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Review Article

Insect Venom Toxin Peptides, its Antimicrobial Effects and Host Immune Responses: A Review

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Abstract

*Present review article explains antimicrobial activity of h*ymenopteran insect venoms. Insects mostly bees, wasps, hornets use venom toxins to defend their hive, nests and mainly colonies in territory. These insects sting very swiftly and inflict venom in its prey. Insect venom glands secret multiple toxin components which are powerful weapons secreted from venom glands. Bees, wasps, and hornet inflict venom for self and territorial defense and impose physiological alterations with multiple symptoms in intruders; but envenomation does not transmit any pathogen. Bee venom severely affects cytoskeletal system and impairs nerve cell function that results in organ paralysis and deformity and even death after multiple bites. In bees severity of microbial infection is increased due to impact of biotic and abiotic factors. Few phenolic compounds such as flavonoids mixed in honey, propolis, and royal jelly assist in making antiviral defense. Insects secrete antimicrobial peptides in venom which protect themselves from infection by generating immune response against pathogens. Purified venom toxins exhibit antibacterial, antifungal and antiviral defense. No doubt venom components from honey bees, wasps and hornets can be used as templates for generation of new therapeutic agents and biopesticides for insect pest management. For this purpose venom gland genome is to be sequenced for finding regulatory genes which synthesize diverse venom components. This overall information generated at molecular level could be used for making diagnostic kits to detect effect of bee venom allergens.

Keywords: Hymenopteran Insects; Venom; Toxins; Biological and Therapeutic Effects

Abbreviations

MAC-1: Macropin; AMPs: Antimicrobial Peptide; AcKTSPI: Kazal-type Serine Protease Inhibitor; PNG-1: Panurgines, Polydim-I (*Polybia dimorpha);* Equmenine mastoparan-EM1 and Equmenine mastoparan-EM2 Peptides; MP-V1: Mastoparan V1; AMG: Anterior Main Gland; PMG: Posterior Main Gland; Polybia-CP: *Polybia paulista,* Melittin; PLA2: Phospholipase A2; VSV: Vesicular Stomatitis Virus; RSV: Respiratory Syncytial Virus; HSV: Herpes Simplex Virus; JV: Junín Virus; RSV: Respiratory Syncytial Virus; VSV: Vesicular Stomatitis Virus; TMV: Tobacco Mosaic Virus; HIV: Human Immunodeficiency Virus; CXCR4: Chemokine Receptor; BmNPV: Bombyx Mori Nucleopolyhedrovirus; RFP: Red Fluorescent Protein; ACPs: Anti-Cancer Peptides; Jak/STAT: Janus kinase/signal Transducer and Activator Of Transcription; JNK: c-Jun N-terminal Kinase; MAPK: Mitogen-Activated Protein Kinases; SF-21AE*: Spodoptera frugiperda;* and *Lymantria dispar* (IPL-Ldfbc1) Cells

Introduction

*Hy*menopteran insects such as honey bees, wasps and hornets are highly venomous. These make hives and protect them. After

feeling a little disturbance in surroundings honey bees and wasps attack in groups while hornets attack in group of two or three insects. Envenomation by hornets is highly painful to human than the wasp stings because hornet venom contains acetylcholine 5% in amount. Various species of honey bees are major plant pollinators and collect nectar from garden flowers and from agriculture fields. Due to rising pollution and depletion of foraging sites, wild bee colonies are decreasing at alarming rate. This local decline is going on at larger scale in some of the geographical regions. For population decline in wild bees many factors like viral diseases and temperature variations and predators are responsible. In has been noted that positive sense strand RNA viruses are targeting bees and infecting them. After bee bite people experience multiple symptoms, but insect envenomation do not transmit the virus. Bee venom severely affect cytoskeletal system and nerve cells that results in organ paralysis and deformity and even death after multiple bites. In case of microbial infection severity is increased due to impact of biotic and abiotic factors. Bees protect themselves from infection by using defensins and generating immune response against pathogens.

This article highlights antiviral defense found in bees, including the Western honey bee (*Apis mellifera*), the Eastern honey bee (*Apis cerana*) and bumble bee species (Bees *Bombus* sp.). Though wild bees maintain antiviral defense but for controlling their heavy decline and mitigation of bee losses immune -genetic studies are to be done to establish relationship between socialization of bees and immune function. Primarily eusocial wasps have an important role in the origin of eusociality that comes after cooperative foraging and social defense. The uniqueness is that all members of a group get infection in maintaining socialization for which they synthesize defensins. These are used to make immune defense. Moreover, human beings use antibiotics to defend themselves in response to viral infection; similarly, bees synthesize defense proteins to encounter the pathogen. Antibacterial peptides synthesized in insects in response to various pathogens were found highly effective and could be used as broad spectrum anti-microbial agents. These also become new alternative of synthetic antibiotics.

Antibacterial peptides from insects can be used as therapeutic agents or potential drugs which could target multidrug resistant pathogens. Today multiple drug resistance in microbes is a biggest challenge for the pharmaceutical companies and researchers. Based on research outcomes spider venom toxins are also found highly effective against various pathogens and could be used as useful resource for drug development. These were found highly effective against drug-resistant microorganisms. The primary functions of solitary wasp are protection of hive while social wasp protects every member and its progenies by developing defense against predators and pathogens. Solitary wasps use stinging for paralyzing the prey while social wasps defend their colonies having progenies from vertebrate predators. There occurs a significant difference in venom components on the basis of socialization hyalurinidase, phospholipase A2 and metalloendopeptidase are common venom components found in both solitary and social wasp. Venom peptides from wasps show diverse biological activities.

