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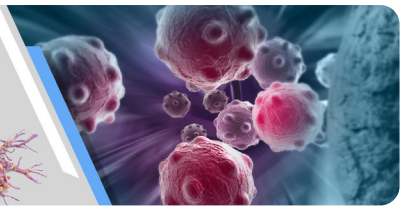

Insect Venoms and their Bioactive Components: A Novel Therapeutic Approach in Chronic Diseases and Cancer

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Abstract

To counteract the growing burden of chronic diseases, discovery of highly selective target specific drugs is of utmost importance in present scenario. Various advanced therapeutic procedures and modern drugs have been developed and approved in last three decades for treating these disorders. The very first limitation of these therapies is their side effects, which are severe and long term. Also, these treatments are a costly affair and of limited therapeutic advantages. To overcome it, exploration and mining of natural products is much necessary. Phytotherapy is already well-established in the field of drug discovery. Focus should also be provided on zoo-therapy, as it is loaded with paramount of possibilities regarding disease treatment. Insect venoms are cocktail of bioactive components with different physiological actions that have undergone evolutionary refinement through a long time-scale. This evolutionary selection over time makes them more suitable candidate for target specific drug discovery. In this review we are trying to throw some light on some significant insect venom components with their mechanism of patho-physiological actions, relevance in the field of advanced drug discovery targeting chronic diseases including cancer.

Keywords: Bioactive Components; Cancer; Chronic Diseases; Insect Venom; Therapeutics

Abbreviations: MPN – Mastoparan; PLA2 - Phospholipase A_2; Ca_v - Voltage Gated Calcium Channel; Cl_v - Voltage Gated Chloride Channels; Na_v - Voltage Gated Sodium Channels; K_v - Voltage Gated Potassium Channels; COX – Cyclooxygenase; CYP450 - Cytochrome P450; LOX – Lipooxygenase; GPCR - G-Protein Coupled Receptors; sPLA2 - Secretory Phospholipase A_2; SK channels - Small Conductance Channels; IgE – Immunoglobulin E; IFN-γ - Interferon γ; MCD - Mast Cell Degranulating Peptide; AaH IT - Beta-Insect Excitatory Toxin 1; CSTX-1 - Omega-Ctenitoxin-Cs1a; VEGFR-2 – Vascular Endothelial Growth Factor; PI3K – Phosphoinositide 3-Kinases; HT 29 – Human Colorectal Adenocarcinoma Cell Line; MAPK- Mitogen-Activated Protein Kinase; CD44 – Cluster of Differentiation 44; BmK AGAP – *Buthus martensii Karsch* Antitumor Analgesic Peptide; BmK CT – *Buthus martensii Karsch* chlorotoxin-like Toxin; Bcl-2 – B-Cell Lymphoma 2; NFκB – Nuclear Factor κ B; CD4 – Cluster of Differentiation 4; IL – Interleukin; K_{Ca} – Ca activated Potassium Channel; MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; AChE – Acetylcholinesterase; TNFα - Tumor Necrosis Factor α; PARP – Poly (ADP-ribose) Polymerase; PEG – Polyethylene Glycol; TXA2 - Thromboxane A2; ERK/MAP - Extracellular Signal-Regulated Kinases / Mitogen-Activated Protein; EGF - Epidermal Growth Factor; MMP 9 - Matrix Metallopeptidase 9; PI3K/Akt/mTOR - Phosphatidylinositol 3-Kinase / Protein Kinase B / Mammalian Target of the Rapamycin; FAK

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- Focal Adhesion Kinase; STAT - Signal Transducer and Activator of Transcription; HYAL – Hyaluronidase; TGF-β - Transforming Growth Factor-β; WWOX - WW Domain-Containing Oxidoreductase; GTP - Guanosine Triphosphate; Erα - Estrogen Receptor-α; LBD - Ligand Binding Domain; VSAP - Vasodilator Stimulated Phosphoprotein

