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Review Article

HYMENOPTERA TOXINS: BIOLOGICAL ACTIVITY, PHARMACEUTICAL AND THERAPEUTIC USES

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ABSTRACT

The present review article explains the salient features of hornet venom toxins, their physiological, biological and pharmacological effect on animals and man. Hornets sting very fast and inflict venom, which is more dangerous than those of bees. Hornet venom contains both proteinaceous and non-proteinaceous peptides i.e. scapin, adolapin, mellitin, mastoparans and enzymes, mainly phospholipase and hyaluronidase, which show multiple biological effects i.e. cytolytic, hemotoxic, neuro-inhibitor, anticancer, anti-parasitic, immune hypersensitive, inflammatory, antimicrobial and anti-insect activities. Hornet stings are more painful to humans than typical wasp stings because hornet venom contains a large amount (5%) of acetylcholine. Hornet toxin components interact with receptors, ion channels and gated channels and affect the permeability functions of cells. Heavy envenomation shows quick pathophysiological lethal effects in man and pet. This article emphasizes the use of various hornet venom components for the production of disease-modifying anti-rheumatic and analgesic, anticancer drugs and insecticides. Hornet venom allergens could be used to prepare the rational design of component-resolved diagnosis of allergy and venom immunotherapy of inflicting patients.

Keywords: Hornets stings, Venom and toxin, Anticancer activity, Anti-parasitic, Immune hypersensitivity activities

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INTRODUCTION

The hornets are hymenopteran insects belonging to genus *Vespa.* These are the largest social wasps, show similar appearance to their close relative's yellow jacket wasps. Like wasps, hornets are also found almost in all parts of the world. The Asian giant hornet *(Vespa mandarinia*) is the world's largest social wasp builds communal nests by chewing wood to make a papery pulp. Most of their species are flower visitors and collect nectar in the morning hours. The hornets are mostly of black to light black color and their size ranges 4.3 to 5.5 cm (2.2 in) in length. They are distinguished from other vespine wasps by the relatively large top margin of the head and by the rounded segment of the abdomen just behind the waist. Hornets use stings to kill prey and defend hives. Hornet stings are more painful to humans than typical wasp stings because hornet venom contains a large amount of acetylcholine. Individual hornets can sting repeatedly, unlike honey bees; these do not die after stinging because their stingers are very finely barbed (only visible under high magnification) and can easily be withdrawn and so are not pulled out of their bodies when disengaging. The hornets are giant natural predators and play an important role in the balance of natural ecosystems through pollination, natural pest control and biodiversity [1].

Hornet species found in Asia shows similarity in behavior and genetics to European hornet (*Vespa crabo*). This species is widely distributed throughout Europe, Russia, North America and Northeast Asia. Wasps native to North America belong to genus *Dolichovespula* are bald-faced hornets, but really they are actually yellow jacket wasps. So far, over 30,000 species of hymenopteran wasps have been reported, among which hornet biodiversity. Worldwide, shows 22 recognized species of genus *Vespa* [2]. The most common types of wasps or hornets, they build nest, which is housed by one queen, who lays eggs and is attended by workers. Workers are genetically sterile, cannot lay eggs. Most species make exposed nests in trees and shrubs, but some like *Vespa orientalis* build their nests underground or in wood or mud cavities. In the tropics, these nests may last year-round, but in temperate areas, the nest dismantle over the winter, with lone queens hibernating in leaf litter or other insulative material until the spring. Hornets are often considered pests, as they aggressively guard their nesting sites when threatened and their stings can be more dangerous than those of bees [3] (table 1).

Source of information

For writing this comprehensive research review on hymenopteran toxins/allergens, various databases were searched. For the collection of relevant information, specific terms such as medical subject headings (MeSH) and key text words, such as "venom allergens", "biological and pharmaceutical effects", therapeutic uses" published till 2020 were used in MEDLINE. Most especially for retrieving all articles pertaining to the use of VIT for insect venom allergy, electronic bibliographic databases was searched and abstracts of published studies with relevant information on the venom toxins/allergens were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporation of recent knowledge, relevant research articles, books, conference proceedings and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including SCOPUS, Web of Science, and EMBASE, Pubmed, PMC, Publon, Swissprot, Google searches" From this common methodology, discoveries and findings were identified and summarized in this final review.

Venom composition

Hymenoptera venom is a complex mixture of many substances such as toxins, enzymes, growth factor activators, and inhibitors (table 1, fig. 1). These are bioactive agents which impose deleterious effects in cells and tissues after venom infliction. Parasitic solitary wasps use bioactive venom components with the functions of prey inactivation and physiology manipulation. Wasp, bee and hornet toxins, mainly proteins, show hemolytic and immune-stimulatory effects (table 1). Venom of *Neoponera villosa* induces hemolysis in human erythrocytes and also induced release of both pro-inflammatory cytokines, as the anti-inflammatory cytokine release by murine macrophages [4]. The various *Vespa species venom* contains kinins, polyamines and hornetin, which showed cytotoxic and anticancer activities (table 1). *Vespa vulagaris* secrete hyluronidase A an enzyme that is highly allergenic and shows cytotoxic activity. Bees also secrete acid phosphatase that *acts* as a

coagulation factor and show antimicrobial activity (table 1, fig. 1). Hornet venom contains enzyme phospholipase, acid phosphatase, and various phospholipases, appear to be relatively more specific to the social wasp venom (table 1). Hornet venom binds to a large number of proteins and receptors and imposes pathophysiological changes in victims. These enzymes cause the disruption of cellular membranes and induce hypersensitive reactions, including life threatening anaphylaxis. Moreover, phospholipase A2 is a major component of bee venoms, while phospholipase A1 (PLA1) is highly abundant in wasps and ants. Common components in both solitary and social wasp venoms include hyaluronidase, phospholipase A2, metalloendopeptidase (table 1, fig. 1). These enzymes trigger an immune response, inducing IgE response in susceptible individuals [5]. Some neurotoxic peptides (e. g., pompilido toxin and dendrotoxin-like peptide), proteins (e. g., insulin-like peptide-binding protein) and allergens also found in solitary wasp venom. Similar to venom found in most venomous animals, parasitoid venoms contain a complex cocktail of proteins with potential agrochemical and pharmaceutical use (table 1, fig. 1).

Enzymes

Phospholipase B (PLB)

Phospholipase B (PLB), also known as lysophospholipase, is an enzyme found in very low concentrations in hornet venoms. Phospholipase A2 (PLA2) is a calcium-dependent enzyme that hydrolyzes the Sn-2 ester of glycerol phospholipids to produce a fatty acid and a lysophospholipid. It destroys phospholipids, disrupting the integrity of the lipid bilayers, thus making cells susceptible to further degradation. In fact, PLA2 reaction products, such aslysophosphatidyl choline, lysophosphatidic acid and sphingosine 1-phosphate, can have cytotoxic or immune stimulatory effects on diverse cell types, causing inflammation and immune responses [6]. With the capacity to cleave acyl chains from both sn-1 and sn-2 positions of a phospholipid, PLB shows a combination of PLA1 and PLA2 activities. Hyaluronidase is commonly known as a "spreading factor" because it hydrolyzes the viscous polymer hyaluronic acid into non-viscous fragments. It also acts as an allergenic agent (table 1; fig. 1). When an extracellular matrix is destroyed by hyaluronidase, the gaps between cells facilitate the invasion of venom toxins (fig. 1). Therefore, venom penetrates in tissues and enters blood vessels, thus catalyzing systemic poisoning. Furthermore, hydrolyzed hyaluronan fragments are pro-inflammatory, pro-angiogenic and immune stimulators, thus inducing faster systemic envenomation [7].