Solitary wasps possess more diverse bioactive components that are used in prey inactivation by physiological manipulation. Solitary wasp venom contains pompilidotoxin and dendrotoxin peptides which are neurotoxic in nature. These also contain insulin peptide binding proteins. Insulin peptide binding proteins is highly specific to solitary wasps Contrary to this, venom allergen 5 proteins; venom acid phosphatases, and various phospholipases, were found relatively more specific to social wasp venom.

Antimicrobial peptides

Antimicrobial peptides are commonly found in all insect groups, and used in making immune defense against various pathogens. These peptides were found highly active against Gram-negative and Gram-positive bacteria, fungi and viruses, etc. These insect origin AMPs show low toxicity to mammalian cells. Macropin (MAC-1) is an antimicrobial peptide (AMPs) isolated from the venom of the solitary bee *Macropis fulvipes.* It is a lecuine and lysine rich toxin peptide having 13 amino acids in its structure. MAC-1 shows broad spectrum activity against both Gram negative and Gram positive bacteria. Similarly, a peptide isolated from bee (*Apis cerana*) venom acts as a Kazal-type serine protease inhibitor (AcKTSPI) and found active against Gram-positive bacteria [3] (Table 1).

Panurgines are antimicrobial peptides (AMPs) isolated from the venom of the wild bee *Panurgus calcaratus.* These peptides display strong antimicrobial activity against Gram-positive and Gram-negative bacteria and many fungal strains. These show low hemolytic activities against human erythrocytes [4]. PNG-1 is α-helical amphipathic dodecapeptide shows amino acid sequences

Species	Against	Activity	Peptides	References
Apismellifera	*S. typhimurium*	Anti-inflammatory, analgesic, and cardiovascular effect, hemolytic, antioxidant activities, catalytic activity, anti-cancerous	Melittin, PLA2	Jacinthe Frangieh., *et al.* 2020
Assassin bugs	*B. subtilis*	digestive, neurotoxic, hemolytic, antibacterial, and cytotoxic effects	S1 proteases, redulysins, Ptu1-like peptides, hemolysins and cystatins	Maike L Fischer., *et al.* 2019
Macropis fulvipes	*S. typhimurium*	Anti-bacterial, Anti-Biofilm Properties	Macropin	Su Jin Ko., *et al.* 2017
Heterometrus xanthopus	*B. subtilis, S. typhimurium, and P. aeruginosa, B. subtilis, S. typhimurium, and P. aeruginosa*	Anti-bacterial	Hadrurin, scorpine, Pandinin 1, and Pandinin 2	Umair Ahmed., *et al.* 2012
Acanthoscurria rondoniae	*B. subtilis,*	Anti-tumoral Activities, Anti-bacterial	Short peptides and cysteine-rich peptides (CRPs)	Guilherme A. Câmara., *et al.* 2020
Scorpion	*B. subtilis*	Anti- HBV activity, cytotoxic effect, Antibacterial and ion channel–modulating activities.	Defensin BmKDfsin4	Zhengyang Zeng., *et al.* 2017
Scolopendra	Gram-positive and Gram-negative bacteria	Anti-bacterial, hemolytic effect	Lysates	Salwa Mansur Ali., *et al.* 2019
Pardosa astrigera	*B. subtilis*	Anti-bacterial, anti-inflammatory effects	Lycotoxin-Pa4a	Min Kyoung Shin., *et al.* 2020
Heterometrus xanthopus	*B. subtilis, S. typhimurium,* and *P. aeruginosa*	Anti-microbial	Hadrurin, scorpine, Pandinin 1, and Pandinin 2	UmairAhmed., *et al.* 2012
House- flies	Gram-negative bacteria	Anti-bacterial	MDAP-2	Pei Z., *et al.* 2018
Bombyx mori	*Escherichia coli* JM109 and *Pseudomonas putida*	Anti-bacterial	Gloverin2	Wang Q., *et al.* 2018
Blaptica dubia	*Staphylococcus aureus, Streptococcus pyogenes, Bacillus cereus, Escherichia coli* K1, *Salmonella enterica*, *Serratiamarcescens, Pseudomonas aeruginosa, Klebsiella pneumonia*	antiamoebic effects	Melittin,PLA2	Akbar N., *et al.* 2018
Mantidis ootheca	Pseudomonas aeruginosa	Antibacterial agent with anti-biofilm activity	MDAP-2	Wang WD., *et al.* 2018
Honey bee	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	Antibacterial activity, Glucose oxidase activity	Melittin,PLA2	Marcela Bucekova., *et al.*2 017