Introduction

Phylum Arthropoda is the largest of all existing animal phyla occupying about 80% of the total all the living animal species. A number of species of this phylum have been a part of human life from time immemorial through many aspects viz. as food and nutritional component, as medicine as well as household usages such as in preparation of dyes, ink, fabrics, ornaments, wax etc. Insects have been a part of traditional medicine as well as cuisine from ancient era in countries like India, China, Africa, Laos, Japan, Papua New Guinea etc [1-5]. For example, entomophagy culture of China, where fried scorpions are enjoyed as delicacies. Dried whole body of the scorpion is also being used as a cure for epilepsy and pain reliever agent in China [6,7]. In Japan larvae of yellow jacket wasps (common name Hebo) are marketed as canned products and consumed for their nutritional values and taste [3,8]. The eggs of red ants are fried and consumed in India and it is also associated with cultural emotion of one of the states, Assam, India. The winged termites of the family Macrotermitinae, merging from termite hills at the end of dry season are captured and consumed in many parts of the world. Queen termites are so rich in fatty acids (linoleic acid), proteins and other micronutrients that the fried or sun dried termite queens are fed to malnourished children in some countries like Uganda and Zambia [9-13]. Development of new therapeutical procedures in the medical field has led to find cures to some extent, of many chronic disorders like rheumatoid arthritis, diabetes, cystic fibrosis etc. Many therapies viz. radiotherapy, chemotherapy etc. are also developed and approved in the field of cancer therapy in past decades. However, these therapies come along with long term side effects and a limited therapeutic advantage. In some cases, the patient acquires resistance towards the therapies (such as radio-resistance, chemoresistance) [14-16]. Moreover, the cost of these expensive therapies is a limiting factor of availability for the suffering patients. For these reasons, a novel and better therapeutic option is required to be developed which is cost effective, safe and readily available. In recent years, modern day therapeutics are turning towards alternative and oriental medicinal practices for treating chronic diseases including cancer as they are highly effective and have seemingly lesser or no side effects as compared to synthetic drugs. Naturopathy is gaining popularity in the field of drug discovery also because of the fact that it is cost effective and of easy availability. Herbal therapies and zootherapies are given wide attention amongst researchers for their isolated bioactive components. A substantial proportion of these nature derived pharmacologically active principles have anti-oxidant, anti-inflammatory, anti-hyperglycemic, anti-microbial, anti-cancer and anti-nociceptive properties that can play important roles in powerful drug discovery against different diseases as well as cancer [17-22]. One such nature's treasure is insect venom. Venoms are secreted by a large number of insect groups as a strategy of defense as well as predation mechanism. It is secreted by a specialized organ or tissue called venom gland and introduced into the prey or predator's body by means of parenteral applicators such as teeth, fangs, nematocytes, setae, spines etc. [23]. Insect venom contains a plethora of bioactive principles that can target different signaling pathways of the cell, which are involved in inducing discomfort, pain, inflammation, headache, vomiting and breathlessness in extreme cases. Most of the animal venoms studied from scorpion, spider, snakes, and wasps are a heterogenous mixture of enzymes of M.W. greater than 10 kDa (mainly Phospholipases and proteases), inorganic salts, polypeptides and small organic molecules [24-26]. Various published and ongoing research works have established that the complex molecular scaffolds present in venom components can modulate the intrinsic signaling pathways that are associated with pain, apoptosis, necrosis, inflammation etc. [27,20]. This property may possess a paramount of importance and possibility in modern day drug discovery, in other words discovery of pharmaceutical liquid gold from proteinaceous venom [19]. Another advantage associated with considering venom as a template for drug designing is that they have undergone a process of evolutionary refinement (natural selection) and evolved to perform optimally and selectively on their target [28]. Here it is tried to cover the later in this review in relation to their mechanism of target modulation.

General Mechanism of Venom Action

It has become evident from the various studies performed in past three decades that insect venoms are endowed with intricate mixture of numerous bioactive principles that targets different cell membrane receptors, thereby modulating signaling pathways and ion channels activating nociceptive pathways, grossly put under cytotoxins. Again, some other type of venom principles, classified under neurotoxins, generate action potential by acting on the nervous system and incapacitate the prey or predator organism [29,20]. Both of these venom delivering mechanisms targets different signal receptors of cells and causes pain, inflammation and asphyxiation in some cases. Venoms of hymenopteran insect's wasps, honey bees contain cytotoxic peptides mastoparan and melittin respectively. These peptides being amphipathic in nature, possess the capacity to disrupt the integrity of the plasmamembrane by interacting with the phospholipids which ultimately leads to pore formation and cell lysis. The cell leaks out the viable cell organelles and approaches to death. Bradykinin is another peptide component of wasp's

