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Chapter 3

Pharmacological and Immunological Properties of Wasp Venom

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Additional information is available at the end of the chapter

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1. Introduction

Animal toxin envenomations have medical as well as ecological significance. Toxin-producing animals are categorized under either venomous group or poisonous group. Venomous animals are capable of producing and delivering the toxin during a biting or stinging act whereas poisonous animals are those whose tissues, either in whole or in part, are toxic. [1] About 75% of the world's animal species are arthropods—a few of which have appreciable interaction with humans and is capable of causing significant medical problems. [2] Hymenopterous insects, snakes and spiders are the three animal groups most often responsible for human deaths attributable to venomous animals. [1] However, the evolution of venom in these animals has its own purpose of balancing the ecosystem and maintaining its position in the food chain. Hymenoptera is an insect order under phylum arthropoda. It is the third largest of all insect order, and perhaps the most beneficial to humans. The order Hymenoptera comprises approximately 115,000 described species which includes wasps, bees, ants, ichneumons, calchids, sawflies etc. Collectively, the Hymenoptera are most important to humans as pollinators of wild and cultivated flowering plants, as parasites of destructive insects and as makers of honey and beeswax. Nonetheless, the order poses significant public health concern as well. [3] The three medically important group of stinging insect of the order Hymenoptera belong to the families of Apidae (bees), Vespidae (paper wasps, hornets and yellow jackets, commonly referred as *wasps*) and Formicidae (ants). [4] The sting from these social wasp become clinically significant if the patient is allergic to Hymenoptera venom or if the patient is exposed to large quantity of the venom due to massive or multiple stings. Most deaths related to wasp stings are the result of immediate hypersensitivity reactions causing anaphylaxis. A single sting is sufficient to cause fatal anaphylaxis in hypersensitive patients. Massive enve-

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nomation can, likewise, cause death in non-allergic individuals, probably due to the toxic effects of the venom. A wide range of clinical sequelae is observed during wasp stings—from simple allergic skin manifestations to severe systemic reactions and toxic reactions leading to death. [5] Wasps, being highly diverse insects, are solitary or social, parasitic or predatory, phytophagous or carnivorous or omnivorous.

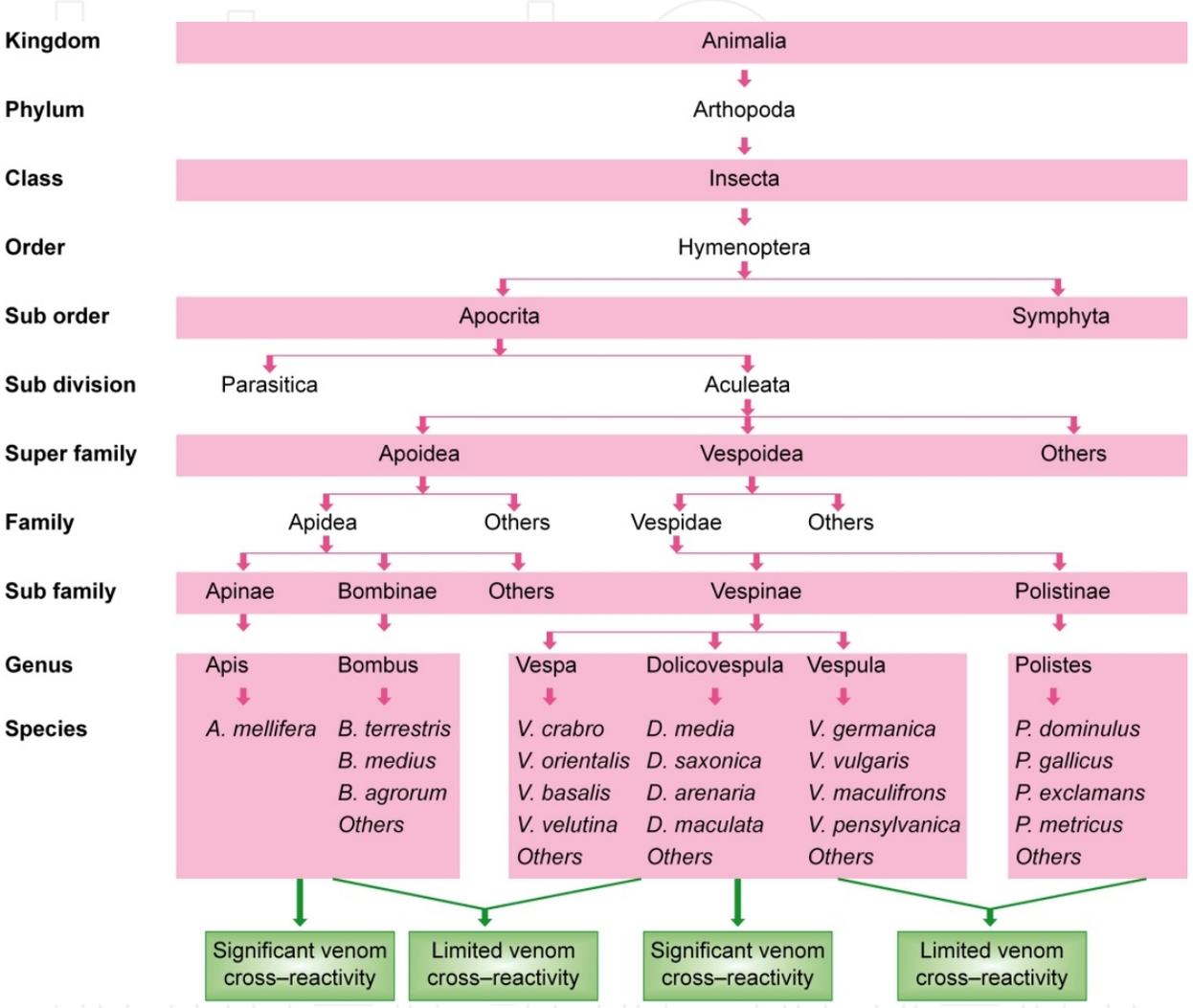

Figure 1. Taxonomy of Hymenoptera and cross reactivity of their venoms.