Blattella germanica	*Micrococcus luteus*	Antibacterial activity, antifungal	Chitosan	HamidrezaBasseri., *et al.* 2019
Periplaneta americana	*Micrococcus luteus*	Antibacterial activity, antifungal	Chitosan	HamidrezaBasseri., *et al.* 2019
Reticuliterme sflavipes	*A. baumannii*	antibiotic activity	PLA2	Yuan Zeng., *et al.* 2016
Bombyx mori	*E.coli*	Antibacterial activity, Antiviral activity	Seroin	C P Singh., *et al.* 2014
Vespa orientalis	*Micrococcus luteus*	Antibacterial activity	AuNps	JafarJalaei., *et al.* 2018
Drosophila melanogaster	*Micrococcus luteus*	Antibacterial activity	Antibacterial activity,	
Stenopsychekodaikanalensis	*Bacillus subtilis, Bacillus flexus*	Antibacterial	β-galactoside binding lectin	Bhuvaragavan Sreeramulu., *et al.* 2018
C. quinquefasciatus	*Bacillus subtilis, Bacillus flexus*	Antioxidant, larvicidal, scavenging, antibacterial	PLA2	Balasubramani Sundararajan., *et al.* 2018
Bombyxmori L.	*Escherichia coli, Klebsiella pneumonia, Bacillus subtilis and Phytophthora meadii*	Anti-pathogenic activities.	Chbp gene	G K S Manjunatha., *et al.* 2018
Hermetiaillucens	*Staphylococcus aureus*	Immunomodulatory activity,	CSαβ peptides-DLP2 and DLP4	Zhanzhan Li., *et al.* 2017
Melipona quadrifasciata quadrifasciata	*S. aureus, methicillin-resistant S. aureus*,	Anti-oxidant, antimicrobial	propolis	A R Torres., *et al.* 2018
Tetragonisca angustula	Gram-positive (*S. aureus, methicillin-resistant S. aureus,* E. faecalis) and gram-negative (*E. coli* and *K. pneumonia*	Anti-oxidant, antimicrobial	propolis	A R Torres., *et al.* 2018
Loxosceles gaucho	*S. aureus*	Anti-infective agents effective against drug-resistant microorganisms, anti-bacterial	U1-SCRTX-Lg1a	Paula Segura-Ramírez., *et al.* 2019
Tetramoriumbicarinatum	*Helicobacter pylori*	Anti-Helicobacter pylori Properties	Bicarinalin	Jesus Guzman., *et al.* 2017
Spider venom	*A. baumannii*	Potent bacteriostatic effect, curing drug-resistant bacterial infections,	Lycosin-II	Yongjun Wang., *et al.* 2016
Lonomiaoblique	*S. aureus*	Hemorrhagic, coagulation disorder	Cysteine proteases, Group III phospholipase A2, C type lectins, lipocalins, protease inhibitors, serpins, Kazal-type inhibitors, cystatins and trypsin inhibitor	Ana B. G. Veiga., *et al.* 2005

Scorpion toxins	*S. aureus*	Neurotoxic, Antibacterial ancestral activity	defensin	Shangfei Zhang., *et al.* 2018
Latrodectus geometricus	*A. baumannii*	Enzymatic activity, toxicity, and antibacterial activity	Latrotoxins, apolipophorins, hemocyanins, chitinases, arginine kinase, allergen antigen 5-like protein, astacin-like metalloproteases, and serine proteases.	Khamtorn, Pornsawan., *et al.* 2020
L. tredecimgut-tatus	*A. baumannii*	Antibacterial	Latroeggtoxin-IV	QianLei., *et al.* 2015

Table 1: Antibacterial venom toxins insects.

LNWGAILKHIIK-NH_2. Lasiocepsin a 27-residue antimicrobial peptide was isolated from *Lasioglossum laticeps* (wild bee) venom. It also exhibits antibacterial and antifungal activity [5]. Polybia-MPII shows very high antimicrobial potential and shows comparatively low erythrocyte hemolysis than other peptides of this same family [6]. Similar antimicrobial activity is reported in mastoparans isolated from the venom of the social wasp *Pseudopolybia vespiceps* against *Staphylococcus aureus* and *Mycobacterium abscessus*, *Candida albicans* and *Cryptococcus neoformans in vitro*. These antimicrobial peptides display pore-forming ability in membrane and could be used as antimicrobial drugs.

Polybia dimorpha is a neotropical wasp, secretes an antimicrobial peptide Polydim-I in venom [7]. This is a cationic peptide displays potent antimicrobial activity against different microorganisms. It disrupts cell wall and but shows no cytotoxic effects in mammalian cells [8]. MP-V1 (Mastoparan V1) is an antimicrobial peptide isolated from the venom of the social wasp *Vespula vulgaris*. It was found active against *Salmonella typhimurium* infection [9]. Few α-helical peptides also found in Equmenine wasp venom [9,10]. Kazal-type serine proteases found in insect venoms exhibit thrombin, elastase, plasmin, proteinase K, or subtilisin A inhibition activity. Both Equmenine mastoparan-EM1 and Equmenine mastoparan-EM2 peptides exhibit potent antibacterial activity [11]. Antimicrobial peptides (AMPs) are also identified in scorpion and spider venoms. These show potent antimicrobial activity against pathogenic bacteria. Scorpion venom contains some bi-functional peptides, which could be used to synthesize/engineer new proteins with an ancestral activity [12]. These insect derived short antimicrobial peptides have shown better bactericidal activity against multidrug resistant *M. tuberculosis* than that of the conventional antibiotics ethambutol, isoniazid and rifampicin [12]. Both peptides Pin2 and Pin2 have shown much potent antimicrobial activity and could be used as an alternative of antibiotics to treat tuberculosis [13]. These show very low hemolytic effects [14-17].