Mast cell degranulating (MCD) peptide

Mast cell degranulating (MCD) peptide is cationic in nature, having 22 amino acid residues. It shows a similar structure to albumin. It is cross-linked by two disulphide bond [8]. This peptide is a potent anti-inflammatory agent; at low concentration, it is a strong mediator of mast cell degranulation and histamine release from mast cells, which are present in the blood supply and in all tissues perfuse by blood [9] (table 1; fig. 1).

Bradykinin

Bradykinin is a physiologically active peptide that belongs to the kinin group of proteins. Bradykinin and related kinins act on two receptors, designated as B1 and B2 (table 1). The former is expressed only as a result of tissue injury and it is thought to play a role in chronic pain. In contrast, the B2 receptor is constitutively expressed, participating in vasodilatation via the release of prostacyclin, nitric oxide, and endothelium-derived. Hyperpolarizing factor contributes lower blood pressure [10] (table 1; fig. 1).

Adolapin

Adolapin is a peptide that exerts a potent analgesic and anti-inflammatory effect in rats and blocks prostaglandin activity [11]. Tertiapin, also from bee venom, is a 21 amino acid peptide that blocks certain types of inwardly rectifying potassium channels [12] (table 1; fig. 1).

Scapin A

The peptides Scapin-1, and Scapin-2 are all 25 amino acid residues in length and share a similar secondary structure, with a disulfide bridge between Cys 9 and Cys 20. These peptides have been isolated from the venom various species, such as Scapin from European *Apis mellifera* [13]. Scapin-1 from Chinese *Apis mellifera* [14] and scapin-2 have been isolated the Africanized honey bee [15] (fig. 1, table 1).

Apamin

Apamin is bee venom peptide that acts as a neurotoxin and induces multiple physiological effects. Albumin acts mainly on the CNS. It blocks Na+K+ channels; in neurons and binds with high affinity to post-synaptic membrane receptors and causes hyper-polarization of adrenergic, cholinergic and purinergic nerve fibers. It also generates neurotensin-induced effects and blocks post-synaptic functions but does not show any lytic activity in mammalian cells [16] (table 1).

Proteases

Protease is an enzyme having high levels of proteolytic activity in connective tissues [17] and cause moderate necrosis [18]. It also occurs in venom of social wasp (*Polistes infuscatus), Vespa orientalis [19] Polybia paulista, Polybiaignobilis, Agelaia pallipes pallipes, Apoica pallens* and ant *(Eciton burchelli)* [20]. These insects also contain several isoenzymes, which are responsible for caseinolytic and gelatinolytic activities [21]. *Bombus* venom protease in association with PLA2, HYAL, and acid phosphatase havetrypticamidase specificity and having strong allergenic reactions. *Bombus* species such as *Bombus impatiens, Bombus fraternus, and Bombus bimaculatus* also exhibit trypticamidase activity [22], coagulant, [23] and hemorrhagic activities [24] (table 1).

Mastoparan-C (MP-C)

Wasp venoms also contain small molecules, such as minerals, amino acids, and physiologically active amines, such as catecholamines. Histamine is a major organic nitrogenous compound found in wasp venom that participates in the inflammatory response by increasing the permeability of capillaries. Few species of wasps such as *Ropalidia,Vespa xanthoptera*, *Vespa ducalis* and *Vespula lewisii* secrete mastoparan molecules that cause allergic inflammation and does mast cell degranulation in mammals (table 2, fig. 2). Different species of Yellowjacket wasps i.e. *Vespa flavopilosa, Vespula vidua, Vespula lewisii, Vespula pensylvanica* and *Vespula squamosa* secrete allergen 5 in their venoms which show anticancer activity (table 2, fig. 2). In addition, *Vespa orientalis*, *Paravespula maculifrons, Vespa xanthoptera* and paper wasp *Polistes exclamans* kinins are responsible for severe pain production and act as neuro-inhibitors (table 2, fig. 2).

Catecholamines, dopamine and nor-adrenaline increase heartbeat, thereby enhancing venom circulation and thus, its distribution [25]. Serotonin is a strong irritant that evokes contribute pain caused by venom. Finally, high levels of Acetylcholine increase perceived pain of a sting by stimulating pain receptors synergically with histamine effects. The black-bellied hornet *(Vespa basalis*) possesses highly toxic venom which is rich in toxin, enzymes and biologically active peptides. It also contains mastoparan B, protease and serotonin, which showed chemotactic activity on human neutrophils. These peptides also exhibit potent hemolytic activity. Serotonin imposes an edematous effect *on* victims. Mastoparan B is a cationic tetra decapeptide isolated from *Vespa basalis* show strong edematous and hemolytic activities. This hemolytic and edema-inducing activities of MP-B, is due to presence of Lys2 amino acid and Trp9 rupture membrane and generate hemolytic activity [26] (table 2, fig. 2).

Biological activities

Hymenopteran insects inflict a large amount of venom in the victim that causes massive inflammation, swelling and pain. It obstructs respiration due to extensive swelling of the tracheal region [27] and how very high lethality and systemic reactions after envenomation [28]. Usually, bees stung victims survived high in number [29] but sometimes stinging occurs in the neck region blocks respiration due to tracheal swelling. Severity of venom increase with increases in the quantity of venom injected [30]. Lethality increases with the age [31, 32] venom toxin hardly acts upon liver and kidney cells that make

metabolic alterations in the body [33], B lymphocytes, secrete a group of immunoglobulins and release γ interferons. Each immunoglobulin released from B-lymphocyte recognizes different epitopes and bind selectively [34-38]. Melittin is a major toxic component found in bee venom show diverse biological activity [39] (table 3, fig. 3). Similarly, venom of *A. dorsata, A. serene* and *A. florae* exhibited nearly identical lethal dose [40, 41]. Hornets deliver just a typical insect sting, while others are among the most venomous known insects. Single hornet stings are not in themselves fatal, except sometimes to allergic victims. Individual hornets can sting repeatedly; unlike honey bees, hornets do not die after stinging because their stingers are very finely barbed (only visible under high magnification) and can easily be withdrawn and so are not pulled out of their bodies when disengaging. Hornet venom imposes allergen-specific reactions and also regulates immune responses and makes physiological changes [42] (table 3, fig. 3).

Hornet stings are more painful to humans than typical wasp stings because hornet venom contains a large amount (5%) of acetylcholine (table 2). Hornets attack very fast in groups and use stings to kill prey and defend hives. Asian giant hornet (*Vespa mandarinia*) inflicts venom very quickly and cause human fatalities in Asian countries [43]. Its toxicity depends on the sting and and volume of venom injected into the host, and varies according to hornet species. Asian giant hornet venom can cause allergic reactions and multiple organ failure leading to death, though dialysis can be used to remove the toxins from the bloodstream. Allergic reactions are commonly treated with epinephrine (adrenaline) injection using a device such as an epinephrine auto-injector, with prompt follow-up treatment in a hospital. In severe cases, allergic individuals may go into anaphylactic shock and die unless treated promptly [44]. Hornets possess black and white with yellow head strips. Single hornet stings are not in themselves fatal, they cause allergic reactions in victims [45].