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venom that acts synergistically with mastoparan (MPN). An enzyme called phospholipase A_2 (PLA2) is responsible for further damage of the phospholipid bilayer and exposes the lipids of the inner leaflet (such as phospatidylserine, phosphatidyl ethanolamine). This in turn activates apoptosis by sending "eat me" signals. [30-33]. Neurotoxic venoms of scorpions, centipedes and spiders have pharmacological properties of targeting ion channels directly related to pain inducing paralysis. Their venoms are a deadly cocktail of peptides, proteins and enzymes with diverse bioactives. Insect neurotoxins mainly reacts with voltage gated calcium channels (Ca_v), sodium channels (Na_v), potassium channels (K_v), acid sensitive ion channels etc. Moreover they show other significant physiological activity, viz. anticoagulant activity, PLA2 activity, platelet aggregating, trypsin inhibitory activity etc. [34-38].

Important Bioactive Components Isolated from Insect Venoms and their Sources

Phospholipase A_2

PLA2 is a major component isolated from venom of wide range insects such as wasps, bees, scorpion, centipede that performs wide range of catalytic activities [39-41]. The glycerophospholipids of the plasmamembrane are hydrolysed by PLA2 at the ester bond in the sn-2 position releasing fatty acids such as oleic acid, arachidonic acid etc. and lysophospholipids (viz. lysophospatidyl choline, lysophospatidyl inositol, lysophospatidyl ethanolamine etc. [41,42]. All these act as a precursor of a class of lipid derived hormones known as eicosanoids. This is an enzyme assisted process, where enzymes namely cyclooxygenase (COX), cytochrome P450 (CYP450), lipooxygenase (LOX) are involved in this conversion mechanism. Elevated levels of eicosanoids in the circulation is directly related to inflammation, pain, swelling, redness etc. [43-46]. Thus eicosanoids are related to immunomodulatory functions. The pro-inflammatory signalling molecules, such as prostaglandins, leukotrienes, thromboxanes etc., derived from hydrolysis of phospholipids of the cell membrane by the PLA2, depolarises the nerve fibres associated with nociception. These signalling molecules bind to the neuron membrane receptors, e.g., ionotropic receptors, G-protein coupled receptors (GPCR), tyrosin kinase receptors etc., elevating the sensitivity of nerve endings or causing hyperalgesia [47,48]. PLA2 derived from honey bee is categorized under group III of secretory phospholipase A_2 (sPLA2) containing a total of eight disulphide bonds [49]. PLA2 isolated from Egyptian honey bee, *Apis mellifera lamarckii* has reportedly shown anti- coagulation and anti- platelet aggregating activities by prolonging prothrombin time [50]. It showed analgesic activity against sensory neuropathic sign of pain induced by oxaliplatin, a cancer drug used to treat metastatic colorectal cancer [51]. Venom of Vespids and fire ants predominantly contain phospholipase A_1 (PLA1) that also functions similar to PLA2 causing hypersensitivity reactions [52].

Mastoparan

The most predominant peptide of wasp venom is mastoparan (MPN). It is a cationic decapeptide with the amino acid sequence of Ile-Asn-Leu-Lys-Ala-Leu-Ala-Ala-Leu-Ala-Lys-Lys-Ile-Leu-NH2. MPN directly interacts with membrane phospholipids causing destabilization and membrane lysis (pore formation) leading to leakage out of vital cell organelles causing cell death [53]. It is linked with stimulatory secretion of histamine from mast cells [54-56]. Reports showed that MPN can directly interact with the G-protein to activate it and this bound conformation mimics the G-protein coupled receptor (GPCR) of cell membrane [57,58]. Besides histamine, this peptide is also involved with other secretory activities from variety of mammalian cells, such as serotonin, insulin, catecholamines, surfactants from platelets, pancreatic islet cells (β cells), type 2 pulmonary alveolar cells, chromaffin cells respectively [38,59,60,56,61]. It also stimulates Ca^{2+} influx and increases intracellular Ca^{2+} concentration [62]. It interacts with the membrane phospholipids of mitochondria resulting into formation of permeability transition pore which in turn leads to swelling and rupturing of outer and inner mitochondrial membranes [62,63]. Involvement of MPN in stimulating G protein that is pertussis toxin sensitive and regulating activities of phospholipase A2 and C in Swiss 3T3 cells, was also established [64].