Spider *Laches anatarabaevi* synthesize cytolytic peptides which act synergistic action when used with neurotoxins. Spiders use venom peptides to paralyze prey or deter aggressors. This is a bifunctional peptide which binds to bacterial membrane and found active against Gram-negative and Gram-positive bacteria. Lasiocepsin is isolated from *Lasioglossum laticeps* (wild bee) venom it contains 27 amino acid residues. This peptide shows antibacterial and anti-fungal activity. Lasiocepsin structurally belongs to the ShK family, it shows strong affinity with anionic phospholipids of membrane [15]. Lasiocepsin peptide permeabilizes through membrane of Gram-negative bacteria and kills them. Lasiocepsin peptide interacts with phospholipids at N terminus site; its penetration power depends on presence of cardiolipin that found at the poles of bacterial cells [16]. Solitary wasps use sting to paralyze the predator but these do not feed upon it. But spiders paralyze their prey and feed them to their larvae.

Vespula vulgaris secrete MP-V1 antimicrobial peptide that was found active against *Salmonella* infection [17]. Polydim-I is a cationic peptide shows powerful antimicrobial activity against different microorganisms [18]. Equmenine wasps *Anterhynchium*

flavor marginatum micado venom contains antimicrobial α-helical peptides as the major peptide component that also showed antimicrobial, histamine-releasing, and hemolytic activities. Wasp venom peptide Mastoparan-EM1 and EM2 display mast cell degranulation activity [19]. EMP-EM peptides strongly bind with bacterial and mammalian cell membranes. The paper wasp *Polistes dominulus* venom was found effective against polymicrobial disease of vineyards [20].

Wasp venoms are complex mixtures of proteinacious and non-proteinacious substances. Endoparasitoid wasp, *Microplitis mediator* secretes VRF1, a metalloprotease homolog venom protein. It modulates egg encapsulation in its host, the cotton bollworm, *Helico verpa armigera.* This endoparasitoid wasp venom protein interferes with the Toll signaling pathway in the host hemocytes [21]. Similarly, another protein Edin express in the fat body of hosts and regulate plasmatocyte numbers. It also regulates mobilization of sessile hemocytes in *Drosophila* larvae [22]. Insect venom is a rich source of diverse peptides which could be used for drug design and innovative therapeutic discoveries [23].

Bee and wasp venom contains several biologically active biomolecules such as peptides and enzymes. These show strong therapeutic potential against micro-organisms mainly causative agents of infectious diseases. Bee venom components also found active against different cancer cell types [24]. Insect venom toxins could be used to cure of central nervous system diseases i.e. Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis in human. The venoms from the anterior main gland (AMG) and posterior main gland (PMG) of the reduviid bugs *Platymeris biguttatus* L. and *Psytalla horrida* Stål secretes distinct protein mixtures possesses S1 proteases, redulysins, Ptu1-like peptides, and uncharacterized proteins, whereas AMG venom contained hemolysins and cystatins. It shows neurotoxic, hemolytic, antibacterial, and cytotoxic effects [25].

Antibacterial activity

Bee and wasp venom contains several biologically active biomolecules such as peptides and enzymes. These show strong therapeutic potential against micro-organisms mainly causative agents of infectious diseases. Polybia-CP isolated from *Polybia paulista* shows strong antibacterial potential against both Gram-positive and Gram-negative bacteria. This is a membrane active peptide and passes through membrane of bacteria. It shows strong action against drug resistant bacteria [26] (Figure 1). The wasp *A. baumannii* MPs Agelaia-MPI and Polybia-MPII had better action against MDR (multidrug-resistant) [27]. Anoplin and its several analogs showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* ATCC 33591 (MRSA), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa*(ATCC 27853), vancomycin-resistant *Enterococcus faecium* (ATCC 700221) [28]. Similarly, opistoporin 1 and parabutoporin isolated from scorpion *Opistophtalmus carinatus* inhibit growth of Gram-negative bacteria [29] (Table 1) (Figure 1).

Figure 1: Showing antibacterial activity of insect venom toxins.

Antifungal activity

A synthetic decapeptide antifungal activity against *Penicillium* rot of apples [30], α-hefutoxin 1 and analogues showed inhibitory effect on the oncogenic channel $K_v10.1$ [31]. A peptide analog from the mastoparan wasps (MK58911) showed antifungal activity against *Cryptococcus* spp. and *Paracoccidioides* spp. This peptide could be used as a new antifungal drug to treat systemic mycoses [32]. Polybia-CP is an antimicrobial cationic peptide purified from the venom of the social wasp *Polybia paulista.* It shows potent antifungal activity against *Candida albicans (C. albicans)* and *Candida glabrata (C. glabrata*). Polybia-MPI, inhibits growth of *C. glabrata,* and could be used for development of antifungal agents. Polybia-

CP enhances the production of cellular reactive oxygen species that aid to its anti-fungal activity [33]. It shows potent antifungal activity against *Candida albicans* and *Candida glabrata*. Similarly, anoplin (GLLKRIKTLL-NH_2) isolated from wasp shows potent anti-microbial activity due to its truncation and acylation. Anoplin could be used as promising drug candidates for drug development [34] (Table 2 and figure 2). Anoplin is an amphipathic, α-helical bioactive decapeptide isolated from wasp venom. Its shows strong anti-fungal, activities against *Leptosphaeria maculans* and protection of *Brassica napus* plants from disease [36]. Mastoparan analog from wasp venom was also found effective against *Candida albicans.* It shows low cytotoxicity and non teratogenicity in *Danio rerio* [35]. Similarly, OdVP2 and OdVP2L peptides were isolated from solitary wasp *Orancistrocerus drewseni* showed antifungal activity [37] (Figure 2). Polybia-CP is a much potent antifungal peptide. Similar antifungal peptides have been identified in the venom glands of *T. stigmurus* [38]. A peptide Ts-FKLFKKILKVL-NH(2) (BP22), bears Tsortosyl group, shows an efficacy of 56% disease reduction, than conventional antibiotic. It also shows antifungal activity against both plant-pathogenic and entomopathogenic fungi [30] (Table 2).

