Review Paper

A Review on Bioactivities of Honey Bee Venom

Abstract

The Honeybee (*Apis mellifera*) is one of the world's most beneficial insects, as it plays a critical role in many terrestrial ecosystems. The use of honeybee products has been documented for thousands of years in many cultures for the treatment of human diseases, and their healing properties have been documented in many religious texts. The present study sets out to compile information on the history, chemical composition and scientific evidence concerning bee venom research. The promising bioactivities have the potential to provide practical directions for further investigation. PubMed database, Google Scholar Library, research articles, books, and relevant web pages have been accessed to accumulate data so that the updated information included in this study is as current as possible. At least 18 pharmacologically active components including various enzymes, peptides, and amines are present in bee venom. Medicinal use of bee venom therapy wields significant *in vivo* and *in vitro* outcomes to some extent mitigate the effects of Parkinson's disease, Alzheimer's disease, HIV, arthritis, liver fibrosis, cancer, tumors, fibrotic diseases, Lyme disease, etc. The effects of bee venom were the first documented in 1888 with the publication of a European clinical study conducted on its impact on rheumatism. According to a study published in the journal, bee venom has been used to treat various conditions for centuries. Such research activities confirm the therapeutic effectiveness of bee venom and as a potential future biomedicine.

Keywords

Bee venom; *Apis mellifera*; melittin; apamin; apitherapy; venom immunotherapy.

Introduction

Apitherapy is defined as the use of various honeybee products that serve as alternative remedies: for example bee venom, melittin, propolis, royal jelly, and pollen.[1] Melittin, the most dominant substance in bee venom, appears to have anti-inflammatory properties and has indicated its ability to fight cancer cells have grown in laboratory conditions. Scientists from Australia have altered the structure of the melittin molecule, by removing the allergen part and they documented some anti-cancer activities of melittin in studies using mice. Specifically, melittin's cancer cell-killing ability and combining the molecule with an antibody to target cancer cells have been reported.[2,3] Propolis, a natural compound made by the honeybee, has indicated antioxidant and antitumor activity in early laboratory and animal studies.[4-7] A study conducted in Japan concluded that honey had some cytotoxic effect against bladder cancer cells in the laboratory and worked against bladder tumors in mice.[8] Furthermore, bee venom can destroy red blood cells.[9]

In China, propolis was authorized as a new medicine.[10] Propolis is a substance that forms the bee's external immune defense system, making the bee hive one of the most sterile environments known in nature.[11] Propolis consists of more than 180 different chemicals.[12] Studies on propolis application have increased because of its therapeutic and biological properties. In dentistry, for example, propolis has served in the treatment of aphthous stomatitis, candidiasis, acute necrotizing ulcerative gingivitis, periodontitis, and pulpitis. Current research involving propolis in dentistry highlights its antimicrobial and anti-inflammatory activities, particularly in cardiology, oral surgery, pathology, periodontics, endodontics and pedodontics.[13] subsequently; propolis appears to be a promising alternative for the control of oral diseases regarding antimicrobial response.[14]

In south-western Nigeria, honey historically was used for the treatment of 18 conditions, some of this being cough, ulcer, fatigue, sleeplessness, sore throat and boils. Bee

venom (BV) was responsible for treating seven ailments, for example, rheumatism, arthritis, high blood pressure, body pains, malaria, headache, stroke. Meanwhile, bee wax proved to be useful for the treatment of frigidity in women and weak penile erection in men, while propolis also helped in the treatment of measles and ringworm.[15] Traditional healers in Tanzania use honey by mixing it with other ingredients to cure coughs, stomach ulcers, malaria, and burns.[16] In Burkina Faso, honey has also been reported for assisting in the treatment of various gastrointestinal disorders, respiratory ailments, fatigue, postnatal disorders, male impotence as well as being applied as a skin cleansing agent.[17] This review focuses chiefly on the available, robust scientific literature that have documents the effectiveness of honeybee venom in treating diseases.

Materials and methods

Research articles, books, and relevant websites were investigated with the aim of accumulating data on the use of honeybee venom therapy in medicine. We also accessed the PubMed database, Google Scholar Library, and the Google search engine to generate and evaluate the maximum amount of the best and updated information for this review.

