bee Venom

Bees produce the venom in their venom glands, associated with the sting apparatus of worker & queens, stored in the venom reservoir, and injected through the sting apparatus during the stinging process.^[1] During the first two weeks of the adult worker's life the production increase and reach to a maximum when the worker bee becomes involved in hive defense and foraging, diminishing as the bee gets older.^[22] A mature defender contains about 100-150 µg

of venom, which injects about 0.15 – 0.30 mg of venom via its stinger, where a honeybee can inject 0.1 mg of venom via its stinger.^[23] The queen bee's production of venom is highest on emergence, probably because it must be prepared for immediate battles with other queens. The young queen contains about 700 µg.^[24]

Extraction Process of Bee Venom

Most commercial venom collectors are composed of four parts: A Battery or accumulator (24 to 30 V), a Transformer from constant to alternating current, with impulse frequency of 50 to 1000 Hz and an impulse duration of 3 to 6 seconds, a Collector frame consisting of an electric wire net and a glass plate, covered by a thin polyethylene membrane. The collector is mounted in or out of the hive. The bees get in contact with the charged wire net and stimulated to sting through the membrane and spray their venom on the glass plate (figure no. 5 represents Commercial Bee Venom Collector). The glass plates are dried in a dark, well ventilated room. The collectors have been used under different conditions: Voltage: from 24 to 30 V, Impulse duration: 2-3 seconds, Pauses: 3 to 6 seconds; impulse frequency from 50 to 1000 Hz. Bees are not harmed during the Bee Venom collection. Repeated 3 hours collection periods, carried out 3 to 4 times per month do not harm bees, resulting in a total harvest of 4 g dry BV. This collection resulted in a decrease of brood manufacturing and honey yield of about 10-15 %. If the collection is less frequent, e.g. 3-4 times per season, the bee performance is not influenced. 10'000 bees are needed for the collection of 1 g dry Bee Venom.^[6, 25]



Figure No. 5: Commercial Bee Venom Collector.^[6]

Bee Venom from different honeybee species is slightly different but its overall activity is similar. In warm and humid zones the Bee Venom can be more toxic than in cold temperate

zones. Regarding the Bee Venom in different *Apis* types, *A. mellifera* and *A. dorsata* venom had same toxicity, whereas, *A. dorsata* venom contains more alarm pheromones.^[6]

Bee Venom Therapy

In Veda, Bible & Quran the use of honey and other bee products for use of human treatment have been traced back thousands of years ago.^[25] The use of honey and other honey bee products are generally used for medical purpose including bee venom, royal jelly, raw honey, beeswax, propolis, and pollen. The use of these honey bee based products is called as “Apitherapy”. The origin of Apitherapy is difficult to point out but can be traced back to Ancient Greece, Egypt and also been practiced in China for 3,000-5,000 years.^[25] The Bee Venom therapy is nothing but the use of live bee stings (or injectable venom) for the treatment of various diseases, assisting the body in healing itself. Bee Venom constitutes of about 18 pharmacologically active components which include enzymes, peptides and amines.^[25] Bee venom therapy utilizes the application of bee venom to treat various diseases that has been used since ancient times in traditional medicine. Honey bee venom is a pharmacologically active product of the hive.^[25,26]

CLINICAL STUDIES

Vitiligo: It is an abnormal pigmentation which is characterized by depigmentation of skin and hair. This is because of melanocyte proliferation, melanogenesis, and migration or increases in dendricity. As reported by Jeon et al. bee venom treatment elevates the melanocyte proliferation about two times as compared to the control in 1 week. By application of bee venom, the expression of MITF-M protein increases to the maximum level on third day and slowly decreases till fifth day. Bee venom treatment increases the ratio of cells with more than two dendrites by 23% in a time-dependent manner. The results showed that by bee venom treatment, the number of migrated cells as compared to the controls increases. It also induced melanocyte dendricity and melanocyte migration. The in-vitro study of bee venom has a positive effect on melanocyte proliferation, melanogenesis, dendricity, and migration. Thus for treatment of vitiligo by repigmenting the skin, bee venom can be useful.^[27]

Facial Wrinkles: The beneficial effects of serum containing bee venom on facial wrinkles was studied by Han et al. where the application of bee venom serum resulted in decreased average wrinkle depth, total wrinkle area and count. It was also reported that the topical application of bee venom is safe for human use. Studies that were conducted on animals

showed that it was well tolerated by them and no dermal irritation was seen. Thus, application of bee venom is effective in improving the skin wrinkles thereby increasing the production of collagen and elastin.^[28]

Acne: As reported by Han et al. they performed a randomized double blind control trial where the therapeutic effects of bee venom on acne was examined. Subjective evaluation was done where bee venom on acne was applied by skin care products which contain bee venom and also products which do not contain bee venom for a period of 2 weeks. The results showed that the subjects that were applied cosmetics containing bee venom relatively showed a reduction by 57.5% in ATP levels, by the count of inflammatory & non-inflammatory lesions compared to the control, thereby measuring a decrease in the count of microbes. Therefore, Han et al. suggested that cosmetic containing bee venom is a good component as a therapeutic agent for acne.^[29]