S. No.	Insect species	Against	Activity	Peptides	References
1.	Spider	*Candida* species	Anti-biofilm, Anti-fungal activity	Lycosin-I	Li Tan., *et al*. 2018
2.	*Galleria mellonella*	*Cryptococcus neoformans*	Anti-fungal	Mastoparan	Junya de Lacorte Singulani., *et al*. 2019
3.	Bee venoms	*Candida* spp	Haemolytic, cytotoxic, antifungal and anti-biofilm activities	LL-III (LL-III/43) and HAL-2 (peptide VIII)	JitkaKočendová., *et al*. 2019
4.	*Pardosa pseudoannulata*	*Cryptococcus neoformans*	Antiviral and antifungal activities	Astacin-like metalloprotease toxins, Kunitz-type serine protease inhibitors, venom allergen 5, hyaluronidase	Lixin Huang., *et al*. 2018
5.	*Pseudo polybiave spices*	*Staphylococcus aureus and Mycobacterium abscessus subsp. Massiliense, Candida albicans* and *Cryptococcus neoformans*	Antifungal activities	Mastoparans	Juliana C Silva., *et al*. 2016
6.	*Tityus stigmurus*	*C. tropicalis and C. krusei, C. albicans*	Anti-biofilm activities	TistH	Manoela Torres-Rêgo., *et al*. 2019
7.	*Macropis fulvipes*	*C. tropicalis*	Hemolytic activity	Macropin	LenkaMonincová., *et al*. 2014
9.	*Apiscerana*	*Bacillus subtilis*, *Bacillus thuringiensis*, *Beauveriabassiana*, and *Fusarium graminearum*	Anti-biofilm activities	Kazal-type serine protease	Bo Yeon Kim., *et al*. 2013
10.	*Bombus ignitus*	*Fulvia fulva* and *Alternaria radicina*	Hemolytic activities	Bombolitin	Young Moo Choo., *et al*. 2010

11.	*Lasiodora*	*Candida parapsilosis* and *Candida albicans*	Cytotoxic, and hemolytic activities	U_1-theraphotoxin-Lp1a (lasiotoxin-1), U_1-theraphotoxin-Lp1c (lasiotoxin-3), U_3-theraphotoxin-Lsp1a (LTx5), and ω-theraphotoxin-Asp3a, phospholipase A_2 (PLA_2) and hyaluronidase	Felipe Roberto Borba Ferreira., *et al*. 2016
12.	*Lachesanatarabaevi*	*Candida albicans*	Cytotoxic, neurotoxic	latarcins (Ltc)	Peter V Dubovskii., *et al*. 2015
13.	*Polybia paulista*	*C. tropicalis*	Anti-biofilm activities	polybia-CP	Kairong Wang., *et al*. 2015
14.	*Panurgus calcaratus*	*Candida albicans*	Cytotoxic, neurotoxic	panurgines	SabínaČujová., *et al*. 2013
15.	*Lasioglossum laticeps*	*Fulvia fulva*	Anti-biofilm activities	Lasiocepsin	LenkaMonincová., *et al*. 2013
16.	*Loxosceles intermedia*	*Candida parapsilosis*	Hemolytic activities	TAG and DAG phospholipids	A V Bednaski., *et al*. 2015
17.	*Heterometrus sp.*	*C. tropicalis*	Anti-biofilm activities	κ-hefutoxin 1	Lien Moreels., *et al*. 2016

Table 2: Anti-fungal activity of animal toxins.

Figure 2: Showing antifungal activity of insect venom toxins.

Anti-trypanosomal

Mastoparan also shows anti-protozoan activity and inhibits development forms of *Trypanosoma cruzi* [39]. Venom from the ectoparasitic wasp *Nasoniavi tripennis* causes cellular injury and involve in the release of intracellular calcium stores via the activation of phospholipase C. It results in oncotic death. Wasp venom stimulates sudden release of calcium from ER compartments, it is distinct from RyRs, L-type Ca^{2+} channels, and the $Ca(^{2+})$-ATPase pump. Calcium is also released from some other intracellular store [40] (Table 3 and figure 3).

Antiviral activity

Bee venom and its components i.e. melittin (MLT), phospholipase A2 (PLA2), and apamin showed inhibitory effects against important disease causing 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* [41]. Honey bee peptide melittin found effective against several viruses including coxsackievirus, 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) [24,42]. Mastoparan-derived peptide MP7-NH2 inactivates viruses and stimulate cell-mediated

S. No.	Insect	Activity	Peptides	References
1.	*Ixodes ricinus*	Antimalarial, Antiplasmodial	Defensins	Joana Couto., *et al*. 2018
2.	*Photorhabdus luminescens*	Trypanocidal activity, parasiticidal activity	Bioactive metabolite	Ana Maria Antonello., *et al*. 2019
3.	*Xenorhabdus nematophila*	Trypanocidal activity, parasiticidal activity	Bioactive metabolite	Ana Maria Antonello., *et al*. 2019
4.	*Galleria mellonella*	Anti-parasitic activity, anti-leishmanial activity	Moricin-B, Moricin-C4, Cecropin-D and Anionic Peptide 2	Isabel A Patiño-Márquez., *et al*. 2018
5.	*Achillea fragrantissima*	Anti-leishmanial and antitrypanosomal activity	Sesquiterpene lactones, flavonoids, chrysosplenol-D and chrysosplenetine, alkamides	Joseph Skaf., *et al*. 2017

Table 3: Anti-protozoal activity of insect venom toxin peptides.