A brief history of apitherapy

Apitherapy is an established outward appearance of alternative therapy and has been used in many cultures and countries since ancient times.[18-21] The origin of apitherapy can be traced back to ancient Egypt and Greece and had also been practiced in China for 3000-5000 years.[22] The famous old Roman scholar, Pliny claimed in his writings that propolis reduces swellings, soothes pain, and heals sores. There is a reference in the Quran on the medicinal properties of the liquid produced by bees, and it is also cited in many religious texts including the Veda and the Bible.[23] In the USA, apitherapy was practiced nearly 100 years ago by a prominent doctor, Dr. Bodog Beck, who started treating people in his New York City office in the late 1920s.

Dr. Beck's book *Bee Venom Therapy* has been a classic text for 60 years. The last surviving student of Dr. Beck is Charles Marz, a beekeeper, who was known by many as the "King of bee venom therapy." He has been practicing apitherapy for over 60 years and had remarkable results; although most of his experience had been in the treatment of arthritis, his greatest success was in the treatment of multiple sclerosis.[22] In Eastern Asia, bee venom has been researched and practiced throughout the Korean peninsula with a focus on clinical applications of meridian therapy.[24] Finally, John Gerard wrote about the healing powers of propolis in his book *The History of Plants* and studies conducted in 1919 confirmed that honey comprised antibiotic properties.[25]

The composition of honeybee venom

There are more than 60 identifiable components in bee venom, and melittin is the most prevalent substance. The honeybee venom consists of enzymes, proteins, peptides, and a variety of smaller molecules (amino acids, catecholamines, sugars, and minerals). The main components are proteins and peptides. The compositions of dry bee venom are listed below in Table 1. Most types of venom induce immediate pain because they contain phospholipases, hyaluronidase, and other enzymes.

Bioactivities of honeybee venom as medicine

Melittin is the main bee venom component and it has many positive biological effects and relatively low toxicity, whereas MCD peptide and Phospholipase A2 are the most toxic components. Diseases of the nervous system lead to changes in glutamate release and uptake due to changing in the activity of glutamate transporters. These have been reported in many neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis. Glutamatergic toxicity occurs in neuronal cells and microglial cells, and it has been found that BV protects against cell death.

Furthermore, BV significantly inhibits the cellular toxicity of glutamate, and pretreatment with BV alters Mitogen-Activated Protein (MAP) kinase activation subsequent exposure to glutamate. These results recommend that treatment with BV may help to reduce glutamatergic cell toxicity in neurodegenerative diseases.[29] Previous studies have investigated the effects of bee venom on the prevention of amphetamine addiction. Furthermore, BV has been reported to induce the activation of catecholaminergic neurons in the hypothalamus of rats.[30, 31]

Parkinson's disease (PD)

Recent studies revealed that BV could protect dopaminergic neurons from degeneration in experimental PD. It has been observed that BV reduces neuro-inflammation in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MRTP)-induced model of PD in mice. BV acupuncture effectively protected dopaminergic neurons against MPTP toxicity in mouse models of PD.[32, 33] BV also protects SH-SY5Y human neuroblastoma cells from MRTP-induced apoptotic cell death.[34]

The neuroprotective effects of bee venom phospholipase A2 are claimed due to the suppression of neuroinflammatory responses in a mouse model of PD.[35] Bee venom acupuncture revealed a neuroprotective effect in a mouse model of Parkinson's disease.[36] Another study reported that the peptide apamin of BV can protect DA neurons in a model system of midbrain cultures that mimics the selective demise of these neurons in PD. The protective effect of apamin was attributed to a small increase in excitability of the DA neurons that generated a moderate and persistent elevation in cytosolic calcium.[37]

The data of one very recent study suggests that BV can induce sustained protection of dopaminergic neurons in an animal model that mimics the chronic degenerative process of PD. The bee venom peptide apamin, a specific blocker of SK channels, only partially reproduced these protective effects. An investigative clinical trial of bee venom (apamin) as a neuro-protective agent in Parkinson's disease patients is currently being conducted.[38]

Alzheimer's disease

Individual reports on the positive effects of apamin in dementia and Alzheimer's disease have been reported by Ludyanski.[39] Specific brain effects of BV in Alzheimer patients have been elucidated.[40] Several analyses indicate that small conductance calcium-activated potassium channels-blockade by apamin may enhance neuron excitability, synaptic plasticity, and long-term potentiation in the CornuAmmonis (CA1) hippocampal region. Due to this, apamin has been proposed as a therapeutic agent in the treatment of Alzheimer's disease.[41, 42]

Multiple sclerosis (MS)

MS is a chronic neurological disease characterized by inflammation, demyelination and axonal degeneration in the central nervous system. BV therapy is widely employed against MS in the hospitals of Japan, South Korea, Taiwan, and other Far East countries.