Peptides isolated from bees and wasps i.e. tropomyosin from *Orancistro cerus, drewsen, iRhynchium brunneum,* paramyosin from *Orancistro cerus drewseni, Rhynchium brunneum,* myosin from *Eumenes pomiformis* affect muscle contraction and assembly of contractile machinery in muscle cells (table 3; fig. 3). Chemotactic peptide and mastparan like peptide secreted from *Cyphononyx fulvognathus wasp venom* showed inflammatory activity due to the presence of *kinins and polymanines* (table 3; fig. 3). *Eumenes pomiformis secrete d*endrotoxin that is responsible for K^+channel blocking, while *Anopliussa mariensis* secrete α-pompilidiotoxin, *Batozonellus maculifrons* β-pompilidiotoxin cause paralysis and block Na^+ channels (table 3; fig. 3). *Vespa affinis* stings cause complications such as myocardial infarction and multiple organ failure. Hornet toxins, increase microvascular permeability and acute pulmonary edema as the primary pathology after envenoming (table 3; fig. 3). Early recognition of acute pulmonary edema in hornet stings is needed more appropriate diagnosis, more often high-quality treatments to avert deaths (table 3).

The wasp, *Agelaia pallipes pallipes* is one of the most aggressive species the Neotropical region, causing many stinging accidents every year, characterized by severe envenoming reactions. These peptides presented activity related to mast cell degranulation, hemolysis, or even the chemotaxis of leukocytes [46]. The *P. paulista* venom contains eighty-four venom proteins. The wasp stings action starts with the diffusion of venom through the tissues and and to the blood, it is followed by tissue hemolysis, inflammation, and allergy-played by antigen-5, PLA1, hyaluronidase, HSP 60, HSP 90, and arginine kinases [47]. Peptides isolated from the venoms of the honey bee (*Apis mellifera*) and the social wasps *Polybia paulista* and Proto nectar in asylveirae showed nociceptive (hyperalgesic) and edematogenic effects. Its venom possesses peptides Melittin (*Apis mellifera*), Polybia-MP-I, N-2-Polybia-MP-I N-2-Polybia-MP-I (*Polybia paulista*), protonectarina-MP-NH2 and Protonectarina-MP-OH (Protonectar in a sylveirae) [48] (table 3; fig. 3).

Hymenopteran stings induce uncontrolled inflammation that results in extensive tissue damage and IgE-mediated hypersensitivity reactions. Venom allergens cause local reactions to severe pain and intense pain. [49]. Inflammatory response initiates with the release and activation of pro-inflammatory cytokines and other mediators, such as nitric Oxide. Cytokines play important roles in mediating cell recruitment and activation necessary for inflammation and repair of tissue damage. Few lepidopteran insects impose allergic urticaria dermatitis and atopic asthma, coagulopathy, renal failure, and intra cerebral hemorrhage [50]. Eicosanoids mediate inflammation. Melittin acts as an anti-inflammatory drug as they have the capacity to inhibit PLA2 activity [51].]. It behaves much better than non-steroidal drugs, methotrexate, and other biological disease-modifying anti-rheumatic drugs [52, 53]. Bee venom shows protective and anti-inflammatory properties [54]. Normally, wearing of protective clothing reduce the risk of venomous stings, inflammation and pain (table 3). Polybia-MP1 (IDWKKLLDAAKQIL-NH2) is a lytic peptide from the Brazilian Wasp venom with known anti-cancer properties [55]. The venoms of bees, wasps, hornet, spiders, and scorpions possess pharmacologically active molecules which show anti-tumor and anti-cancer activity [56, 57] (table 3; fig. 3).

Melittin inhibits tumor cell growth and induces apoptosis. It could be used as a potential alternative or complementary medicine for the treatment of human cancers [58]. It acts as a natural detergent with the capacity to form, tetramer aggregates on membranes, which lead to disorders in the structure of phospholipid bilayers, changes in membrane potential, aggregation of membrane proteins, as well as the induction of hormone secretion [59]. Furthermore, this membrane disruption directly or indirectly leads to alterations in enzymatic systems, such as G-protein [60], protein kinase [61], adenylcyclase [62] and phospholipase [63]. Melittin can even inhibit calmodulin, a calcium-binding protein that plays a crucial role in cell proliferation [64]. Tumorous cells expose anionic phospholipids, mainly Phosphatidylserine, on the external leaflet of the plasma membrane [65]. Melittin displays anti-proliferative activity [66] and inhibit angiogenesis at cancerous sites [67]. Melittin-based recombinant immunotoxins prepared after fusion of genes that encoded an antibody fragment derived from the murine monoclonal Antibody K121 found effective *in vitro* [68]. Recombinant immunotoxin of melting Fused to an anti-asialo glycoprotein receptor (ASGPR) a single-chain variable fragment antibody (CA) shows anti-invasive activity in hepatocellular carcinoma cells [69]. More specifically, CTLA-4-targeted scFv-melting fusion protein acts as a potential immunosuppressive agent showed selective cytotoxicity assist in organ transplants [70]. Melittin coupled to avidin, when released induces immediate cell lysis [71] and stop cancer cell latency [72] (table 3; fig. 3).

Anti-parasitic activity

Insects possess anti-parasitic peptides, which show the much wider application in drug therapy. Both host insects and general arthropods, which live in association and co-exist with parasites, secrete anti-parasitic compounds. These compounds are used as an alternative medicine for the treatment of protozoa-related diseases, mainly caused by endemic parasites i.e. *Leishmania* sp., *Plasmodium* sp., and *Trypanosomes* [73]. AMPs isolated from crude animal venoms/secretions from bee/wasp venoms showed potential to treat protozoan-borne diseases [74] and become a new class of anti-malarial drugs. These antimicrobial peptides (AMP) derived from insect venom have multiple therapeutic use. Bee venom AMPs (anoplin, duramycin, mastoparan X, melting, TP10 and Vida3) specifically target sporogonic stages of *Plasmodium* for toxicity against a mosquito cell line and *P. berghei*ookinetes [75]. More exceptionally anoplin and mastoparanX, were found toxic in an *Anopheles gambiae* cell line at a concentration of 25 μM. Most AMPs affect membrane integrity and produce lethal pores in microorganisms, including protozoan pathogens, whereas others act on internal targets or by modulation of the host immune system.

These antimicrobial peptides successfully kill malaria parasites, *Plasmodium* spp., in their blood or mosquito stages, or both [76]. Venom Peptides from parasitoid wasps show strong anti-parasitic potential [77]. Venom components of *Asobara japonica* impair cellular immune responses of host *Drosophila melanogaster*. The endoparasitoid female wasp *Asobara japonica* naturally injects toxins that kill *Drosophila* larvae and Insecticidal venom is neutralized [78, 79] (table 3; fig. 3).