Figure 3: Showing antifungal activity of insect venom toxins.

antiviral defense. MP7-NH2 inactivates mainly enveloped viruses [43] (Table 4 and figure 4). Scorpion-venom-derived mucroporin-M1 was found active against RNA viruses (measles viruses, SARS-CoV, and H5N1 and HIV-1. Kn2-7 is a scorpion venom peptide that inhibits HIV-1 replication and progression particle [44]. This is a promising candidate development of therapeutic agent against HIV-1 [45]. Cationic peptides showed anti-infection and anti-tumoral activity [46]. T22 [Tyr5,12, Lys7]-polyphemusin II) has been shown to have strong anti-human immunodeficiency virus (HIV) activity. T22 inhibits the T cell line-tropic (T-tropic) HIV-1 infection through its specific binding to a chemokine receptor CXCR4, which serves as a coreceptor for the entry of T-tropic HIV-1 strains. Bee venom toxins show biological activities mainly antiviral [47] (Table 4 and figure 4).

Figure 4: Showing antiviral activity of insect venom toxins.

Tick saliva also contains defensins against microbes mainly viruses. It plays a major role in the innate immunity of ticks [48]. T22 [Tyr5,12, Lys7]-polyphemusin II) inhibits human immuno-

S. No.	Insect	Biological effect	Peptides	References
1.	*Apis mellifera*	Cytotoxic and anti-herpetic effect	Propolis	K Labska., *et al*. 2018
2.	*Bombyx mori*	Cytotoxicity	Seroin	C P Singh., *et al*. 2014
3.	Calliphora vicina	Cytotoxicity, antiviral activity	Tridecapeptidealloferon	Yejin Kim., *et al*. 2012
4.	*Drosophila*	Antiviral immunity,		Alfred W Bronkhorst., *et al*. 2019
5.		Larvacidal activities, insecticidal activity	Genipin glycoside	Qing Xia., *et al*. 2018
6.	*Apis mellifera*	Anti oxidant activity and irritation property	Melittin	Alexander J McMenamin., *et al*. 2018
7.	*Apis cerana*	Antiviral immunity	Cecropin A1	Alexander J McMenamin., *et al*. 2018
8.	*Bombus sp*	Antibacterial, antiviral	Prodigiosin	Alexander J McMenamin., *et al*. 2018
9.	*Apis mellifera*	Antibacterial, antiviral, anti -inflammatory, antiallergic, and vasodilatory actions	Propolis, flavonoids	M Viuda-Martos., *et al*. 2018
10.	*Aedesaegypti*	Anti-flavi-viral, mosquitocidal, anti-Zika virus, adulticidal activity	Catalytically-active $sPLA_2$	ShengzhangDong., *et al*. 2019
11.	*Haemaphysalis longicornis*	Virucidal activity	Defensin-like peptide, HEdefensin	Melbourne Rio Talactac., *et al*. 2017
12.	*Bombyx mori*	Antiviral activity against BmNPV	Prodigiosin	Wei Zhou., *et al*. 2016
13.	*Lonomia obliqua*	Antiviral activity	Defensin-like peptide	A C V Carmo., *et al*. 2012
14.	*Bombyx mori* L	Antiviral, antifungal	Red fluorescent protein (RFP	G K S Manjunatha., *et al*. 2018
15.	*Musca domestica*	*In vitro* anti-influenza activity		FurongWang., *et al*. 2013
16.	*Bombyx mori*	Potential antiviral factor	Serine protease	Hiroshi Nakazawa., *et al*. 2004
17.	*Lonomia obliqua*	Antiviral, insecticidal, and fungicidal activities	rAVLO	Katia N Greco., *et al*. 2009
18.	*Aedes albopictus*	antiviral, insecticidal, and fungicidal activities	Ribavirin (Rbv) ribavirin (Rbv)	H J Liao., *et al*. 1993

Table 4: Anti-viral activity of insect venom toxin peptides.

deficiency virus (HIV) activity. T22 inhibits replication of HIV-1 through its specific binding to a chemokine receptor CXCR4, which serves as a co-receptor for the entry of T-tropic HIV-1 strains. Prodigiosin showed antiviral activity *Bombyx mori* nucleopolyhedrovirus (BmNPV)-infected cells *in vitro,* with specific modes of action [49]. The hemolymph of *Lonomia oblique* caterpillars contain an antiviral protein. This antiviral protein needs baculovirus/Sf9 cell system for expression [50].