2. Epidemiology of stings

The insect order Hymenoptera is established on every continent except Antarctica. [6] In countries with predominantly moderate climate, they are present in the environment for a larger part of the year. [7] The season for wasp starts from spring and lasts till early fall. The stinging incidents are high during late summer and early fall with the numbers reaching a peak in August. [5] Various environmental factors such as temperature, humidity, solar radiation, rainfall and

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wind speed influences the wasp activity. Activities occurred at all temperatures above 7°C and below 41°C with maximum activity occurring between 20 – 35°C. [8]

The epidemiology of hymenopteran stings occur often throughout the world; more prevalent in adult males involved in outdoor occupations or hobbies. Among the hymenopterans, the sting is more often from vespids, particularly paper wasps and yellow jackets (not hornets), than apids, such as bumblebees and honeybees. [9] Single stinging events usually occurs when large number of hungry wasps are attracted to the food of humans eating outdoor or if it is accidentally stepped on, swatted or otherwise disturbed. In contrast, mass stinging events occur when wasps respond to a human intruder as a threat to their colony, for example, when someone inadvertently stumbles into a colony or otherwise disturbs their hives by throwing rocks at or shooting at or chopping a tree containing the colony. [10] Many times the incident takes place when the adults set fire on the colony to collect the larva which is considered very nutritious. Such practice is very common in the countryside.

Limited and under-estimated data exist on the epidemiology of hymenopteran stings. Depending upon the climate, 56.5 – 94.5 % of the general adult population remember receiving hymenoptera sting at least once in his life. The prevalence of sensitization, which is indicated by a positive skin test and/or detection of specific IgE in patients with no previous case history, is estimated between 9.3 – 28.7 % in adults. The prevalence of large local reactions in the general population ranges from 2.4 – 26.4 %, up to 38 % in beekeepers. European epidemiological studies reports a prevalence of systemic reactions between 0.3 – 7.5 % among the adults whereas in the USA, the prevalence ranges form 0.5 – 3.3%. [7,11]

3. Components present in the wasp venom: Classification, list, structure and function

Wasp venom components are generally categorized as: a) high molecular weight proteins that includes phospholipases, hyaluronidases, antigen 5 etc.; b) low molecular weight peptides that includes mastoparans, wasp kinins and chemotactic peptides, and c) bioactive molecules such as histamine, serotonin, catecholamines, acetylcholine, tyramine etc..

Vespid venom is more variable in their composition among the species, different to that of apid (bee) venom. They are complex mixture of powerful allergens and pharmacologically active compounds, primarily made up of proteins. The vespid venom contains three major proteins that act as allergens and a wide variety of vasoactive amines and peptides. The important allergens are antigen 5, phospholipases and hyaluronidase. Antigen 5 is the major allergen in all vespid venom and has been most thoroughly studied among the others. [4] Two additional proteins, Vmac 1 and Vmac 3 from *V. maculifrons*, with allergenic activity have been described, but are incompletely characterized. [4, 12] Similarly, serine-protease has been identified as an important allergen for vespid-allergic individuals in European *Polistes* [13, 14] venom and dipeptidylpeptidase IV [15] and vitellogenin [16] in *V. vulgaris* venom. The vasoactive amines in vespid venom includes serotonin, histamine, tyramine and catecholamines. Wasp kinins and mastoparans are the peptides unique to vespid venom.

3.1. Antigen 5

Animal tests have shown that antigen 5 is not a toxin. [17] It is a member of a conserved family of proteins found in eukaryotes, including yeasts and have sequence identity with other proteins of diverse origin and tissues, such as mammalian cystein-rich secretory proteins in salivary and reproductive organs, secretory proteins of helminths produced during sexual maturation, human brain tumor proteins, reptile venom, pathogensis-related proteins of plants and fire ant venom. [17, 18] The mature antigen 5 from yellow jacket and hornet have 201 and 205 amino acids respectively, with several highly conserved regions. Almost all of the sequence variations seen in hymenoptera antigen 5 were found on the surface. The highly cross reactive groups within the genera have few changes. The antigen 5 homolog from ants do not exhibit antigenic cross reactivity with those from vespid wasps due to the low degree of surface conservation and changes in loop lengths. [18] However, in hyperimmune sera, occasionally, antigenic cross reactivity has been observed between vespid antigen 5 and homologs from other animals. [19]

3.2. Phospholipases

The wasp venom phospholipase (PL) belongs to a different superfamily than those of bee venom phospholipase. Vespid wasp phospholipases have PLA_1B specificity and are members of GX class lipase, lipoprotein lipase superfamily, pancreatic lipase homologous family and RP2 sub-group of phospholipase. [18, 20] The PLs from vespid wasp venom usually do not contain carbohydrate and have highly homologous regions surrounding the active sites. The cross reactivities of the PLs generally follow the phylogeny: closely related species are highly cross reactive and those that are further removed are less cross reactive.

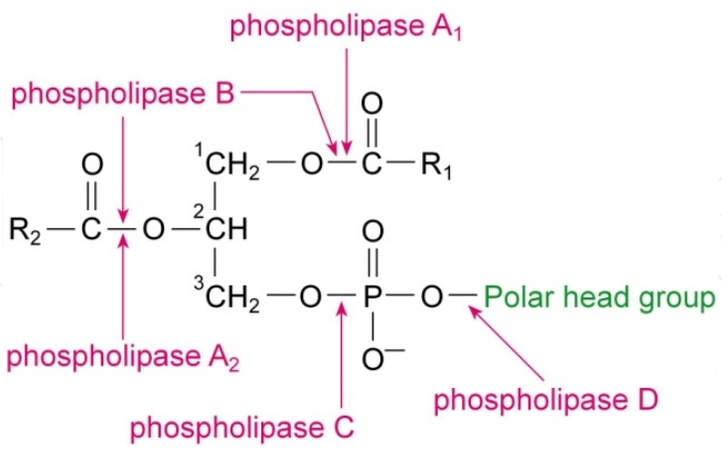

Figure 2. Site of Phospholipase action.

The characterized PLs in vespid venom are PLA_1, PLA_2 and PLB. The vespid venom PLs has an offensive as well as defensive role. The venom is not only used as toxins for preyed insects,

but also digests their cell wall components of diacylphospholipids such as phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine to fatty acids and lysophospholipids by the containing PLs. PLBs are more universally digestive enzymes than PLA_1 and PLA_2, which seems to be a kind of enzymatic adaptation of the carnivorous insects, i.e, vespids against vegetarian insects, i.e, apids that contain only PLA_2 in the venom. Besides the enzymatic activity, PLBs also possesses the haemolytic activity and cardiotoxicity. [21]