Castro et al. conducted a study., their objective being to evaluate the safety of bee venom extract as a potential treatment for patients with progressive forms of MS. This preliminary study suggests safety, however, due to the small numbers studied, there were no definite conclusions regarding efficacy. Consequently, little evidence emerged to support the use of honeybee venom in the treatment of MS.[43]

Bee sting therapy is increasingly used to treat patients with multiple sclerosis (MS) in the belief that it can stabilize or ameliorate the disease. A randomized cross-over study reported that treatment with bee sting therapy in patients with relapsing multiple sclerosis did not reduce disease activity, disability, or fatigue and did not improve these patients' quality of life.[44]

Amyotrophic lateral sclerosis (ALS)

A study was done by South Korean researchers to determine whether BV suppresses motor neuron loss and microglial cell activation in hsoD1^{G93A} mutant mice suggested that BV could be a potential therapeutic agent for anti-neuro-inflammatory effects in an animal model of ALS.[45]

One study revealed that BV inhibits cell death and activation of pro-apoptotic signaling in glutamate-stimulated cells. Also, BV attenuates cell toxicity though inhibition of the JNK(June N- terminal Kinase) and p38 pathways. These findings emphasize the clinical importance of BV for treating glutamate-mediated syndromes and inflammatory diseases. These include, for example, ALS. Further investigation of this activity *in vivo* is required to explain more fully the mechanisms involved and to permit the full exploitation of the therapeutic potential of BV.[46]

Neuralgia

There is a case report describing the effects of bee stings on painful post-herpetic neuralgia in a 51-year-old man. The patient was stung by three bees and one day after the bee stings, the patient's painful post-herpetic neuralgia was completely relieved, and the relief lasted for 1 and a half months. The researchers then suggested that BV therapy should be further investigated as a potential treatment modality for post-herpetic neuralgia.[47]

A very recent study done by the researchers at the Korea Institute of Orient Medicine demonstrated that a neuropathic pain, cold allodynia, could help in treatment. Their finding was that diluted bee venom (DBV) reduced cold allodynia in sciatic nerve chronic constriction injury (CCI) rats. The possibility that spinal adrenergic receptors could mediate these effects arose. Single or repetitive stimulation of DVB could alleviate CCI-induced cold allodynia via activation of spinal α2-adrenoceptor.[48]

HIV

Melittin is a potent toxin found in bee venom. It can penetrate holes in the protective viral envelope that surrounds the human immunodeficiency virus, as well as other viruses. Free melittin in large-enough quantities can inflict considerable damage. Researchers at Washington University, School of Medicine have demonstrated that nanoparticles containing the bee venom toxin melittin can destroy the HIV virus that causes AIDS. A new study shows that melittin on the nanoparticles fuse with the viral envelopes and form little pore-like attack complexes. They rupture the envelopes, stripping them off the virus and these nanoparticles do not harm normal cells.[49]

Arthritis

Bee venom appears to offer new hope to arthritis patients. There are at least two mechanisms involved in the anti-arthritic action of BV: (a) alteration of the immune response, probably via antigen competition; and (b) an anti-inflammatory action via corticosteroids or through an as yet undetermined mechanism.[50] One study has been done to evaluate the anti-nociceptive effect of BV injections into a specific acupoint (Zusanli) compared to a non-acupoint in an animal model of chronic arthritis. It demonstrated that BV injection into the Zusanli acupoint has both anti-inflammatory and anti-nociceptive effects on Freund's adjuvant-induced arthritis in rats. These findings raise the possibility that BV acupuncture is a promising alternative medicine therapy for the long-term treatment of rheumatoid arthritis.[51, 52]

Osteoarthritis (OA)

OA is the most common form of joint disease, one that can occur in any joint but usually it affects the hands, knees, hips or spine. A study has been done to compare BV therapy with traditional needle acupuncture for relieving the pain of patients with knee OA. The study showed that a significantly higher proportion of subjects receiving BV acupuncture reported

substantial pain relief when compared to those receiving traditional needle acupuncture therapy.[53]

Another recent analysis was done to investigate bee venom (BV) and hyaluronic acid (HA) in the intra-articular treatment of osteoarthritis in an experimental rabbit model. The authors of this study revealed that intra-articular application of HA and BV for an experimental model of osteoarthritis has no significant influence upon recovery after therapy.[54]