The midgut mucosa and serosa and other membrane structures acts as natural barrier of pathogens and assist in making innate immune defense. Red fluorescent protein (RFP) is purified from the digestive juice of *B. mori* larvae. It shows antifungal and antibacterial properties. N-terminal sequence of RFP analysis having chbp gene and it belongs to lipocalin gene family found involve in anti-pathogenic activities. RFP from the midgut of the silkworm larvae showed antiviral activity against the BmNPV. It also shows antibacterial activity against*, Klebsiella pneumonia, Bacillus subtilis* and, *Phytophthora meadii* [51]. PEF (protein-enriched fraction) isolated from the larvae of the housefly showed strong antiviral activity against influenza virus. It stops virus entry into the cells. PEF

has a great potential as a resource of healthy products [52] (Table 4). BmSP-2 is an insect digestive enzyme that acts as an antiviral factor against BmNPV at the initial site of viral infection [52]. Rbv protein is isolated from hemolymph of *Lonomia oblique;* it shows potent antiviral activity against measles, influenza and polio viruses [53]. This protein function as a constitutive agent to make the innate immune defense. These effects may be mediated by changes in the GTP pools of treated cells [54]. Seroins are proteins isolated from *Bombyx mori* show strong anti-viral activity. Seroins could be used as potent candidates for development of transgene-based disease resistant silkworm strains [55]. Melittin and phospholipase A2 (PLA2) are major components of bee venom. Bees and wasps venom also contain anti-cancer peptides (ACPs), most of them are small cationic and hydrophobic peptides which show antioxidant, antimicrobial, neuroprotective or antitumor effects [56] (Table 4).

Anti-cancer peptides

Anti-cancer peptides **(**ACPs) are small cationic and hydrophobic peptides. Anticancer peptides much ably kill cancer cells by causing irreparable membrane damage and cell lysis, or by inducing apoptosis. Mastoparan induce mast cell granulation through exocytosis (Table 5). It facilitates mitochondrial permeability through a transition opening of a pore [57].

Miscellaneous

Animal venoms possess hundreds of molecules, mostly peptides which display diverse biological activities mainly pharmaco-

Species	Peptides	Biological effects	Activity	References
Solitory wasp and hunting Wasps	Pompilidotoxin and dendrotoxin-like peptide), insulin-like peptide binding protein)	Active against bacteria and fungi	Antimicrobial Peptide Neurotoxic peptides	Si Hyeock Lee., *et al*., 2016
Neotropical Social Wasp *Polybia dimorpha*	Polydim-I	Cytotoxic effects, cell wall disruption	Anti-mycobacterial	Rogerio Coutinho das Neves., *et al*. 2016
Polybia paulista	Polybia-CP	Membrane-Active Action Mode	Antimicrobial Peptide	Kairong Wang., *et al*. 2012
Social wasp *Vespula vulgaris*	Mastoparan V1 (MP-V1),	Anti-Salmonella Activity Modulation	antimicrobial peptide	Yeon Jo Ha., *et al*. 2017
Solitary eumenine wasp *Anterhynchium flavo marginatum micado*	Eumeninemastoparan-AF	histamine-releasing factor	Antimicrobial, and hemolytic	Marcia Perez dos Santos Cabrera., *et al*. 2019
Solitary eumenine wasp *Eumenesmicado*	Eumenine mastoparan-EM1 (and eumenine mastoparan-EM2,mastoparan peptides, linear cationic α-helical peptides	Moderate degranulation activity, leishmanicidal activity	Antibacterial activity	Katsuhiro Konno., *et al*. 2019
Parasitoid wasps *Leptopilin aboulardi*	Edin	Cellular cytotoxicity	Mast cell (MC) degranulation	Leena -MaijaVanha-aho., *et al*. 2015
Endoparasitoid wasp, *Microplitis mediator*	VRF1, a metalloprotease homolog venom protein	Toll signaling pathway in the host hemocytes	Anti viral	Zhe Lin., *et al*. 2018

The wild bee *Panurgus calcaratus*.	Panurgines	Hemolytic activity against human erythrocytes.	Antifungal therapeutic, antimicrobial peptides	Čujová S., *et al*. 45
Lasioglossum laticeps (wild bee)	Lasiocepsin	Membrane -permeabilising activity	Antibacterial and antifungal activity	Bednaski AV., *et al*.
Pseudo polybiavespiceps	Mastoparans, Polybia-MPII	Potent action against *S. aureus*, apoptosis and inflammation	antimicrobial drugs,	Juliana C Silva., *et al*. 2017
Social wasp *Polybia paulista*	Polybia-CP	Membrane-active action mode	Antifungal activity	Kairong Wang., *et al*. 2014.
Solitary wasp *Orancistrocerusdrewseni*	OdVP1, OdVP2 and OdVP3	Moderate degranulation activity, leishmanicidal activity	Strong antifungal activities	JiHyeongBaek., *et al*. 2010
Polybia paulista wasp venom	Mastoparan	Parasitic infection	Anti trypanosomal	Juliana Freire Chagas Vinhote., *et al*. 2017
Ectoparasitic wasp *Nasonia vitripennis*	Metalloprotease	The activation of phospholipase C, and culminates in oncotic death	Anti trypanosomal	David B Rivers, *et al*. 2005.

Table 5: Wasp venom peptides.

logical and therapeutic [58]. Polistine wasps use venom stinging as an effective weapon against predators. It contains neurotoxin which are haemolytic, and algogenic in nature [59]. Honey, propolis, and royal jelly, contain phenolic compounds mainly flavonoids [59]. These show anti-bacterial, antiviral, anti-inflammatory, anti-allergic and vasodilatory activities [60]. Flavonoids inhibit important physiological activities such as lipid peroxidation, platelet aggregation, capillary permeability and fragility. It also inhibits cyclo-oxygenase and lipoxygenase enzyme activity [60]. Honeybees prepare propolis a resinous substance that is used in traditional medicine against *Varicella zoster* virus [61]. It shows antimicrobial, anti-inflammatory, and immune modulatory effects.