Antimicrobial activity

Antimicrobial peptides (AMPs) have been widely studied as an alternative to conventional antibiotics, especially for the treatment of drug-resistant infections [80]. Melittin shows strong antimicrobial properties due to its hemolytic nature. This venom peptide involves interactions with the lipid groups of the membrane [81, 82] and forms pores in the membrane and operate from various cellular actions such as orientation and aggregation states [83]. A hybrid undecapeptide derived from the well-known cecropin A and melittin showed antifungal and antibacterial activities. It also displays low cytotoxicity [84] similar to retro and retro-enantio analogs [85]. It also acts as an antibiotic and anti-malarial agent [86]. Despite the therapeutic efficacy of antimicrobial peptides, they show poor bioavailability *in vivo* caused by instability, cytotoxicity and hydrophobicity [87]. Antimicrobial peptides are also applied for fighting economically important plant pathogens [88]. In this category linear undecapeptides derived from cecropin-Melittin hybrids have been tested against phytopathogenic bacteria [89]. A peptide BP76 is also used for phytosanitary compositions [90]. Novartis has patented a method to produce contact lenses with an antimicrobial metal-containing layer-by-layer (LbL). In its Label design, at least one layer has a negatively charged polyphonic material, having-COO-Ag groups or silver nanoparticles. Melittin and its analogs display antiviral activities that are caused due to the selective reduction of the biosynthesis of some viral proteins. It is reported for the Melittin analog Hecate on herpes virus-1 [91] and strong melittin action on HIV-1-infected lymphoma cells [92]. Previously melittin was present to provide an improved composition complementary to azidothymidine (AZT) to inhibit the reverse transcriptase and growth of HIV-infected cells [93]. Melittin is also carried in a nanoparticle construct designed to be used as a topical vaginal virucide [94]. More specially, cationic antimicrobial peptide anoplin are lipophilic in show hemolytic activity and proteolytic stability [95]. AMPs from insect venom are antimicrobial"weapons" are promising antimicrobial Agents [96]. MP-V1 from the Venom of Social Wasp *Vespula vulgaris* displays much higher antimicrobial activity [97] (table 3; fig. 3).

Phospholipase A1 (vPLA1) from the black-bellied hornet (*Vespa basalis*) catalyzes the hydrolysis of emulsified phospholipids and shows potent hemolytic activity that is responsible for its lethal effect (table 3). AMPs from insects could be used as peptide antibiotics [98]. These could be used one kind of ideal alternatives of Synthetic pesticides and the development of novel antimicrobials. Nine different AMPs were isolated from the venom gland of the wasp *Vespa tropica.* These AMPs have been classified into two different families based on sequence similarity, mastoparan and vespid chemotactic peptides (VCPs), and named as mastoparan-VT1 to-VT7, VCP-VT1 and-VT2 [99]. Among these nine AMPs, mastoparan-VT1 and VCP-VT1 are identical to peptides from other wasps. These nine AMPs, mastoparan-VT1 and VCP-VT1 are identical to peptides from other wasps. These AMPs exerted broad-spectrum antimicrobial activity [100] (table 3; fig. 3).

Antiviral activity

The venoms of bees and wasps are complex mixtures of biologically active proteins and peptides, such as phospholipases, hyaluronidase, phosphatase, β-glucosidase, serotonin, histamine, dopamine and nor-adrenaline [101]. Bee venom and its components, i.e. melting (MLT), phospholipase A2 (PLA2), and albumin showed inhibitory effects against viruses, i.e. Influenza A virus (PR8), Vesicular Stomatitis Virus (VSV), Respiratory Syncytial Virus (RSV), and Herpes Simplex Virus (HSV) *in vitro* and *in vivo* [102]. Bee venom toxin peptide mastoparans and its derivatives show broad-spectrum antiviral activity against enveloped viruses [103]. More especially, mastoparan-derived peptide MP7-NH2 could inactivate viruses of multiple types and activate cell-mediated antiviral immune responses. Moreover, melittin a venom-derived peptide isolated from European honey bee *Apis mellifera* show anti-viral activity against human immunodeficiency virus (HIV) [104, 105]. It also demonstrates anti-cancer, anti-inflammatory, anti-diabetic, anti-infective, and adjuvant properties. Melittin also curbs infectivity of a diverse array of viruses, including coxsackie virus, enterovirus, influenza A viruses, human immunodeficiency virus (HIV), herpes simplex virus (HSV), Junín virus (JV), respiratory syncytial virus (RSV) Vesicular stomatitis virus (VSV), and tobacco mosaic virus (TMV). This peptide-based therapeutics are found effective against Human immunodeficiency virus (HIV), Influenza virus and Hepatitis virus B and C [106] (table 3; fig. 3).

Proteolytic activity

Trophallactic fluid secreted from larvae of wasps (subfamily-vespinae) possesses multi-cellular organisms. Larvae exhibit the capacity to fully digest and metabolize proteins [107] (fig. 1).

Analgesic activity

Normally opioid drugs are used as analgesics for sequential treatment of pain. Mastoparan Agelaia-MP I abundant class of peptides found in wasp venom. These show dose-dependent anti-nociceptive activity in mice. Agile-MP I induced partial and reversible blockade of the amplitude of action potential, probably interacting with voltage-gated sodium channels. It shows a significant potential impact on the central nervous system (CNS) [108]. Both melittin and albumin showed the anti-nociceptive effect to degenerative diseases of the nervous system. Venom enzymes and peptides show natural stability as an injectable solute, they also possess ability to synergize their actions by enhancing cell–cell interactions [109] (fig. 2).

Anti-diabetic

Diabetes is a metabolic disorder characterized by hyperglycemia resulting from perturbations in insulin secretion, insulin action or both. Diabetes, type 2 results in highest mortality rate worldwide. It occurs due to abnormal insulin secretion and patients display a state of impaired glucose tolerance to frank type 2 diabetes [110, 111]. For treatment of this storage disease/disorder insulin release mechanism is applied by injecting toxins isolated from animal venoms [112]. Venom toxin peptides induce electrical activity of the ion channels present in pancreatic β cells that are involved in the insulin secretion process**.** These interact and modulate the electrical activity of pancreas cells. It interacts and induces molecular, cellular and physiological mechanisms of insulin granule biogenesis. This initiates with the synthesis of pre-proinsulin in the rough endoplasmic reticulum and the conversion of pre-proinsulin to proinsulin. Proinsulin begins to be packaged in the Trans-Golgi Network and is sorted into immature secretory granules. These immature granules become acidic via ATP-dependent proton pump and proinsulin undergoes proteolytic cleavage that results in formation of insulin and C-peptide. During the granule maturation process, insulin is crystallized with zinc and calcium in the form of dense-core granules. It stops degradative pathways of insulin secretion and dense-core insulin granule synthesis in affected cells [113]. *Apis mellifera* bee tea showed anti-hyperglycemic and anti-diabetic activity [114] (table 3; fig. 3). Similarly, Iranian Honeybee (*Apis mellifera*) venom affect blood glucose and insulin in diabetic rats [115].