Phospholipase A_1 (PLA_1) is an enzyme that hydrolyzes ester bonds of phospholipids at the *sn*-1 position and produces 2-acyl-lysophospholipids and fatty acids. Vespid-venom PLA_1s belong to the pancreatic lipase family and exhibit PLA_1 activities but do not show any lipase activities. The tertiary structure of lipases have two surface loops, the lid and the β9 loop, which covers the active site and are implicated in substrate recognition. The amino acid sequence alignment of the pancreatic lipase family members (eg, phosphatidylserine-specific PLA_1 (PS-PLA_1), membrane-associated phosphatidic acid-selective PLA_1 (mPA- PLA_1), vespid PLA_1, hepatic lipase (HL), endothelial lipase (EL), pancreatic lipase, and pancreatic lipase-related protein 2 (PLRP2)) revealed two molecular characteristics of PLA_1s: first, lipase members exhibiting PLA_1 activity have short lids; and second, lipase members exhibiting only PLA_1 activity have short β9 loops. Thus, pancreatic lipase and LPL which exclusively exhibit triacylglycerol lipase activity have long lids and long β9 loops, while PS- PLA_1, mPA- PLA_1, vespid PLA_1 which only shows PLA_1 activity have both short lids and short β9 loops whereas EL and PLRP2 which exhibit both PLA_1 and triacylglycerol lipase activity have short lids but intact β9 loops [22, 23] PLA_1, thus, possess direct cytolytic effects, besides their role in allergic and inflammatory processes.

PLA_2 catalyzes the specific hydrolysis of ester bonds at the *sn*-2 position of 1,2-diacyl-3-*sn*-glycerophospholipids into their corresponding lyso compounds with release of free fatty acids. Thus, it is able to disrupt the phospholipid packings from several types of biological membranes leading to pore formation and/or cell lysis. [20, 24] Vespid PLA_2 has very potent cytolytic actions.

3.3. Hyaluronidase

Hyaluronidases (Hyal) are a widely distributed glycoside hydrolases that cleaves β-1,4-glycosidic bonds between N-acetylglucosamine and D-glucuronic acid of hyaluronic acid (HA) [14], one of the primary components of the extracellular matrix in all the vertebrates. They are also present in almost all venoms, acting as a "spreading factor" by facilitating the penetration of the other harmful venom components and enhancing their action in various tissues into the bloodstream. They are the "allergenic factors" in vespid and apid venom and are able to induce severe and fatal anaphylactic IgE-mediated reactions in humans. [25] They are the phylogenetically most strongly conserved Hymenoptera allergens. Sequence homologies between *Vespula* and *Dolichovespula* species hyaluronidases are 90% or greater, whereas those for antigen 5 and PLA_1 are only around 60% to 65%. In agreement with this, immunologic cross-reactivity between different vespid genera is strong with hyaluronidases but more restricted with antigen 5 and PLA_1. Vespid hyaluronidases are significantly similar with honey bee hyaluronidase which shows 50% sequence homology with vespid homologs Ves v 2, Ves

g 2 and Dol m 2. In accordance with this, hyaluronidases have been identified in inhibition studies using patients' sera as the most important cross reactive allergens in yellow jacket and honeybee venom. [14]

Hyaluronidase of wasp venom is an allergen. The asparagine-linked carbohydrate often appears to constitute the common IgE-binding determinant. Irrespective of the nature of the protein, protein-linked glycans can bind IgE, which turns many proteins, especially those of higher molecular mass, into apparent allergens. Hyaluronidase is the dominating glycoprotein in the wasp venom and contains α-1,3-fucose-containing N-glycan which is responsible for allergenicity. The cross-species survey performed by Kolarich et al shows that venom from six wasp species (*V. vulgaris, V. germanica, V. flavopilosa, V. maculifrons, V. pensylvanica* and *V. squamosa*) contained the difucosylated paucimannosidic N-glycans MUF^3F^6 and MMF^3F^6 as the major glycan structures. [26] The allergic response is initiated by the epitope that cross-links the Fc-receptor-bound IgE antibodies on the surface of mast cells. This is followed by rupture of mast cell membrane and the release of stored mediators, such as histamine, which are responsible for the immediate type hypersensitivity reaction. [27]

Hyaluronidases, on the basis of mechanism of action, are classified into three classes: a) the group of endo-β-N-acetyl-D-hexosaminidases that hydrolyse the high molecular weight substrate (HA) to tetrasaccharide as the main end product, represented by the testicular enzymes; b) the β-endoglucuronidases group represented by hyaluronidases from leeches and hookworm, and; c) the group of lyases that act via β-elimination, yielding disaccharides as the main products represented by the bacterial hyaluronidases. The enzymes of the first class also catalyses transglycolation reactions, producing hexa-, di- and octa- saccharides during hydrolysis of HA. Hymenoptera venom hyaluronidases belong to the first class. Unlike the latter two classes of hyaluronidases, this first class acts not only on HA, but also on chondroitin 4-sulfate and chondroitin 6-sulfate. [25]

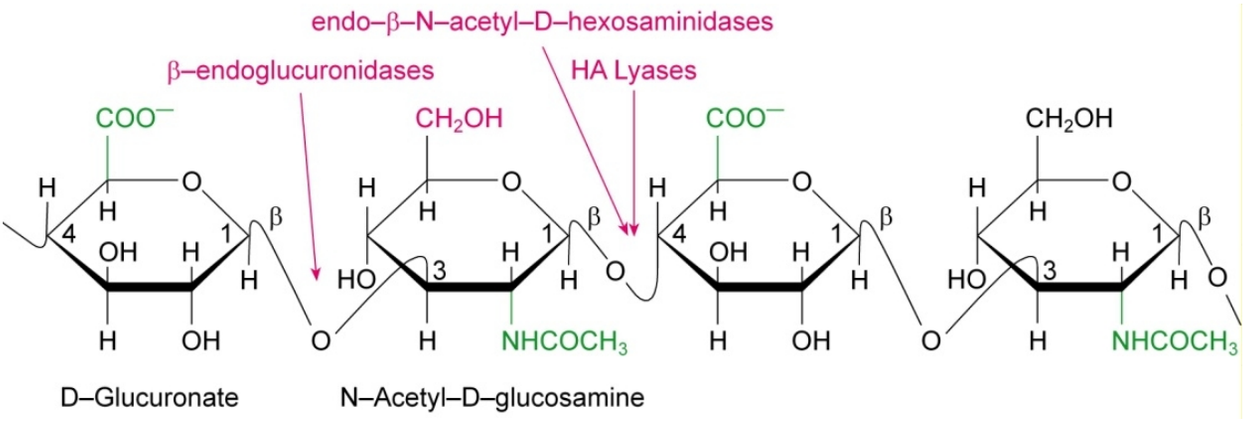

Figure 3. Hyaluronic Acid and Site of Action of Different Hyaluronidases.