Royal jelly shows antibacterial, anti-inflammatory, anti-hypercholesterolemic, vasodilative and hypotensive activities. Honey bee venom components prepare antiviral defense by using RNA interference (RNAi), endocytosis, melanization, encapsulation and autophagy. It also operates through conserved immune pathways including Jak/STAT (Janus kinase/signal transducer and activator of transcription), JNK (c-Jun N-terminal kinase), MAPK (mitogen-activated protein kinases) and the NF-kB mediated Toll and immune deficiency pathways [62] (Table 5).

Mellitin, a major component isolated from bee venom, *Apis mellifera*, shows antimicrobial activity against gram positive bacteria. Insects also synthesize variety of immune-induced molecules which show antibacterial and antifungal property [63]. Cationic peptides are also known as alloferons. These were isolated from blow fly *Calliphora vicina* (Diptera) (Table 5).Crude venom of wasp *Nasonia vitripennis* shows lethal effects. Wasps, bees and hornet venom shows hemolytic activity to *Sarcophaga peregrina* (NIH SaPe4), *Drosophila melanogaster* (CRL 1963), *Trichoplusia ni* (TN-368 and BTI-TN-5B1-4), *Spodoptera frugiperda* (SF-21AE), and *Lymantria dispar* (IPL-Ldfbc1) cells [64]. Moreover, peptides and proteins such as pilosulin-like peptides, phospholipase A_2s, hyaluronidase, venom dipeptidyl peptidases, conotoxin-like peptide, and icarapin-like peptide antimicrobial, hemolytic, and histamine-releasing activities. Pilosulin-like peptides 1-6 were chemically synthesized and some of them displayed antimicrobial, hemolytic, and histamine-releasing activities [65] (Table 5). These could be used as important tools for the development of new therapeutic drugs.

Mode of action of peptides

Insect toxins comprise a diverse array of chemicals ranging from small molecules, polyamines and peptide toxins. Many of these venom components target nervous system and neuromuscular ion channels and so rapidly affect the behavior of animals to which the toxin is applied or injected. Melittin, acts on the membrane surface of nerve cells while mastoparan shows strong cytolytic effects. Philanthotoxins found in digger wasps specially target ligand-gated ion channels. These act on nervous system and at neuromuscular junctions. Apamin isolated from bee venom acts upon calcium-activated potassium channels, and influence release of neuropeptides. The crude honey bee (*Apis mellifera*) shows effects on skeletal, smooth as well as cardiac muscles. Crude venom also causes neurotoxicity and inhibits autonomic as well as neuromuscular system. Honey bee venom, shows induction of apoptosis in malignant cells. It shows inhibitory, anti-invasive and cytotoxic effect on several types of cancer lines. Bee venom components melittin shows showed anti-proliferative and anti-metastatic properties and apoptosis in malignant glioma cells.

Mastoparan

Mastoparan destroys bilayer membranes and come across through pores. Both low and high concentrations of mastoparan affect membrane permeabilization through transition pore. G-protein participates in regulation of the permeability through transition pore [66]. Mastoparan severely affects mitochondrial permeability through bi-functional mechanism. Polybia-MPII induces myonecrosis and apoptosis, by involving caspases signaling activity. It results in mitochondrial damage, and cytokine activation [66]. This peptide binds to membrane lipids due to electrostatic attraction. It partially accumulates, neutralizes the opposite charges and induces pore formation in biological membrane. Mastoparan as an inducer of mast cell granules exocytosis has been also related to many essential mechanisms of cell function [57].

Cationic polydim-I

This peptide binds to membrane lipids due to electrostatic attraction. It partially accumulates, neutralizes the opposite charges and induces pore formation in biological membrane. It could be used against multi-drug resistant pathogens mainly bacteria in the hospital environment [67].

Brefeldin A

It interferes in Golgi apparatus endoplasmic reticulum operated functions. Mastoparan activates heterotrimeric G proteins, promotes binding of beta-COP to Golgi membranes *in vitro.* It antagonizes the effect of brefeldin A on beta-COP in perforated cells as well as in isolated Golgi membranes [68].

Sifuvirtide

Sifuvirtide stops HIV-1 fusion. It interacts with lipid structures during fusion after its delivery [69].

Prodigiosin

Prodigiosin selectively target virus-infected cells, inhibit viral gene transcription, and virus-mediated membrane fusion. Prodigiosin found cell cytoplasm where it interact with cytoplasm factors and inhibit virus replication [70].

Conclusion

Insect venom toxin peptides showed diverse biological activity i.e. vasodilatory, anti-septic and cytotoxic hypotensive, antioxidant activity, anti-allergic, anti-hypercholesterolemic, anti-rheumatic and analgesic, anticancer effects. Insect venom toxins also possess remarkable antibacterial, antifungal antiviral, and insecticidal activity. Antimicrobial peptides isolated from venoms of different insects could be used as useful resources for new anti-infective agents. Due to diverse biological activity of insect venom toxins and its fast action of venom toxins make them important for the pharmaceutical industry. No doubt antimicrobial peptides isolated from venoms of different hymenopteran insects could be used for designing anti-infective therapeutic agents. These peptides could be used as templates for designing appropriate and more potent structures by using drug design and drug delivery systems. For pharmacological use of venom toxins, component specific effects are to be explored in various animal models. It is only possible after coordinating efforts being done in the field of biochemistry, pharmacology and immunology. This wider knowledge on insect toxins will help in production of new highly potent drug molecules to fight against various disease pathogens and will open new ways and innovations in the field of therapeutic and pharmaceutical research.

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Conflict of Interest

The authors declare no competing financial interests.

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