Rheumatoid arthritis (RA)

RA is an autoimmune disease where the body perceives tissue in the joints as being a foreign object and fights the tissue through an immune response.[55, 56] The clinical effects of bee-sting (venom) therapy in the treatment of RA were investigated by Liu et al. They concluded that combined application of bee-venom therapy and medication is superior to simple use of medication in relieving RA. When bee-sting therapy is used, the commonly-taken doses of Western medicines may be reduced, and the relapse rate declines.[57]

Lyme disease

One study revealed that the extraordinary sensitivity of *Borrelia burgdorferi* to melittin might provide both: firstly, a research reagent useful in the research on selective permeability in microorganisms; and secondly, essential clues to the development of effective new drugs against Lyme disease.[58]

Liver fibrosis

A study reported that melittin suppresses the expression of pro-inflammatory cytokines through the nuclear factor (NF-κB) signaling pathway and prevents TAA-induced liver fibrosis by inhibiting liver inflammation and fibrosis, the mechanism of which is the

interruption of the NF-κB signaling pathway. These results suggest that melittin could function as an active agent for preventing liver fibrosis.[59]

Cell regeneration and healing activity

Using bee venom to combat skin diseases has been used since the beginning of the 20th century. The following skin diseases, eczemas-like dermatitis, psoriasis, furunculosis, have been successfully treated, and it has been used for the healing of cicatrices and against baldness. The immune boosting effect of BV originated from melittin. A study using an *in vitro* wound healing model demonstrated that BV could be applied topically to accelerate wound healing through the cell regeneration process. Further, *in vivo* studies are needed to evaluate the effect of BV treatment in topical application.[60] It has been reported that propolis promotes epithelial formation as well as vascular and fibroblastic neoformation of the connective tissue. It can, therefore, be hypothesized that the topical application of propolis to surgical wounds may promote faster epithelial and connective tissue healing.[61]

Cancer and tumors

Api-toxin has been widely used in the treatment of some immune-related diseases, as well as in recent times for the treatment of tumors. Several cancer cells including renal, lung, liver, prostate, bladder, mammary cancer cells and leukemia cells, can be targets of bee venom peptides such as melittin and phospholipase A2. The cells' cytotoxic effect through the activation of PLA2 by melittin has been suggested to be the critical mechanism for the anti-cancer activity of BV. The inducement of apoptotic cell death through several cancer cell death mechanisms, for instance, the activation of caspase and matrix metalloproteinases, is important for the melittin-induced anti-cancer effects. The conjugation of melittin with hormone receptors and gene therapy carrying melittin can be useful as a novel targeted therapy for some types of cancer, such as prostate and breast cancer.[59, 62] However, a bee

venom peptide lasioglossin II exhibits cytotoxic activity against various cancer cells *in vitro*.[63] Consequently, it seems that melittin, a potent anticancer peptide, may be the better choice than whole BV. BV acupuncture and melittin were used to control neuropathy caused by cancer chemotherapy.[64]

The possible tumor growth- and metastasis-inhibiting effects of bee venom in mice and tumor cell cultures were investigated. Intravenous administration of bee venom in mice significantly reduced the number of metastases in the lung. Researchers proposed that bee venom has an indirect mechanism for inhibiting tumor growth and the promotion of tumor rejection. It is a mechanism based on the stimulation of local cellular immune responses in lymph nodes. Apoptosis, necrosis, and lysis of tumor cells are other possible mechanisms by which bee venom inhibits tumor growth.[65]

Other findings demonstrate that anti-tumor and anti-metastatic effects of bee venom depend highly on the route of injection and close contact between components of the bee venom and tumor cells. These data show that honeybee products given orally or systemically may play an important role in the control of tumor growth and tumor metastasizing ability.[66]

Polypeptides in bee venom (PBV) produced a significant growth inhibition against SMMC-7721 human hepatoma cell line. Analysis of the mechanisms of cell death indicated that PBV induced apoptotic cell death and hence PBV could be employed as a chemotherapeutic agent against tumors.[67] Melittin inhibits tumor cell metastasis by reducing cell motility and migration by suppressing the Rac1-dependent pathway, suggesting that melittin is a potential therapeutic agent for hepatocellular carcinoma.[68]