3.4. Mastoparan

Mastoparans are low molecular weight peptides, generally tetradecapeptides, extracted from the venom sac of social wasps that act in the defense system of these insects. They are rich in hydrophobic and basic residues which are distributed in the peptide chain in such a way that, in adequate environment, they form amphipathic helical structures [28] which favours electrostatic interactions with the negatively charged phospholipid head groups of the biological membranes. This characteristic may lead to peptide insertion into the membrane bilayer and thus interact directly with G proteins on the cytoplasmic face attacking the transmembrane signalling [29] and sometimes to membrane destabilization with its consequent lysis. [30, 31] These peptides, thus, present important biological activities such as antimicrobial, mast cell degranulation, haemolytic activities, [28] activation of G-protein mediated mechanisms, stimulation of phospholipase A_2, C and D, mobilization of Ca^{2+} from mitochondria and sarcoplasmic reticulum, activation of ryanodine receptor, modulation of various enzymes, such as Na^{+}-K^{+}-ATPase of rat brain, induction of the mitochondrial permeability transition and cell death by necrosis and apoptosis. [32]

Mastoparans are discovered in wasp venom in a screening test for mast cell degranulating agents. They are also the potent stimulants of purified PLA_2 from different sources. They bind to phospholipids making them the better substrates. They facilitate the PLA_2 of both venom and victim, thereby promoting generation of arachidonic acid, the precursor of prostaglandins and leukotrienes which are mediators of adverse reactions associated with immediate type hypersensitivity. The high affinity binding of mastoparan to calmodulin has led to speculate the role of the peptides in inhibition of calmodulin-mediated reactions. [33] Mastoparan is a potent stimulator of exocytosis from diverse mammalian cells. It causes secretion of histamine from mast cells, serotonin from platelets, catecholamines from chromaffin cells and prolactin from the anterior pituitary. In case of histamine secretion, the effect of mastoparan is mediated by an increase in cytoplasmic Ca^{2+} that is itself caused by an increase in the intracellular second messenger inositol-1,4,5-triphosphate (IP_3). Such IP3-mediated increase of intracellular Ca^{2+} is controlled at the level of phospholipase C (PLC) by one or more of a group of GTP-binding regulatory proteins, or G proteins. [29] Mastoparan induced apoptosis or oncosis is initiated by Ca^{2+} release from intracellular release from intracellular stores via PLC and IP3, and the disruption of plasma membrane integrity occurs secondarily. [34] Mastoparan, an activator of G_i and mast cells, selectively stimulates an PLD_2, independently of G_i, ADP-ribosylation factor-1 (ARF-1), protein kinase C and calcium, in intact cells and in isolated preparations enriched in plasma membranes where PLD_2 is located. [35] PLD catalyses the hydrolysis of the major membrane phospholipid, phosphatidylcholine (PC) to generate phosphatidic acid (PA) and choline. PLD is involved in the exocytosis of secretory granules from mast cells and neutrophils. One possible function of PLD that would rationalise its role in exocytosis may be related to the ability of PA to regulate PI(4)P 5-kinase. PI(4)P 5-kinase is one of two kinases required for the synthesis of PIP_2 (PI3). This unique lipid is essential for many membrane trafficking events including exocytosis. The product of PC hydrolysis by PLD is PA, which therefore has the potential to dynamically regulate the synthesis of PIP_2 in specific membrane compartments, ie, where PLD is active. [36]

mitochondria which in turn activates PLA_2. The activated PLA_2 in turn increases the fatty acid level in host fat body. [30]

Hence, the multitude of mechanisms employed to manipulate host metabolism ensures an abundance of lipid resources during development, providing parasitoid larvae with a unique opportunity to consume host lipids instead of synthesizing them de novo. Manipulation and consumption of host lipids probably provides a selective advantage for parasitoid larvae, because *de novo* lipid synthesis is energetically expensive. [101]

8.1.5. Apoptosis

Venom for parasitoid wasps induces cellular injury and culminates in oncotic death. [88] Crude venom alone has been shown in *in vitro* assays to evoke disruption of plasma membrane integrity, blebbing, rounding, swelling and cell death thought to be linked to a G-protein dependent oncotic mechanism. [103] Various candidates in venom triggers the apoptotic cell death such as venom phenoloxidase, calreticulin, laccase, endonuclease G, and gamma-glutamyl transpeptidase-like venom protein. [88]

8.1.6. Nutritional functions

Nutritional and physiological milieu of the host is manipulated for the better nurturing of the parasitoid's offspring by the venom injected by the female wasp. For example, teratocytes of endoparasitoids have a secretory and nutritive function whereas venom of some ectoparasitoids changes the host metabolism to provide nutrients. [88] The discovery of trehalase in parasitoid wasp venom protein ensures the provision of glucose for developing wasp larvae from trehalose, which is the main reserve sugar in the hemolymph of flying insects. Several other digestive proteins in venom such as trypsin and other serine proteases, trypsin-like enzymes, lipase-like venom protein, and acid phosphatases are involved in assuring the optimal nutrition for its offspring. [88, 104, 105]

9. Conclusion

Wasp is a common name for any insect species of the order Hymenoptera and sub-order Apocrita, excluding bees and ants. A highly diverse group of insects, they are social or solitary, parasitic or predatory, phytophagous or carnivorous or omnivorous. The most primitive Hymenoptera possess ovipositors to insert eggs into plant tissues. In some parasitic groups, this structure and the glands associated with it have been modified to inject venom to paralyse other insects that they use for their developing larvae. These parasitic wasps are extremely beneficial to natural ecosystem and agriculture as biological pest controller. Their stings are not so painful to humans and are of none clinical significance.

Social wasps, however, are evolved with a venom system that is specialized as a defence weapon. The sting produces a range of clinical manifestations in humans—from simple skin allergic manifestation that do not require any medical treatment to fatal anaphylaxis and toxic

reactions where immediate medical intervention is utmost. Yellow jackets, hornets and paper wasps are three medically important stinging social wasps. Stinging social wasp venom comprises of various allergens, toxins and bioactive molecules that imparts physiological and pathological changes upon envenomation in humans. Immune-mediated and non-immune mediated mechanisms, both are involved.

Wasp stings are alkaline and are traditionally addressed by the application of vinegar or lemon juice to neutralize the venom. Besides, there are many local practices being observed, which might need scientific evidence to be proven, such as placing ice packs, freshly sliced cucumber, potato and onion on the sting sites and applying the aloe vera gel, garlic paste, ethanol and curds on the sting sites.