Antiseptic activity

Bracon hebetor, an ectoparasitoid showed dose-dependent abrogation of nitric oxide (NO) production. It suppresses the levels of pro-inflammatory mediators and cytokines without posing any cytotoxicity via the nuclear factor kappa B (NF-kB) and mitogen-activated protein [116]. Insect venom toxins show very strong action against human pathogens, which could act as anti-septic agents (table 3). Insect venom toxins are biologically active natural products [117] which could become a natural source of analgesics [118] (fig. 2).

Anti-oxidative activity

Bee Venom suppresses high fat diet-induced obesity by inhibiting adipogenesis. It enhances fat desorption [119]. Mastoparan-B is a toxin peptide isolated from the venom of *Vespa basalis* the most dangerous hornet found in Taiwan. MP-B, influences of mast cell degranulation and hemolytic activities (table 3). It acts as an antioxidant at low concentration in competing with nitric-oxide oxygen molecules and possesses good anti-oxidative enzyme

activities resembled to superoxide dismutase and glutathione peroxidase [120] (fig. 2).

Cytogenotoxic effects

The venoms of wasps are a complex mixture of biologically active low molecular mass compounds, peptides, and proteins (table 3). Venoms of *Polybia occidentalis* and *Polybia fastidious* act on the human leukocytes DNA and inhibit cell cycle. It severely affect constitution of genetic material in plant model *Lactuca sativa L.* (lettuce) [121] (fig. 2).

Insecticidal activity

Hymenoptera insects possess complex mixtures of toxins in its venoms which are used for self-defense, to repel intruders and to capture prey. These selectively target receptors found on brain cells of insects and stop insect movements. These could be used as good source for new insecticidal compounds for making new, highly potent drugs. Several insecticidal peptides or polyamine-like compounds have been purified and characterized from the venom of arachnids and hymenopterans [122]. These are used as bio-insecticides for insect control [123]. Venom toxin peptides show catalytic activity and form pores in biological membranes [124]. Peptides isolated from the venom of social Wasp *Charter gellus communis* (Hymenoptera: Vespidae) show hyperalgesic, edematogenic and hemolytic effects. Wasp origin peptides and proteinaceous toxins target voltage-gated sodium (NaV) channels could be used as pharmacological tools [125, 126]. Toxin-based bioactive drugs are mainly prescribed [127] for anaphylaxis and fatal sting management [128, 129]. It is also used in clinical treatments for *V. velutina* induced toxic reactions and allergic effects [130]. Hymenoptera venom allergens are also used for the rational design of component-resolved diagnosis of allergy, mainly for improving the outcome of venom immunotherapy (VIT) [131] (table 3, fig. 3).

Therapeutic uses

Melittin, hyaluronidase and PLA2 are the main component of bee venom which impose allergic reactions in man [132]. Melittin is an amphiphilic peptide comprising 26 amino acid residues, its amino-terminal region is predominantly hydrophobic and, the carboxyl-terminal region is hydrophilic. Melittin is the principal active component of apitoxin and is responsible for breaking up and killing cells. When several melittin peptides accumulate in the cell membrane, phospholipid packing is severely disrupted, thus it leading to cell lysis [133, 134] fig. 3). Melittin triggers not only the loss of a wide range of plasmatic membranes, but also of intracellular ones such as those found in mitochondria. PLA2 and melittin act synergistically, breaking up membranes of susceptible cells and enhancing their cytotoxic effect [135] Melittin induced cell damage, in turn, may lead to the release of other harmful compounds, such as lysosomal enzymes from leukocytes, serotonin from thrombocytes, and histamine from mast cells, which can all lead to pain ((table 3; fig. 3). Melittin is the most known bee venom peptide that is widely used in so many clinical applications. It acts as an immunologic adjuvant and therapies used for the treatment of rheumatoid arthritis, arteriosclerosis, cancer, and endosomolytic properties for drug delivery. It strongly acts like as an antibiotic and help to finish microbial infections. It is also used in antiretroviral therapy to reduce the passage of HIV-1 and to limit the viral load in infected people [136]. Both Melittin and its analogs are capable of eliciting strong immune responses against viral antigens. These reduce the risk of toxic side effects associated with the use of adjuvant [137]. Macrophages secrete pro-inflammatory cytokines, a main cellular component in the development of atherosclerotic plaques [138]. It dissolves atherosclerotic plaques formed in blood vessels and is used for the treatment of atherosclerosis [139, 140]. This molecular mechanism of the anti-atherosclerotic effects of melittin is established in mice models [141] (table 3; fig. 3).

Albumin is a peptide neurotoxin comprising 18 amino acid residues that tightly cross-linked by the presence of two disulphide bonds [142]. It shows many hyperpolarising-inhibitory effects, including alpha-adrenergic, cholinergic, purinergic, and neurotensin-induced relaxations [143]. Unlike melittin, apamin is a peptide with a highly specific mode of Action. It binds and occludes the pore of small conductance Ca2+-triggered K+channels (SK), thus acting as an allosteric inhibitor [144] and depressing delayed cell hyperpolarization. This binding specificity of albumin and its electrical properties could be exploited in biomedical research. Albumin acts mainly on the CNS, where SK channels are widely expressed [145] (fig. 3). SK channels are of three types based on their conductance and third small conductance (SK or K3) [146]. These channels are activated solely by increase in intracellular Ca2+contribute to regulating the excitability and function of many cell types, including neurons, epithelial cells, T-lymphocytes, and skeletal muscle cells [147]. SK channels are activated by sub micromolar concentrations of Ca2+, and this activation is mediated by calmodulin [148]. In excitable cells, the activation of SK channels generates a hyperpolarizing K+current which contributes to the after hyperpolarisation (AHP) that follows an action potential. This AHP modulates cell firing frequency and spike frequency adaptation, thereby influencing neuronal excitability. SK channels have been implicated in diverse physiological functions such as synaptic enhancement and long¬ term potentiation. Apamin injections accelerate acquisition of the bar-pressing response and also accelerate bar-pressing rates [149, 150]. Wasp and honey bee and hornet toxin peptides because convulsions due to presence of albumin a rigid octadecapeptide but it is no longer be considered an exclusive neurotoxin. [151]. Contrary to this apamin is show cellular toxicity in vital organs [152, 153] (table 3; fig. 3).

Hymenoptera venom allergy

Allergen immunotherapy (AIT) is used to desensitize the allergen injected by venomous insects. It successfully switches off the allergy over time and become an effective treatment for allergies to bee and wasp stings [154]. It is mostly used to stop systemic allergic sting reactions. This is also used for the treatment of chronic inflammatory disease, especially arthritis. Hymenoptera venom proteins and peptides are used for Diagnosis and treatment of venom allergic patients [155]. In allergen immunotherapy, hypo sensitization are considered for therapeutic purposes by changing the dose level. The effect depends to some degree on the original intensity of hypersensitivity [156]. Hypersensitivity is mostly developed in beekeepers because of frequent exposure of honey-bee stings. This long-term exposure to venom toxins induces immune tolerance in them. This is the main reason that the prevalence of systemic reactions to bee stings in beekeepers is very low (approximately 14% to 42%) while very high immune tolerance (67-90%) is observed due to continued exposure of toxins. All it happens after adaptive immune responses in them [157] (table 3; fig. 3).