The results of one study demonstrated that low concentration BV possesses a potent suppressive effect on anti-apoptotic responses of tumor necrosis factor (TNF-α/Act D)-treated hepatocytes. It suggests these compounds may contribute substantial therapeutic potential for the treatment of liver diseases.[69] Also, the tumor-specific anti-angiogenic activity of BV takes effect during different stages of tumor progression by blocking the tyrosine phosphorylation

of vascular endothelial growth factor receptor 2 (VEGFR-2). Thus the application of BV in lung cancer treatment is validated.[70]

Fibrotic diseases

BV suppressed CCl_4-induced hepatocyte necrosis markers of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). It also inhibited the secretion of interleukin (IL)-1βand tumor necrosis factor (TNF)-α. Moreover, BV inhibited carbon tetrachloride (CCl_4)-induced expression of transforming growth factor (TGF)-β1, α-smooth muscle actin (SMA) and fibronectin. Similarly, ethanol-treated hepatocytes (ETH) exhibited the ability to suppress IL-1β significantly, TNF-α, TGF-β1 and fibronectin when cultured with BV. These results suggest that BV possesses anti-fibrogenic properties that are mediated by the suppression of pro-inflammatory cytokines and fibrogenic gene expression. BV has the substantial therapeutic potential for the treatment of fibrotic diseases.[71]

Benign prostatic hyperplasia (BPH)

Bee venom in one study was used to reduce inflammation and correct the imbalance between prostate-cell proliferation and cell death, which is associated with the development of BPH, a common disorder in aging men. The efficacy of bee venom against testosterone-induced BPH rats is decreased prostate weight compared to the untreated group, and bee venom suppressed serum dihydrotestosterone concentration levels and the levels of proliferating cell nuclear antigen in the histological analysis. These results suggest that bee venom has good potential to treat benign prostatic hyperplasia.[72]

Antimicrobial activity

A study has been done to investigate the antimicrobial activity of bee venom and its main component, melittin, exhibited a broad spectrum of antibacterial activity against 51 strains of

both Gram-positive and Gram-negative bacteria. These had strong anti-MRSA and anti-VRE activity, and they showed a remarkable fungicidal activity with minimum fungicidal concentration values between 30 and 200 µg/ml.[73]

Bee venom Immunotherapy

Venom Immunotherapy (VIT) is used for preventing or reducing sensitivity to allergens that cause an allergic reaction. The VIT treatment carries a small but significant risk of systematic reaction and is highly effective in treating patients with systemic allergic reactions (SARs) to Hymenoptera (one of the largest orders of insects, comprising sawflies, wasps, bees and ants) venom. VIT is highly effective for reducing allergic sensitivity in people and has been shown to reduce the risk of systematic reactions in people with bee sting allergies by more than 95%. This immunotherapy of bee venom can result in protection against adverse (or allergic) reactions from stings in the great majority of cases.[74-88]

The sublingual immunotherapy (SLIT) of honeybee venom can significantly reduce reactions in people who are allergic to bee stings.[89, 90] SLIT is well-established allergen-specific immunotherapy, and an effective strategy to reorient inappropriate immune responses in allergic patients.[91] Much higher allergen doses are commonly used in sublingual immunotherapy than in subcutaneous immunotherapy with fewer side effects.[92]

Venom Immunotherapy treatment failure may be associated with a variety of risk factors. A cohort study has been done to evaluate the association of baseline serum tryptase concentration (BTC) including other parameters with the frequency of VIT failure during the maintenance phase. Furthermore elevated BTC wields a strong ability to reduce the number of treatment failures. The most important factor associated with VIT failure was a honeybee venom allergy.[93]

General discussions

This review indicates that bee venom therapy may be considered a potential source of alternative medicines or drugs. It reveals the much practical potential for the treatment of rheumatic diseases, peripheral nervous system disorders, arthritis, HIV, Parkinson's disease, cancers, and tumors. It helps patients to strengthen their immune system, increase the number of white blood cells and can help overcome high blood pressure. It is also remarkable to note that we have a high number of historical records of treating people in this way. It is clear that melittin is a potent anti-inflammatory agent and induces the production of cortisol in the body. Apamin increases cortisol production in the adrenal gland and is also a mild neurotoxin. Adolapin, comprising 2-5% of peptides, acts as an anti-inflammatory and analgesic agent because it blocks the cyclooxygenase pathway. Phospholipase A2 comprises 10-12% of peptides, and it is the most destructive component of API-toxin.[94]