Bradykinin / Wasp kinins

The heterogeneous mixture of wasp and ant venoms contain kinin polypeptides of about 8-19 amino acid sequences. A venom constituent similar to bradykinin was first reported in the venom of *Vespa vulgaris* and categorised under wasp kinin [65-68]. Wasp kinins are neurotoxic in nature and similar to the sequence of bradykinin [69]. The bradykinin like wasps kinins differ in the presence of amino acid residues in the positions 3 or 6. On this basis, wasps kinins are of three main types, bradykinin, Hyp^3-bradykinin (hydroxyproline replaces proline) or Thr^6-bradykinin (threonine replaces serine) [66,70]. The latter Thr^6 is more potent in blocking the pre-synaptic signal transmission in insect central nervous system (CNS) than bradykinin itself [71,72]. Kinins can permanently paralyze the prey by irreversible blockage of CNS. Cascade of reports have established that kinin peptide causes contractions and relaxations of smooth muscle preparations of visceral organs such as fundus, colon, rectum (mild contractions) and duodenum and ileum (strong contractions) in rat [73-75]. Slow and delayed contraction of guineapig ileum and rabbit intestine along with reducing blood pressure in cat and rabbit, were also recorded upon treatment with wasp kinin [76].

Melittin

The predominant component of bee venom (apitoxin)

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is a small basic peptide of 26 amino acid residues called melittin. The sequence reads as Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-NH_2 [77-79]. Being amphipathic in nature, this peptide portrays surfactant and detergent like activities and interacts with cell membrane by wedge and edge effects to create membrane pores [79]. It binds with anionic phospholipids (viz. phospatidyl-serine, phospatidyl-ethanolamine, phosphatidyl-inositol etc.) and disrupts the bilayer structure leading exocytosis and cell death [80]. Melittin carries out lytic action along with secretion of histamine from mast cells and liberates haemoglobin from red blood cells (haemolytic agent) [81-83]. It is also associated with nerve fibre depolarisation, secretion, stimulation and activation of various hormones, enzymes including leuteinizing hormone, phospholipase C and D, adenylate cyclase, protein kinase C, G-protein etc. [84-88]. Another physiological activity of melittin is that it assists in enhancement of phospholipase A2 (PLA_2) activity on cell (Shier, 1979).

Apamin

Apamin of bee venom is a neuropeptide component of about 18 amino acid long sequence (-Cys-Asn-Cys-Lys-Ala-Pro-Glu-Thr-Ala-Leu-Cys-Ala-Arg-Arg-Cys-Gln-Gln-His-NH_2). This peptide shows a very specific mode of action, unlike melittin, which effects various physiological activities of the cell. Apamin interacts and blocks (allosteric inhibition) the Ca^{2+} dependent K^+ channel pores and inhibits the actions of small conductance channels (SK channels), widely expressed in the CNS. Thus, it depresses the amplitude of various after hyperpolarisation signals. These signals are important for stimulation of Ca^{2+} dependent SK channels and this activation is mediated by calmodulin. Excitation of SK channels plays a crucial role in functioning of different cell types, viz. muscle cells, neurons, epithelial cells, T lymphocytes etc and in blockage of hyperpolarising inhibitions, such as cholinergic, adrenergic excitations [89-99,30].

Hyaluronidase

Hyaluronidase is a venom allergen found in venom of several stinging and biting insects including bees, wasps, ants, fleas, scorpion, spider, hornet etc [100-105]. Its presence in insect venom was first reported in *Phoneutria nigriventer* and *Lycosa raptoral* in 1953, but purified and characterized from the venom of *Dugesiella hentzi* tarantula in the year of 1973 [106,107]. Hyaluronidase is a glycoprotein that primarily acts on hyaluronan, chondroitin sulfate, dermatan sulfate to degrade these into disaccharides and tetrasaccharides [105]. Its hydrolysing activity is enhanced and inhibited by the presence of modulators such as, histamine, anti-histamine, adrenaline, acid phosphatase, heparin, flavonoids, vitamin C etc. [108,109]. This venom glycoprotein is not toxic itself but labelled as "spreading factor" due to its role in hydrolysing the extracellular matrix opening the gap junctions, which in turn leads to enhancement of diffusion of other venom toxins in the blood circulation of their prey, which in turn increases the physiological and pathological effects of envenomation [110-115]. Moreover, it is identified as an venom allergen as it is responsible for inducing IgE mediated fatal anaphylactic shock and hypersensitivity in case of human encounter [103,110].