Wasp stings usually manifests allergic symptoms—normal local allergies to systemic anaphylaxis. Allergy, in general, is a public health threat of pandemic proportions today. Respiratory allergies, food and drug allergies and allergic reactions to insect venom are the commonly reported allergic incidents. Allergic patients not only suffer from the debilitating disease resulting in decreased quality of life, career progression and personal development but also constitute a significant burden on health economics and macroeconomics due to the days of lost productivity and underperformance. The symptomatic treatment for allergy are not sustainable which includes short-term symptom relieving or long-term anti-inflammatory drugs—the effect of which are suboptimal, relapse of the symptoms very shortly after ceasing daily use of medication even after years of a continuous and effective treatment, and the possible fear of adverse effect due to the long-term use of drugs. [106] These symptomatic medications as well imparts financial burden. Allergen-specific immunotherapy is an effective treatment used by allergists and immunologists for common allergic conditions, particularly allergic rhinitis/conjunctivitis, allergic asthma and stinging insect hypersensitivity [107] and can achieve substantial results for patients—improves the quality of life, reduces the long-term costs and burden of allergies and prevents the progression of allergic disease. Currently, it is the only curative treatment for Hymenoptera venom allergy. [106] However, various factors should be taken into consideration on a case-by-case basis, taking into account individual patient factors, before proceeding with the allergen specific immunotherapy such as the degree to which symptoms can be reduced by avoidance measures and pharmacological therapy, the amount and type of medication required to control symptoms, the adverse effects of pharmacological treatment and patient preferences. This form of therapy carries the risk of anaphylactic reactions, hence taking into consideration the indications and contraindications, it should be prescribed and practiced by physicians who are adequately trained in the treatment of allergy. Moreover, injections must be given under medical supervision in clinics that are equipped to manage anaphylaxis. [107] These requirements and preparations obviously make the allergen specific immunotherapy not so readily available and expensive but considering the beneficial effects of allergen specific immunotherapy and unsustainability of pharmacotherapy, allergen specific immunotherapy emerges as a reliable curative approach.

Parasitic wasps have their own significant space in this ecosystem and contribute as a biological pest controller. They are not only important in agricultural system, but as well have significant role in controlling the disease spreading, such as the toxicity of venom can inhibit the multiple

developmental stages of several mosquitoes and house flies, both of which are a major vector of human disease. The utility of their venom components provide a promising frontier in development of new classes of bioinsecticides.

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References

[1] Ennik F. Deaths from Bites and Stings of Venomous Animals. The Western Journal of Medicine 1980; 133: 463—468.

[2] Vetter RS, Visscher PK. Bites and Stings of Medically Important Venomous Arthropods. International Journal of Dermatology 1998; 37: 481—496.

[3] Sharkey MJ. Phylogeny and Classification of Hymenoptera. Zootaxa 2007; 1668: 521—548.

[4] Fitzgerald KT, Flood AA. Hymenoptera Stings. Clinical Techniques in Small Animal Practice 2006; 21: 194—204.

[5] Dongol Y, Paudel YP, Shrestha RK et al. Acute Renal Failure Following Multiple Hornet Stings. Clinical Kidney Journal 2012; 5: 158—161.

[6] Hoggard SJ, Wilson PD, Beattie AJ et al. Social Complexity and Nesting Habits Are Factors in the Evolution of Antimicrobial Defences in Wasps. PLoS One 2011; 6(7): e21763.

[7] Antonicelli L, Bilo MB, Bonifazi F. Epidemiology of Hymenoptera Allergy. Current Opinion in Allergy and Clinical Immunology 2002; 2, 341-346.

[8] Kasper ML, Reeson AF, Mackay DA et al. Environmental Factors Influencing Daily Foraging Activity of *Vespula germanica* (Hymenoptera, Vespidae) in Mediterranean Australia. Insectes Sociaux 2008; 55: 288—295.

[9] Diaz JH. Recognition, Management, and Prevention of Hymenopteran Stings and Allergic Reactions in Travelers. Journal of Travel Medicine 2009; 16 (5): 357–364.

[10] Vetter RS, Visshcher PK, Camasine S. Mass Envenomations by Honey Bees and Wasps. West Journal of Medicine 1999; 170: 223—227.

[11] Bilo BM, Bonifazi F. Epidemiology of Insect Venom Anaphylaxis. Current Opinion on Allergy and Clinical Immunology 2008; 8: 330—337.

[12] Kolarich D, Loos A, Leonard R et al. A Proteomic Study of the Major Allergens from Yellow Jacket Venoms. Proteomics 2007; 7, 1615–1623.

[13] Monsalve RI, Vega A, Marques L et al. Component-Resolved Diagnosis of Vespid Venom-Allergic Individuals: Phospholipases and Antigen 5s are Necessary to Identify *Vespula* or *Polistes* Sensitization. Allergy 2012; 67: 528–536.

[14] Jin C, Focke M, Leonard R et al. Reassessing the Role of Hyaluronidase in Yellow Jacket Venom Allergy. Journal of Allergy & Clinical Immunology 2010; 125: 184–190.

[15] Blank S, Seismann H, Bockisch B et al. Identification, Recombinant Expression, and Characterization of the 100 kDa High Molecular Weight Hymenoptera Venom Allergens Api m 5 and Ves v 3. Journal of Immunology 2010; 184: 5403—5413.

[16] Blank S, Seismann H, McIntyre M et al. Vitellogenins are New High Molecular Weight Components and Allergens (Api m 12 and Ves v 6) of *Apis mellifera* and *Vespula vulgaris* Venom. PLoS ONE 2013; 8(4): e62009.

[17] King TP. Immunochemical Studies of Stinging Insect Venom Allergens. Toxicon 1996; 34: 1455—1458.

[18] Hoffman DR. Hymenoptera Venom Allergens. Clinical Reviews in Allergy and Immunology 2006; 30: 109—128.

[19] Hawdon JM, Jones BF, Hoffmann DR et al. Cloning and Characterization of Anclyostoma-secreted Protein. A Novel Protein Associated with the Transition to Parasitism by Infective Hookworm Larvae. The Journal of Biological Chemistry 1996; 271(12): 6672—6678.

[20] Santosa LD, Santos KS, de Souza BM et al. Purification, Sequencing and Structural Characterization of the Phospholipase A_1 from the Venom of the Social Wasp *Polybia paulista* (Hymenoptera, Vespidae). Toxicon 2007; 50: 923–937.

[21] Abe T, Sugita M, Fujikura T et al. Giant Hornet (*Vespa Mandarinia*) Venomous Phospholipases: The Purification, Characterization and Inhibitory Properties by Biscoclaurine Alkaloids. Toxicon 2000; 38: 1803-1816.

[22] Aoki J, Nagai Y, Hosono H et al. Structure and Function of Phosphatidylserine-specific Phospholipase A_1. Biochimica et Biophysica Acta 2002; 1582: 26– 32.