Epilepsy is a common chronic central nervous system disorder characterized by repeated malicious seizures. Current medications that have been implemented by medical practitioners mostly suppress the seizures and induce symptomatic relief. However, they do not affect epileptogenesis. A computational study and molecular dynamics simulation results indicated that interaction between S100B (calcium binding protein) and melittin resulted in the structural distortion and inaccessibility of calcium binding domain of the S100B protein. This is required to maintain ionic imbalance due to over-expressed S100B in disease conditions. For this reason, it has been suggested that the regulation of S100B by melittin has the potential to successfully treat epilepsy.[95]

Melittin is a powerful anti-inflammatory and antimicrobial agent that has also recently been shown to inhibit the HIV. In the March 2013 issue of *Antiviral Therapy*, researchers at Washington University's School of Medicine demonstrated that nanoparticles containing melittin could destroy the HIV virus that causes AIDS.[96] BV alone significantly produced anti-arthritic effects. There is plenty of research evidence of individuals using bee venom

therapy to successfully treat Lyme disease, and several practitioners are starting to advocate the use of bee venom therapy to cure Lyme disease as well.

Researchers at the Korea Institute of Oriental Medicine, Republic of Korea revealed that bee venom should be considered as a candidate of therapeutic agents for Amyotrophic lateral sclerosis (ALS), which is the most common adult-onset neurodegenerative disease.[97] Concerning cancer, propolis has received special attention in the field of oncology research as a source for prevention and treatment. Accordingly, a large number of compounds such as caffeic acid phenethyl ester (CAPE), artepillin C, and propolin A-C which can engage in anticancer activity have been reported as originating from propolis. Therefore, CAPE can be considered as a potential anti-angiogenic agent that reduces neovascularization.[61]

Recent studies have reported that propolis prevents and mitigates diabetes and hypertension. Chinese propolis helped to reduce fasting blood glucose (FBG) and improve oxidative stress and lipid metabolism in the alloxan-induced diabetic rat.[11] An Italian study states that this natural compound and its active principle, CAPE, were able to overcome the harmful effects of IL-1β. The data demonstrated the protective action of propolis in cartilage alteration appears to be greater than that elicited by Indomethacin, which is commonly employed in joint diseases.[98]

Conclusions

By scientific statements, honeybee venom should be considered a candidate of therapeutic agents for regulating various pathological events. As a traditional type of medicine, bee venom has performed strongly against some critical diseases. Thus by appropriate dosing and composing of its components, it can be effectively used as a medicine with much future potential. By reviewing several pharmacological research studies on bee venom's fight against various diseases and disorders, it was observed that the components of honeybee venom not only have different bioactivities to boost the immune defense; they also acted in

several different pathways according to diseases encountered. Since clinical studies are largely missing and need to be undertaken, more scientific experiments with bee venom treatment should be conducted in order to have more worthwhile evidential documentation of the bioactivities against diseases. We can conclude that honeybee venom has much promise as a medication supplement and one mankind will benefit from this ideal natural medication.

Declaration

❖ List of Abbreviation

BV	Bee Venom
MAP	Mitogen-Activated Protein Kinase
PD	Parkinson's disease
MS	Multiple Sclerosis
ALS	Amyotrophic Lateral Sclerosis
DBV	Diluted Bee Venom
CCI	Chronic Constriction Injury
OA	Osteoarthritis
HA	Hyaluronic Acid
RA	Rheumatoid Arthritis
NF	Nuclear Factor
PBV	A polypeptide in Bee Venom
TNF	Tumor Necrosis Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
SMA	Smooth Muscle Actin

ETH	Ethanol Treated Hepatocytes
BPH	Benign Prostatic Hyperplasia
VIT	Venom Immunotherapy
SLIT	Sublingual Immunotherapy
BTC	Baseline Serum Tryptase Concentration
CAPE	Caffeic Acid Phenethyl Ester
FBG	Fasting Blood Glucose

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639

640 **Table 1.** The composition of honeybee venom.[26-28]

Class of molecules	Components
Enzymes	Phospholipase A2

	Hyaluronidase
	Acid Phosphomonoesterase
	Lysophospholipase
	glucosidase
Peptides	Melittin
	Pamine
	Mast Cell Degranulating Peptide (MCD)
	Secapin
	Procamine
	Adolapin
	Protease inhibitor
	Tertiapin
Active amines	Histamine
	Dopamine (DA)
	Noradrenaline
Amino Acids	Aminobutyric acid
	Amino acids
Sugars	Glucose & fructose
Phospholipids	
Volatile compounds	Complex ethers
Minerals	P, Ca, Mg

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