Ectatomin

Ectatomin is a class of novel positively charged proteins isolated from the venom of tropical ant species *Ectatomma tuberculatum* and *E. qudridens*. The toxicity level of ectatomin surpasses that of bees and solitary wasps [116]. The structural moiety of this class of venom consists of two amphiphilic homologous polypeptide chains, each consisting of 34-37 amino acid sequences with clusters of basic lysine residue. These two chains are connected by disulphide bond at the centre (between Cys22 of A and Cys20 of B chain) [117]. Two subgroups of ectatomins are Et and Eq, subdivided on the basis of position and presence or absence of intrachain disulphide bond. Ectatomin shares homology with interferon γ-inducible protein (IFN-γ- inducible protein) and tyrosine-related transforming proteins. It acts as a cell penetrating peptide or pore forming peptide by interacting with membrane receptors and activating a cascade of reactions (specifically protein kinase A, C, tyrosine kinase etc.). It ultimately leads to leakage of ions across membrane, lysis and cell death [118]. This cytolysin toxin is also involved in modulation of Ca^{2+} channel activities, which results in conformational change of Ca^{2+} channel and elevated calcium currents. This presumably modulates the cascade of β adrenergic signal transduction reactions [117,119,120].

Mast Cell Degranulating Peptide (MCD)

MCD is another cytolysin toxic peptide component of bee venom consisting of 22 amino acid residues, predominantly containing arginine or lysine (basic in nature). ^{1}H-NMR analysis showed a similar built structure to apamin, of α helical chains with two disulphide bridges [121-123]. As the name indicates, MCD degranulates mast cells, releasing histamines (De Souza and Palma 2009; Nakajima, 1986). Thus, this peptide is associated with activation of histamine mediated cellular responses, viz. inflammation, reddening, pain at the site of encounter by bee stinging [124]. MCD also targets K_v channels leading prolonged action potential of neurons, hyper-excitation of central nervous system (CNS) and seizures [125,126].

Other Arthropods as Venom Source

Scorpion Toxin: Genus *Scorpio* includes one of the most potent toxin producing group of arachnids, scorpions. Scorpion venom is a deadly amalgamation of neurotoxic peptides, proteins, amines and nucleotides, which they use against prey or predators to paralyze them in instant

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[127,128]. This toxin primarily targets the ion channels associated with autonomic nervous system, such as, voltage gated K_V, Ca_v, Na_v, Cl_v channels. It forms a stable interaction with the channel proteins owing to the fact that it has highly stable three dimensional backbone with 3-4 disulphide bonds [129]. This neuropeptide blocks K_V and Cl_v channels and also acts upon voltage sensitive Na_v and Ca_v channels [130-132]. By affecting opening and closing of these ion channels, it prolongs depolarisation of the membranes of nerve, skeletal muscle and cardiac muscle cells, increases action potential and neurotransmitters get released. It slows down inactivation of Na_v channels, which in turn results in multiple repetitive stimulus firing in motor nerves of the prey leading to immediate paralysis [133]. First isolated scorpion toxin with highly specific excitatory anti-insect property is AaH IT, which portrays highest affinity towards Na_v channels of arthropods [134]. Chlorotoxin is small peptide component of scorpion venom (36 amino acid residues long) that modulates functioning of Cl_v channels and paralyzes normal cells in insects but not toxic towards normal human cells [135,136].

Spider Toxin: After insects, spiders occupy the second position of largest taxonomic group of phylum Arthropoda. Spider venom is a neurotoxic combination of different components, viz., polyamines, amines, nucleotides, ions, organic acids (primarily citric acid), neuropeptides, enzymes etc. [137,138]. Venoms of some species of spiders including *Cupiennius salei* and *Aphonopelma hentzi* contain higher concentration of potassium and lower concentration of sodium ions. This causes increased excitation and depolarisation across cell membranes, in turn leading to rapid paralysis of the victim [139]. A cytolytic agent named cupiennin 1 isolated from the venom of *C. salei* was reported to act synergistically with neurotoxic component CSTX-1, enhancing its toxicity [140-142]. Cationic peptide components of spider venom are cytolytic and antimicrobial in nature. These peptides bear positively charged amino acid side chains that interact with negatively charged polar heads of the phospholipids of the cell membrane. This ultimately changes the lipid bilayer membrane configuration and leads to pore formation. Venom peptides that are rich in cystine residues act as neurotoxic peptides owing to formation of stable complexes with various receptors and ion-channels of cell membranes [143]. Some ion channel blocker constituents of spider venom are namely, ω-agatoxin-1a (targets on inhibition of Ca_v channels), μ-diguetoxin-Dc1a (Na_v channels blocker), κ-hexatoxin-Hv1c (K_y channels blocker), π-theraphotoxin-Pc1a (blocks acid sensing ion channel) etc. [144,145].