[23] Aoki J, Inoue A, Makide K et al. Structure and Function of Extracellular Phospholipase A_1 Belonging to the Pancreatic Lipase Gene Family. Biochimie 2007; 89: 197-204.

[24] Costa H, Palma MS. Agelotoxin: A Phospholipase A_2 from the Venom of the Neotropical Social Wasp Cassununga (*Agelaia pallipes pallipes*) (Hymenoptera-Vespidae). Toxicon 2000; 38: 1367-1379.

[25] Jacomini DLJ, Pereira FDC, dos Santos Pinto JRA et al. Hyaluronidase from the Venom of the Social Wasp *Polybia paulista* (Hymenoptera, Vespidae): Cloning, Structural Modeling, Purification, and Immunological Analysis. Toxicon 2013; 64: 70–80.

[26] Kolarich D, Leonard R, Hemmer W et al. The N-glycans of Yellow Jacket Venom Hyaluronidases and the Protein Sequence of its Major Isoform in *Vespula vulgaris*. FEBS Journal 2005; 272: 5182—5190.

[27] Markovic-Housley Z, Miglierini G, Soldatova L et al. Crystal Structure of Hyaluronidase, A Major Allergen of Bee Venom. Structure 2000; 8: 1025—1035.

[28] Leite NB, da Costa LC, dos Santos AD et al. The Effect of Acidic Residues and Amphipathicity on the Lytic Activities of Mastoparan Peptides Studied by Fluorescence and CD Spectroscopy. Amino Acids 2011; 40: 91—100.

[29] Higashijima T, Uzu S, Nakajima T et al. Mastoparan, a Peptide Toxin from Wasp Venom, Mimics Receptors by Activating GTP-binding Regulatory Proteins (G Proteins). The Journal of Biological Chemistry 1988; 263(14): 6491—6494.

[30] Brigatte P, Cury Y, de Souza BM et al. Hyperalgesic and Edematogenic Effects of Peptides Isolated from the Venoms of Honeybee (*Apis mellifera*) and Neotropical Social Wasps (*Polybia paulista* and *Protonectarina sylveirae*). Amino Acids 2011; 40: 101—111.

[31] Rotem S, Radzishevsky I, Inouye RT et al. Identification of Antimicrobial Peptide Regions Derived from Genomic Sequences of Phage Lysins. Peptides 2006; 27: 8—26.

[32] Rocha T, de Souza BM, Palma MS et al. Myotoxic Effects of Mastoparan from *Polybia paulista* (Hymenoptera, Epiponini) Wasp Venom in Mice Skeletal Muscle. Toxicon 2007; 50: 589—599.

[33] Argiolas A, Pisano JJ. Isolation and Characterization of Two New Peptides Mastoparan C and Crabolin, from the Venom of the European Hornet, *Vespa crabro*. The Journal of Biological Chemistry 1984; 259(16): 10106—10111.

[34] Rivers DB, Rocco MM, Frayha AR. Venom from the Ectoparasite Wasp *Nasonia vitripennis* Increases Na^+ Influx and Activates Phospholipase C and Phospholipase A_2 De-

pendent Signal Transduction Pathways in Cultured Insect Cells. Toxicon 2002; 40: 9—21.

[35] Chahdi A, Choii W, Kim Y et al. Mastoparan Selectively Activates Phospholipase D_2 in Cell Membranes. The Journal of Biological Chemistry 2003; 278(14): 12039—12045.

[36] Jones D, Morgan C, Cockcroft S. Phospholipase D and Membrane Traffic: Potential Roles in Regulated Exocytosis, Membrane Delivery and Vesicle Budding. Biochimica et Biophysica Acta 1999; 1439: 229—244.

[37] Sharma JN, AL-Sherif GJ. The Kinin System: Present and Future Pharmacological Targets. American Journal of Biomedical Science 2011; 3(2): 156—169.

[38] Mendes MA, Palma MS. Two New Bradykinin-related Peptides from the Venom of the Social Wasp *Protopolybia exigua* (Saussure). Peptides 2006; 27: 2632—2639.

[39] Duncan AM, Kladis A, Jennings GL et al. Kinins in Humans. American Journal of Physiology—Regulatory, Integrative and Comparative Physiology 2000; 278: R897—904.

[40] Mortari MR, Cunha AOS, Carolino ROG, et.al. Inhibition of Acute Nociceptive Responses in Rats After I.C.V. Injection of Thr^6-Bradykinin, Isolated from the Venom of the Social Wasp, *Polybia occidentalis*. British Journal of Pharmacology 2007;151: 860—869.

[41] Griesbache T, Althuber P, Zenz M et al. *Vespula vulgaris* Venom: Role of Kinins and Release of 5-Hydroxytryptamine from Skin Mast Cells. European Journal of Pharmacology 1998; 351: 95—104.

[42] Konno K, Palma MS, Hitara IY et al. Identification of Bradykinins in Solitary Wasp Venoms. Toxicon 2002; 40: 309—312.

[43] Saidemberg NBB, Saidemberg DM, de Souza BM et al. Protonectin (1–6): A Novel Chemotactic Peptide from the Venom of the Social Wasp *Agelaia pallipes pallipes*. Toxicon 2010; 56: 880—889.

[44] Fitch CD. The Serine Protease from the Venom of *Polistes dominulus* Contains Allergenic Epitopes. PhD Thesis. Interdisciplinary Program in Biological Sciences, East Carolina University, April 2010.

[45] Ho CL, Lin YL, Chen WC et al. Immunogenecity of Mastoparan B, A Cationic Tetradecapeptide Isolated from the Hornet (*Vespa basalis)* Venom, and Its Structural Requirements. Toxicon 1995; 33(11): 1443—1451.

[46] de Graaf DC, Aerts M, Danneels E et al. Bee, Wasp and Ant Venomics Pave the Way for a Component-Resolved Diagnosis of Sting Allergy. Journal of Proteomics 2009; 72: 145—154.

[47] Bilo BM, Rueff F, Mosbech H et al. Diagnosis of Hymenoptera Venom Allergy. Allergy 2005; 60: 1339—1349.

[48] Diaz JH. Recognition, Management and Prevention of Hymenoptera Stings and Allergic Reactions in Travelers. Journal of Travel Medicine 2009; 16(5): 357—364.

[49] Viswanathan S, Prabhu C, Arulneyam J et al. Yellow Jacket Envenomation-related Acute Renal Failure. NDT Plus 2011; 4: 167—169.

[50] Ellis AK, Day JH. Clinical reactivity to insect stings. Current Opinion in Allergy and Clinical Immunology 2005; 5: 349—354.