Apitherapeutics

Apitherapy is an alternative therapy in which honey bee products are directly used against honey bees. Apitherapy is used to treat multiple sclerosis, arthritis, infections, and shingles. It is used to treat illnesses wounds, burns, tendonitis as well as pain and acute and chronic injuries. In Apitherapy, honeybee products are applied topically, or intake orally, or provided injection. Apitherapists promote the medical use of products from the beehive (bee venom, propolis, pollen, honey, royal jelly and dead bees. It is also a fact that the majority of patients show un-willingness to apitherapy because they feel that they cannot tolerate such treatments. Therefore, therapeutic modifications are needed for increasing acceptability [158] (table 3; fig. 3). It is true that significant numbers of modern-day pharmaceuticals are derived from natural products, mainly venoms of various origins show therapeutic potentials. In the present time due to the increasing rate of drug resistance of the pathogen organisms and target cells as well as the dependence or tolerance of the body towards the drug, venom toxins are seen novel candidates for making pharmaceutical agents. Wasp venoms are also a rich source of therapeutically important toxins, which includes short cationic peptides, kinins, polyamines and poly DNA viruses. These have diverse therapeutic significance.

Mode of action

Insect toxins comprise a diverse array of chemicals ranging from small molecules, polyamines and peptide toxins. Many target nervous systems and neuromuscular ion channels and so rapidly

affect the behavior of animals to which the toxin is applied or injected. Other modes of action have also been identified. Wasps, bees, flies, and ants generate a rich arsenal of channel-active toxins, some of which offer selective pharmacological probes that target particular ion channels, while others act on more than one type of channel. Philanthotoxins from the digger wasp target ligand-gated ion channels, both in the nervous system and at neuromuscular junctions. Apamin from bee venom targets calcium-activated potassium channels, which can in turn influence their lease of neuropeptides. Melittin acts on the membrane surface. Mastoparan is a powerful peptide toxin present in the venom of wasps. Its toxic actions can be engineered out, leaving a potent antimicrobial molecule of interest. Hymenopteran wasps contain albumin that interacts neuronal receptors and play an important role in prey paralysis in small insects [159]. This interaction may play a crucial role in most of the cellular process; formation of complexes, binding specificity could be utilized for the design molecules [160]. The crude honey bee (*Apis mellifera*) venom also acts on the skeletal, smooth as well as cardiac muscles. It also shows neurotoxicity of inhibitory nature involving the autonomic as well as neuromuscular system [160]. This secretory phospholipases A2 (sPLA2s) have specific receptors in brain membranes called N-type receptors. It binds to the N receptor recognition domain of the toxin. Neo nicotinoids are agonists of nicotinic acetylcholine receptors; they disturb acetylcholine receptor signaling leading to neurotoxicity. The main element which imposes this neurotoxicity is Phospholipase A2 that displays N-type receptor binding. Bee venom toxins also bind to to cell surface receptors, ion channels and ion gated channels or by passive diffusion by making pinholes in cellular parasites [161](fig. 3). Honey bee venom, shows induction of apoptosis in malignant cells [162]. It shows the inhibitory, anti-invasive and cytotoxic effect on several types of cancer lines [163]. Bee venom components melittin shows showed anti-proliferative and anti-metastatic properties and apoptosis in malignant glioma cells [164, 165] (fig. 3). These stops progression of cancer and inhibit metastasis in cancer cell lines [166]. Besides this, honeybees prepare a sticky substance (called propolis/bee glue) by mixing saliva poplar tree resin; this natural product shows therapeutic benefits against breast cancer. Milestone is also used as a Promising Adjuvant treatment for brain tumors [167-169]. Till date so many major toxins/allergens have been identified in many species of wasps and bees, which are of very high medical importance [170, 171]. These toxins have been characterized for their biological activity and their differential gene profiling has been done [172, 173]. There is need of molecular docking important data on toxins for development of effective therapeutics through A combination of transcriptomic, proteomic, peptidomic, glycemic and venomic approaches [174, 175] (fig. 3). More often, the data available in various databases on peptide toxins can be used for comparative transcriptome analysis of the venom sac and gland of several species [176-178]. It will assist in identifying its confirmatory biological activity in animal models [179, 180]. These toxin peptides can be used to develop new diagnostic and therapeutic approaches for the treatment of poisonous animal stings and bites [181]. Production of anti-venom serum against important toxins and allergens can be used in immunotherapy to encounter envenomation (table 3; fig. 3). Severe allergies or allergies may not be completely relieved by other treatments; hence, allergen immunotherapy can be applied. It involves a series of injections of purified allergen extracts, usually given over a period of a few years. No doubt hornet, honey bee and wasp venoms are of therapeutic and biotechnological use.

Table 1: Toxins found in wasp venom allergens and their molecular weight and biological effects

Species	Toxin	Mw	Biological effects	Source
Vespa, *protopolybia*	Kinnin and polyamines	32,000	Cytotoxic, anticancer	24
Vespa flavitarsus	Hornetin	32,000	Antimicrobial, anticancer, neurotoxicity	25
Vespa vulagaris	Hyluronidase A	43000	Cytotoxic	98
Polibia polista	Cationicpepetides (Polibia MP-1)	1611.98	Antifungal	120
Bees	Phospholipase A_2	16000 14500 (–CHO)	Hydrolysis of lecithins	174
Bees, wasps	Hyaluronidase	43000 39000 (–CHO)	Allergenic activity	174
Bees	Acid phosphatase	48000 (monomer)	Inflammation, coagulation factor, apoptosis of ovarian cells, antimicrobial activity	174
Honeybees	Melittin	11360 (tetramer)	cytotoxic effect	174
Bumblebees	Tryptic amidase	27250	Proteolytic activity	174
Wasps, ants	Phospholipase A_1B	33500	Allergenic activity	174
Wasps, ants	Antigen 5	23000	Pain, allergenic activity	174
Fire ants	Sol 2	26432 (dimer)	Antimicrobial activity	174
Fire ants	Sol i 4	13340	Antimicrobial activity	174
Jack-jumper and bulldog ants	Myr p 1	9103 (precursor)	Antimicrobial activity	174
Jack-jumper and bulldog ants	Myr p 2	8144 (precursor)	Antimicrobial activity	174

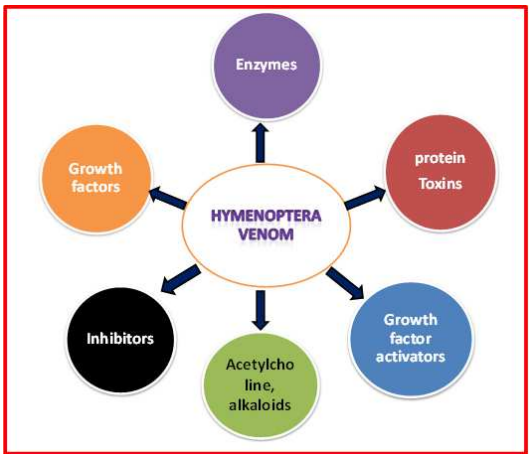

Fig. 1: Hymenopteran venom toxins and its constituent molecules

Table 2: Showing major hymenopteran insect venom derived toxins/allergen with their major biological activity