Atopic Dermatitis: It is a type of skin disorder usually characterized by a defective skin barrier, drying of the skin, pruritus, eczema and also by some allergic responses. It is a chronic, inflammatory skin disorder which may worsen if not treated properly. Bee Venom because of its anti-inflammatory mechanism, it can be useful for treating atopic dermatitis. As reported by You et al. they did evaluation of about 136 subjects which were random distribution in different groups. Some subjects were applied bee venom containing moisturizer and silk protein and moisturizer without bee venom for a period of 4 weeks. The results indicates that application of the moisturizer with bee venom showed significantly lower eczema area and severity index and visual analogue scale, value compared to the patients who applied moisturizer without bee venom. There were as such no outstanding differences in the incidence of side effects induced by bee venom on the subject's skin.^[30]

Applications of Bee Venom in Skin Care

- **Shrinks Pores:** Bee venom is the best solution for pores. Its astringent properties help in removing excess oil and fluid from both the pores of skin and its uppermost layers.^[31]
- **Relieves Inflammation:** One of the most important benefits of Bee Venom is its powerful anti-inflammatory effects. The soothing Adolapin which bee venom houses, it can quickly reduce the burning, redness, and swelling on skin.^[31]
- **Minimizes Wrinkles:** Bee venom is known for its wrinkle-eliminating properties. It helps in stimulating blood flow inside body which makes the blood easier to flow to the

surface of the skin. This ease of blood flow stimulates both the collagen and elastin production. Aside from this, what's unique about Bee Venom is its ability to strengthen tissues to be able to stop premature aging.^[28]

- **Fades Blemishes:** Bee venom properties which smooth are wrinkles & frown lines and shrink pores are also the ones who help fade acne blemishes. It also contains a peptide known as Melittin. Melittin has anti-bacterial and antimicrobial effects which are useful in fighting against acne.^[29]
- **Relaxes Muscles:** The Bee Venom is helpful in relaxing the muscles as it strengthens collagen and elastin to remain taut.^[31]

Buying and Storage of Bee Venom

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 color of both crystals and powder should be very light yellow. Liquid venom should be clear and colorless. The dark 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 extremely expensive, the producer should be one who is well-known and who are often trusted to produce a high quality product. The producer as well as the buyer should have adequate storage facilities.

The dried venom should be stored refrigerated or preferably frozen and it should always be kept in dark bottles in the dark. All producers as well as the buyers should closely observe these conditions. Dried venom can be kept frozen for several months, but it should not be kept refrigerated for more than a few weeks. Liquid venom as well as diluted venom can be stored for same periods if maintained in well-sealed, dark glass containers.^[1]

Quality Control of Bee Venom

There are not any 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 analysis of some of its more stable or more easily measured components such as Melittin, Dopamine, Histamine, or those for which contamination is suspected.^[1]

Allergy to Bee Venom

As reported by J.O. Schmidt, a bee sting is strictly a sting from a bee (any type of honeybee species). The sting from any of the species of bee can be painful. The stinging of bee differs from insect bites, and the toxin or venom also differs. The body's reaction to a bee sting may

differ significantly from one species to another and from person to person. Wasps are the most aggressive stinging insects. These insects aggressively defend their nests. The bee sting may trigger a dangerous anaphylactic reaction which is potentially lethal in action in the people who are allergic to bee stings.^[32] Schumacher et al., studied the median lethal dose (LD₅₀) for an adult human being is about 2.8 mg of venom per kg of body weight, i.e. a person weighing 60 kg has a 50% chance of surviving injections of about 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 rather be lethal for such a person. For a child weighing 10 kg, as little as 90 stings can be lethal. Therefore, quick removal of the stings is beneficial. However, most human deaths result from one or few bee stings due to allergic reactions, failure of heart or suffocation from swelling around the neck or the mouth. However, bee venom can be beneficial in treating large number of ailments when used in smaller doses.^[33]

Safety aspects of Bee Venom

The Bee venom is safe for human treatment only under the supervision of a qualified Health Care Professional. Although, normal to severe life-threatening reaction may occur, so proper medical care should be given and an allergy test should be performed by health professional.^[32]

Toxicity

As reported by Ernest et al., the toxic reactions from bee stings in non-sensitized individual may require 50 simultaneous stings. These reactions include vomiting, diarrhea, hemoglobinuria, acute renal failure with elevated serum levels of BUN, rhabdomyolysis, and thrombocytopenia creatinine and creatine phosphokinase. Stings in this region tend to increase the risk of lethality. The individual components of honey bee venom are known to act synergistically. Melittin from bee venom acts synergistically with the other component phospholipase A2 on phospholipid structures.^[33] It is said that hyaluronidase facilitates the distribution of other venom components through tissues neighboring the sting site, and melittin may facilitate entry of other more toxic components into the bloodstream, because anaphylactoid manifestations comprise only a part of the symptom complex that results from massive envenomation, specific treatment for anaphylaxis may be inadequate in the management of these patients, and anti-venom treatment may sometimes be suitable.^[34]

CONCLUSION

As discussed, the application of Bee venom on animals shows no cutaneous irritation potential. These findings may provide a developmental basis of bee venom for a cosmetic ingredient or external application for topical uses. As bee venom is invaluable natural ingredient, it has raised popularity due to its variety of potential health & skin benefits. It is useful because of its ability to fool the skin into believing that it has been stung, thereby increasing the production of collagen and blood circulation, & also the presence of large number of active chemical constituents & their properties makes it efficient to be used in cosmetic products. However, using these products can cause minor side effects on the skin. So before using the product, a patch test & allergy test should be performed by a trained professional. In-depth studies should be done on dermal applications including the cytotoxic & phototoxic effects & other evaluation parameters. Lastly, more studies to be conducted on bee venom of various species of honey bees including the application of venom on humans as well as the lethality.

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