[51] Freeman TM. Hypersensitivity to Hymenoptera Stings. The New England Journal of Medicine 2004; 351: 1978—1984.

[52] Moffitt JE, Golden BK, Reisman RE et al. Stinging Insect Hypersensitivity: A Practice Parameter Update. Journal of Allergy & Clinical Immunology 2004; 114: 869—886.

[53] Seismann H, Blank S, Braren I et al. Dissecting Cross-reactivity in Hymenoptera Venom Allergy by Circumvention of α-1,3-core Fucosylation. Molecular Immunology 2010; 47: 799—808.

[54] Pantera B, Hoffmann DR, Carresi L et al. Characterization of the Major Allergens Purified from the Venom of the Paper Wasp *Polistes gallicus*. Biochimica et Biophysica Acta 2003; 1623: 72—81.

[55] Tanabe S. Epitope Peptides and Immunotherapy. Current Protein and Peptide Science 2007; 8: 109—118.

[56] Malandain H. IgE-reactive Carbohydrate Epitopes—Classification, Cross-reactivity, and Clinical Impact. European Annals of Allergy and Clinical Immunology 2005; 37: 122—128.

[57] King TP, Lu G, Gonzalex M et al. Yellow Jacket Venom Allergens, Hyaluronidase and Phospholipase: Sequence Similarity and Antigenic Cross-reactivity with their Hornet and Wasp Homologs and Possible Implications for Clinical Allergy. Journal of Allergy & Clinical Immunology 1996; 98(3):588—600.

[58] Przybilla B, Rueff F. Insect Stings: Clinical Features and Management. Deutsches Arzteblatt International 2012; 109(13): 238—248.

[59] Gawlik R, Rymarczyk B, Rogala B. A Rare Case of Intravascular Coagulation after Honey Bee Sting. Journal of Investigative Allergology and Clinical Immunology 2004; 14(3): 250—252.

[60] Watemberg N, Weizman Z, Shahak E et al. Fatal Multiple Organ Failure Following Massive Hornet Stings. Clinical Toxicology 1995; 33(5): 471—471.

[61] Seismann H, Blank S, Cifuentes L et al. Recombinant Phospholipase A_1 (Ves v 1) from Yellow Jacket Venom for Improved Diagnosis of Hymenoptera Venom Hypersensitivity. Clinical and Molecular Immunology 2010; 8: 7

[62] Muller UR, Johansen N, Petersen AB et al. Hymenoptera Venom Allergy: Analysis of Double Positivity to Honey Bee and *Vespula* Venom by Estimation of IgE Antibodies to Species-specific Major Allergens Api m 1 and Ves v 5. Allergy 2009; 64: 543—548.

[63] Jappe U, Raulf-Heimsoth M, Hoffmann M et al. *In vitro* Hymenoptera Venom Allergy Diagnosis: Improved by Screening for Cross-reactive Carbohydrate Determinants and Reciprocal Inhibition. Allergy 2006; 61: 1220—1229.

[64] Mari A. IgE to Cross-reactive Carbohydrate Determinants: Analysis of the Distribution and Appraisal of the *in vivo* and *in vitro* Reactivity. International Archives of Allergy and Immunology 2002: 129: 286—295.

[65] Kochuyt AM, Hoeyveld EM, Stevens EAM. Prevalence and Clinical Relevance of Specific Immunoglobin E to Pollen Caused by Sting-induced Specific Immunoglobin E to Cross-reacting Carbohydrate Determinants in Hymenoptera Venoms. Clinical & Experimental Allergy 2005; 35: 441—447.

[66] Eberlein B, Krischan L, Darsow U et al. Double Positivity to Bee and Wasp Venom: Improved Diagnostic Procedure by Recombinant Allergen-based IgE Testing and Basophil Activation Test Including Data about Cross-reactive Carbohydrate Determinant. Journal of Allergy & Clinical Immunology 2012: 130: 155—161.

[67] Haeberli G, Bronnimann M, Hunziker T et al. Elevated Basal Serum Tryptase and Hymenoptera Venom Allergy: Relation to Severity of Sting Reactions and to Safety and Efficacy of Venom Immunotherapy. Clinical & Experimental Allergy 2003; 33: 1216—1220.

[68] Krishna MT, Ewan PW, Diwakar L et al. Diagnosis and Management of Hymenoptera Venom Allergy: British Society for Allergy and Clinical Immunology (BSACI) Guidelines. Clinical & Experimental Allergy 2011; 41: 1201—1220.

[69] Sturm GJ, Heinemann A, Schuster C et al. Influence of Total IgE Levels on the Severity of Sting Reactions in Hymenoptera Venom Allergy. Allergy 2007; 62: 884—889.

[70] Muller U, Schmid-Grendelneier P, Hausmann O et al. IgE to Recombinant Allergens Api m 1, Ves v1, and Ves v 5 Distinguish Double Sensitization from Crossreaction in Venom Allergy. Allergy 2012; 67: 1069—1073.

[71] Kucharewicz I, Bodzenta-Lukaszyk A, Mroczko B et al. Basal Serum Tryptase Level Correlates with Severity of Hymenoptera Sting and Age. Journal of Investigative Allergology and Clinical Immunology 2007; 17(2): 65—69.

[72] Patil SU, Shreffler WG. Immunology in the Clinic Review Series; Focus on Allergies: Basophils as Biomarkers for Assessing Immune Mudulation. Clinical & Experimental Immunology 2011; 167: 59—66.

[73] Hamilton RG. Diagnosis and Treatment of Allergy to Hymenoptera Venoms. Current Opinion in Allergy and Clinical Immunology 2010; 10: 323—329.

[74] Bilo MB, Bonifazi F. The Natural History and Epidemiology of Insect Venom Allergy: Clinical Implications. Clinical & Experimental Allergy 2009; 39: 1467—1476.

[75] Rueff F, Dugas-Breit S, Przybilla B. Stinging Hymenoptera and Mastocytosis. Current Opinion in Allergy and Clinical immunology 2009; 9: 338—342.

[76] Rueff F, Placzek M, Przybilla B. Mastocytosis and Hymenoptera Venom Allergy. Current Opinion in Allergy and Clinical Immunology 2006; 6: 284—288.

[77] Watanabe AS, Fonseca LAM, Galvao CES et al. Specific Immunotherapy Using Hymenoptera Venom: Systematic Review. Sao Paulo Medical Journal 2010; 128(1): 30—37.

[78] Bilo MB. Anaphylaxis Caused by Hymenoptera Stings: From Epidemiology to Treatment. Allergy 2011: 66(S95): 35—37.