S. No.	Species name	Common name	Allergen type	Biological activity	Source
1.	*Vespa mandarinia*	Asian giant hornet	Allergen5, chemotactic peptide	Inflammatory activity, antimicrobial activity, causes allergic reaction in human	1
2.	*Vespa velutina*	Asian predatory wasp	Agatoxinlike, analgesic polypeptide, oriento toxin like peptide	Hemolytic activity, paralysis (calcium channel blocking),	5
4.	*Vespa bicolor*	Black shield wasp	Mastoparan	Allergic inflammation (mast cell degranulation)	5
5.	*Vespa crabo*,	European hornet	Calsyntenin, leucine-rich repeat domain containing protein	Paralysis (calcium channel blocking), antimicrobial activity	5
6.	*Vespa xanthoptera*	Japanese yellow hornet	chemotactic peptide	Inflammatory activity, antimicrobial activity	5
7.	*Vespa affinis*	Lesser banded hornet	Phospholipase A1	Production of lipid mediator	6
8.	*Vespa germanica*	German or European wasp	Allergen 5	Allergenic activity	7
9.	*Agelia pallipes*	Agalia	Wasp chemotactic peptide	Allergenic inflammation Antimicrobial activity, mast cell degranulation	7
10.	*Agelia vicina*		AV, Tx 7,8	Paralysis (K^+channel blocking)	7
11.	*Dolicho vespula maculate*	Yellowjackets	Allergen 5	Allergenic activity	7
12.	*Vespa orientalis*	Oriental hornet	Oriento toxin like peptide	Paralysis (pre-synaptic effect, lysophospholipase activity	19
13.	*Protopolibia exigua*	Neotropical social wasp	Mastopran	Allergic inflammation, mast cell degranulation	24
14.	*Polistes infuscatus*	Golden or northern paper wasp	Allergen5, wasp kinin	Pain, allergenic activity	19
15	*Polistes infuscatus*	Paper wasp	Wasp kinin,mastoparan	Pain production, allergic inflammation(mast cell degranulation)	19
16	*Polistes jadwiqae*	Paper wasp	Wasp kinin,mastoparan	Pain production, allergic inflammation(mast cell degranulation)	19
17.	*Paravespula lewisii*	Yellowjackets	Wasp chemotactic peptide	Inflammatory activity, antimicrobial activity	19
18.	*Paravespula maculifrons*	Western yellow jackets	Wasp kinin	Pain production	19
19.	*Protonectarina sylveira*	Brazilian wasp	Wasp chemotactic peptide	Inflammatory activity, antimicrobial activity	48
20.	*Polistes exclamans*	Paper wasp	Wasp kinin, allergen 5	Pain production, allergenic activity	89
21.	*Vespa tropica*	Oriental hornet	Wasp kinin, mastoparan	Pain production, Allergic inflammation (mast cell degranulation)	99
22.	*Polistes major*	Paper wasp	Wasp kinin	Pain production	90
32.	*Vespa basalis*	Black-bellied hornet	Dipeptidyl peptidase IV	Metabolism of organic compound	120
23.	*Ropalidia*	Yellow jackets	Mastoparan	Allergenic inflammation(mast cell de-granulation)	170, 171
24.	*Vespa xanthoptera*	Japanese yellow hornet	Wasp kinin, Mastoparan	Pain production, allergenic inflammation(mast cell degranulation)	170, 171
25.	*Vespa analis*	Yellow-vented hornet	Leucine-rich repeat domain containing protein, wasp kinin, mastopran, acetylcholinesterases,	Paralysis, pain, allergic, hemolytic factor, inflammatory response, synaptic organization, coagulation factor	170, 171
26.	*Vespa ducalis*		Mastoparan	Allergic inflammation (mast cell degranulation	170, 171
27.	*Vespa flavopilosa*	Red wasp	Allergen 5	Allergenic activity	170, 171
28.	*Vespula lewisii*	Italian wasp	Mastoparan	Allergic inflammation (mast cell degranulation	170, 171
29.	*Vespula pensylvanica*	Western yellow jacket	Allergen 5	Allergenic activity	170, 171
30.	*Vespula squamosa*	Southern yellow jacket	Allergen 5	Allergenic activity	170, 171
31.	*Vespula vidua*	Long yellow jacket or widow yellow jacket	Allergen 5	Allergenic activity	170, 171

Table 3: Toxin peptides found in various species of wasp, bee and hornet with its biological activities

Species	Peptides	Biological activities	References
Eumenes pomiformis	Dendrotoxin-like	Paralysis (K^+channel blocking)	175, 177
Anterhynechium flavomarginatum	Mastoparan-like	Allergic inflammation Antimicrobial activity	175, 177
Cyphononyx fulvognathus	Wasp chemotactic peptide	Inflammatory activity Antimicrobial activity	175, 177
Orancistro cerus drewseni	Tyrosine 3-monooxygenase	Regulation of dopamine synthesis	175, 177
Orancistro cerus drewseni Rhynchium brunneum	Actin	Regulation of hemocyte cytoskeleton gene expression	175
Orancistrocerus dresweri	Arginine kinase	Paralysis	175
Rhynchiumbrunneum	ATP synthase	ATP synthesis	176, 177
Eumenes pomiformis	Alcohol dehydrogenase	Oxidation of ethanol to acetaldehyde	177
Eumene spomiformis	Glutamate decarboxylase	Involvement in beta-cell-specific autoimmunity	177
Eumenespomiformis	Insulin-like peptide-binding protein	Developmental arrest (Inhibition of insulin signaling)	177
Eumene spomiformis	HECT E3 ubiquitin ligase	Regulation of cell trafficking	177
Eumene spomiformis	Hyaluronidase	Venom dissemination	177, 178
Rhynchium brunneum	Farnesoic acid *O*-methyltransferase	Regulation of biosynthetic pathway of juvenile hormone	178
Rhynchium brunneum	Acetyl-CoA synthase	Involvement in metabolism of acetate	178
Rhynchium brunneum	Amidophosphoribosyltransferase	Regulation of cell growth	178
Rhynchium brunneum	Cytochrome P450 monooxygenase	Metabolism of toxic compounds	178
Rhynchium brunneum	Carboxylesterase	Lipid metabolism	178
Rhynchium brunneum	Citrate synthase	Catalyzing the citric acid cycle	178
Rhynchium brunneum	DNA-directed RNA polymerase	Synthesis of mRNA precursor	178
Rhynchium brunneum	Glyceraldehyde-3-phosphate dehydrogenase	Direct hemolytic factor	178
Rhynchium brunneum	Glycogenin	Synthesis of glycogen	178
Rhynchium brunneum	Myo inositol monophosphatase	Regulation of inositol homeostasis	178
Rhynchium brunneum *Eumenespomiformis*	Phospholipase A2	Hydolysis of lecithins	177, 178
Rhynchium brunneum	Protein tyrosin phosphatase	Regulation of cellular processes	178
Rhynchium brunneum	Serine/threonine-protein phosphatase	Regulation of biochemical pathways	178
Orancistro cerus drewseni	Metalloendopeptidase	Inhibition of platelet aggregation	177, 178
Rhynchium brunneum	Neprilysin	Inhibition of platelet aggregation	178
Rhynchium brunneum	Ankyrin	Attachment of membrane proteins to membrane cytoskeleton	178
Orancistro cerus drewseni Rhynchium brunneum	Bmkettin	Development of flight muscles	176, 178
Orancistro cerus drewseni Rhynchium brunneum *Eumenespomiformis*	Calponin	Regulation of myogenesis	176, 178
Orancistro cerus drewseni Rhynchium brunneum *Eumenespomiformis*	Muscle LIM protein	Regulation of myogenesis	176, 178
Orancistro cerus drewseni *Eumenes pomiformis*	Muscle protein 20 Myomesin	Regulation of muscle contraction	176, 178
Rhynchium brunneum	Myosin heavy chain	Regulation of muscle functions	179
Orancistroceru drewseni Rhynchium brunneum *Eumenes pomiformis*	Myosin light chain	Modulation of the affinity of myosin for actin	176, 178
Orancistr oceru sdrewseni Rhynchium brunneum Eumenespomiformis	Paramyosin	Regulation of thick filament in muscles	176, 178
Orancistrocerus drewseni Rhynchium brunneum Eumenespomiformis	Titin	Assembly of contractile machinery in muscle cells	176, 178
Orancistro cerus drewseni Rhynchium brunneum	Tropomyosin	Muscle contraction	176, 178
Orancistro cerusdrewseni Rhynchium brunneum	Troponin	Muscle contraction	176, 178
Orancistrocerus drewseni Rhynchium brunneum Eumenespomiformis	Tubulin	Regulation of hemocyte skeleton genes expression	176, 178
Rhynchium brunneum	Chemosensory protein	Transferring metabolism-related small molecules	178
Orancistrocerusdrewseni Rhynchium brunneum	Cytochrom C	Protein wire	176, 178
Orancistro cerus drew seni Rhynchium brunneum *Eumenes pomiformis*	Heat shock proteins	Prevention of protein misfolding	175, 178
Rhynchium brunneum	Sialin	Nitrate transporter	179
Rhynchium brunneum	Sugar transporter	Maintenance of glucose homeostasis	179
Batozonellusmaculifrons	β-pompilidiotoxin	Paralysis (Na^+channel blocking)	181
Anoplius samariensis	α-pompilidiotoxin	Paralysis (Na^+channel blocking)	181