[79] Koterba AP, Greenberger PA. Stinging Insect Allergy and Venom Immunotherapy. Allergy Asthma Proceedings 2012; 33: S12—14.

[80] Bilo BM, Bonifazi F. Advances in Hymenoptera Venom Allergy. Current Opinion in Allergy and Clinical Immunology 2007; 7: 567—573.

[81] Bonifazi F, Jutel M, Bilo BM et al. Prevention and Treatment of Hymenoptera Venom Allergy: Guidelines for Clinical Practice. Allergy 2005; 60: 1459—1470.

[82] Wachholz PA, Durham SR. Mechanisms of Immunotherapy: IgG Revisited. Current Opinion in Allergy and Clinical Immunology 2004; 4: 313—318.

[83] Akdis M, Akdis CA. Mechanisms of Allergen-specific Immunotherapy. Journal of Allergy & Clinical Immunology 2007; 119: 780—789.

[84] Mueller UR. Cardiovascular Disease and Anaphylaxis. Current Opinion in Allergy and Clinical Immunology 2007; 7: 337—341.

[85] Li JT, Nelson H, Lockey R. Allergen Immunotherapy: A Practice Parameter Second Update. Cox L, Ed., Journal of Allergy & Clinical Immunology 2007; 120: S25—85.

[86] Finegold I. Issues in Stinging Insect Allergy Immunotherapy: A Review. Current Opinion in Allergy and Clinical Immunology 2008; 8: 343—347.

[87] Ober AI, MacLean JA, Hannaway PJ et al. Life-threatening Anaphylaxis to Venom Immunotherapy in a Patient Taking an Angiotensin-converting Enzyme Inhibitor. Journal of Allergy & Clinical Immunology 2003; 112(5): 1008—1009.

[88] Danneels EL, Rivers DB, de Graaf DC. Venom Proteins of the Parasitoid Wasp *Nasonia vitripennis*: Recent Discovery of an Untapped Pharmacopee. Toxins 2010; 2: 494—516.

[89] Pan J. Host Interaction and Regulation in Parasitoid Wasps. Connexions Module 2010: m34732.

[90] Vincent B, Kaeslin M, Roth T et al. The Venom Composition of the Parasitic Wasp *Chelonus inanitus* Resolved by Combined Expressed Tags Analysis and Proteomic Approach. BMC Genomics 2010; 11: 693.

[91] Jiang H, Kanost MR. Characterization and Functional Analysis of 12 Naturally Occurring Reactive Site Variants of Serpin-1 from *Manduca sexta*. Journal of Biological Chemistry 1997; 272: 1082—1087.

[92] Zhu Y, Gorman M, Jiang H et al. *Manduca sexta* Serpin-3 Regulates Prophenoloxidase Activation in Response to Infection by Inhibiting Prophenoloxidase-Activating Proteinases. Journal of Biological Chemistry 2003; 278: 46556—46564.

[93] Parkinson NM, Conyers C, Keen J et al. Towards a Comprehensive View of the Primary Structure of Venom Proteins from the Parasitoid Wasp *Pimpla hypochondriaca*. Insect Biochemistry and Molecular Biology 2004; 34: 565—571.

[94] Kellenberger C, Roussel A. Structure-activity Relationship within the Serine Protease Inhibitors of the Pacifastin Family. Protein & Peptide Letters 2005; 12: 409—414.

[95] Beck MH, Strand MR. A Novel Polydnavirus Protein Inhibits the Insect Phenoloxidase Activation Pathway. Proceedings of National Academy of Sciences USA 2007; 104: 19267—19272.

[96] Parkinson N, Conyers C, Smith I. A Venom Protein from the Endoparasitoid wasp *Pimpla hypochondriaca* is Similar to the Adams Family of Proteins. Toxicon 1996; 34: 1269—1276.

[97] de Graaf DC, Aerts M, Brunain M et al. Insights into the Venom Composition of the Ectoparasitoid Wasp *Nasonia vitripennis* from Bioinformatics and Proteomic Studies. Insect Molecular Biology 2010; 19(S1): 11—26.

[98] Beck M, Theopold U, Schmidt O. Evidences for Serine Protease Inhibitor Activity in the Ovarian Calyx Fluid of the Endoparasitoid *Venturia canescens.* Journal of Insect Physiology 2000; 46: 1275—1283.

[99] Dani MP, Richards EH, Isaac RE et al. Antibacterial and Proteolytic Activity in Venom from the Endoparasitic Wasp *Pimpla hypochondriaca* (Hymenoptera: Ichneumonidae. Journal of Insect Physiology 2003; 49: 945—954.

[100] Rivers DB, Brogan A. Venom Glands from the Ectoparasitoid *Nasonia vitripennis* (Walker) (Hymenoptera : Pteromalidae) Produce a Calreticuliun-like Protein that Functions in Developmental Arrest and Cell Death in the Flesh Fly Host, *Sarcophaga bullata* Parker (Diptera: Sarcophagidae). In Insect Physiology: New Research; Maes RP, Ed. Nova Science Publishers: New York, NY, USA 2008: pp. 259—278.

[101] Visser B, Ellers J. Lack of Lipogenesis in Parasitoids: A Review of Physiological Mechanisms and Evolutionary Implications. Journal of Insect Physiology 2008; 54: 1315—1322.

[102] Nakamatsu Y, Tanaka T. Venom of *Euplectrus separatae* Causes Hyperlipidemia by Lysis of Host Fat Body Cells. Journal of Insect Physiology 2004; 50: 267—275.

[103] Abt M, Rivers DB. Characterization of Phenoloxidase Activity in Venom from the Ectoparasitoid *Nasonia vitripennis* (Walker) (Hymenoptera: Pteromalidae). Journal of Invertebrate Pathology 2007; 94: 108—118.

[104] Tang B, Chen X, Liu Y et al. Characterization and Expression Patterns of a Membrane-bound Trehalase from *Spodoptera exigua.* BMC Molecular Biology 2008; 9: 51.

[105] Parkinson NM, Conyers CM, Keen JN et al. cDNAs Encoding Large Venom Proteins from the Parasitoid Wasp *Pimpla hypochondriaca* Identified by Random Sequence Analysis. Computational Biochemistry and Physiology 2003; 134: 513—520.

[106] Calderon MA, Demoly P, van Wijk RG. EAACI: A European Declaration on Immunotherapy. Designing the Future of Allergen Specific Immunotherapy. Clinical and Translational Allergy 2012; 2: 20.

[107] Moote W, Kim H. Allergen-specific Immunotherapy. Allergy, Asthma & Clinical Immunology 2011; 7(Suppl 1): S5.

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