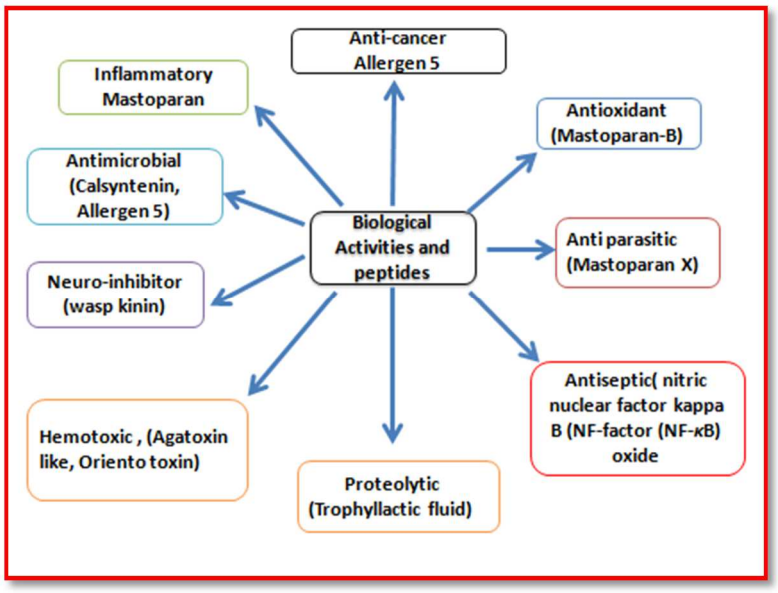

Fig. 2: Hymenopteran venom toxins and its various biological activities

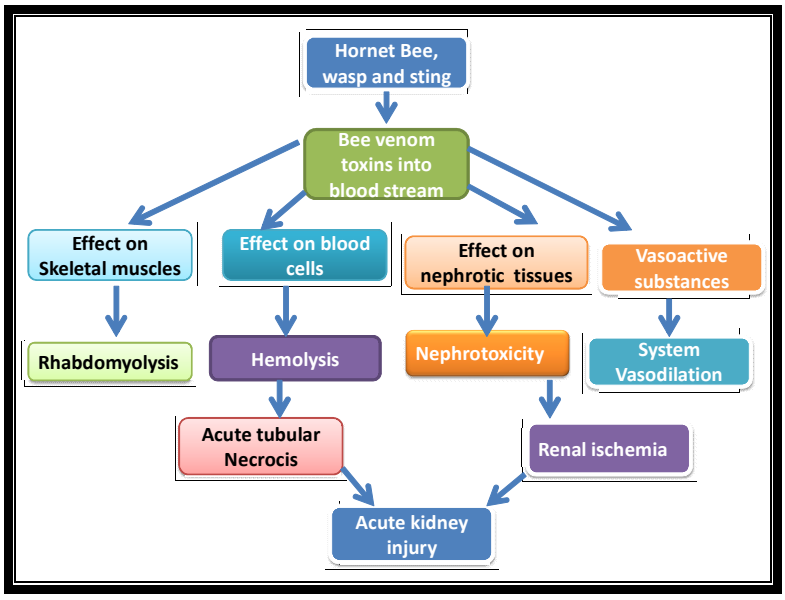

Fig. 3: Hymenopteran venom toxins and its effect on vital organ systems

CONCLUSION

Hymenoptera venom is a complex mixture of many substances such as toxins, enzymes, growth factor activators, and inhibitors. It contains few biologically important enzymes, i.e. phospholipases acid phosphatase, Proteases and therapeutically important peptides such as Mastoparan-C (MP-C), scapin A, apamin, Mast cell degranulating (MCD) peptide, Bradykinin, AMPs which display diverse therapeutic potential. Hymenopteran insect venom toxins are highly specific as they show diversity in structure and function. Insect venom is a good source of proteinaceous toxins and enzymes mainly smaller protein toxins, and non-proteinaceous molecules. These components are highly active toxic agents as they generate multiple clinical and pathophysiological changes such as severe inflammation and pain. Bee venom is also used in healing treatment for various disorders. More especially bio-molecules found in hornets, bees and wasps have shown anti-tumor and anti-cancer activity, antioxidant, anti-parasitic, antiseptic, proteolytic, catalytic, hemotoxic, neuro-inhibitor, anticancer, antimicrobial, immune hypersensitive, inflammatory, antimicrobial and anti-insect activities. Insects possess anti-parasitic peptides which show much wider application in alternate drug therapy. These compounds are used as an alternative medicine for the treatment of protozoa-related diseases, mainly caused by endemic parasites: *Leishmania* sp., *Plasmodium* sp., and *Trypanosomes*. Honey bee venom shows an anti-parasitic effect against *Entamoeba histolytica* and *Giardia lamblia* trophozoites in the sub-culture method due to quick transport through a membrane or their binding. Venom toxin structures are also important and there is a need to make interconnection among biochemistry, pharmacology and immunology areas for the expansion of knowledge and for the generation of innovation in the field of therapeutic and pharmaceutical research.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no competing financial interests.

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