Centepede Toxin: Centepedes belong to class Chilopoda of terrestrial arthropods and of predatory in nature. In this group of arthropods, the first pair of appendages are modified into poison claws or forcipules that act as piercing forceps. Venom of centipede is a neurotoxic pool of different peptides, enzymatic and non-enzymatic components, that once injected can initiate rapid paralysation of the prey [35,146]. These neurotoxic peptides principally acts on voltage gated ion- channels as well as showcases different physiological activities, viz, anticoagulantion, platelet aggregation, inhibition of trypsin activity, PLA2 activity etc. [34]. Summation of all these activities leads to cell lysis and tissue damage. Some isolated neurotoxic peptide constituents from the venom of S. *subspinipes mutilans* are namely, κ-SLPTX-Ssm1a (modulates Na_v, K_v channels), κ-SLPTX-Ssm2a (inhibitor of K_v channels), κ-SLPTX-Ssm3a (selective inhibitor of K_v channel) etc. (Yang et al., 2012). Another two toxic peptide components called ω-SLPTX-Ssm1a and ω-SLPTX-Ssm2a are reported by Yang et al., to act on Ca_v channels and modulate the rate of calcium influx. Peptide toxin SsmTx-I from *S. subspinipes mutilans* was reported to act as K_V2.1 modulator by inhibiting K_V2.1 current [147].

Regulating Pathways of Different Venom Toxins

Phospholipase A_2

Phospholipase A2 triggers the activation of arachidonic acid signaling pathway which leads to thromboxane A2 (TXA2) synthesis in a reaction catalyzed by thromboxane synthetase (to form TXA2) and cyclooxygenase-1 (COX-1) (to form prostaglandin G2/H2). When TXA2 is released to the bloodstream, it binds to TXA receptors present on the surface of circulating inflammatory cells, adjacent platelets, and atherosclerotic plaque components and this amplifies and perpetuates the atherothrombotic process [148].

Mastoparan

The disruption of p38 MAPK activity secondary to the disruption of G protein-coupled signaling caused by mastoparan results in decreases in both IL-6 and NF-κB reporter activities in human dermal microvessel endothelial cells and in a murine macrophage cell line [149].

Bradykinin

Kinins and their cognate receptors can take part in regulation of cell proliferation [150]. Therefore, bradykinin-mediated activation of ERK/MAP kinase pathways is well studied and several different cellular mechanisms are suggested [151]. It is observed that increase in intracellular calcium concentrations in endothelial cells, produced either by GPCR stimulation or artificially, activates tyrosine kinases and ERK/MAP kinase module [152].

Melittin

Bee venom, melittin has significant inhibitory effects on the EGF-induced invasion and migration of breast cancer cells. Also, melittin reduces the EGF-stimulated F-actin reorganization at the leading edge. Particularly, melittin

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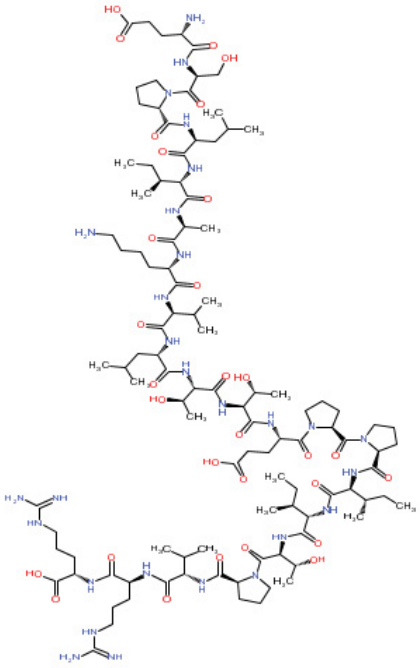
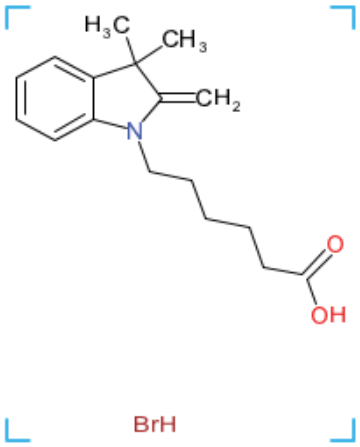
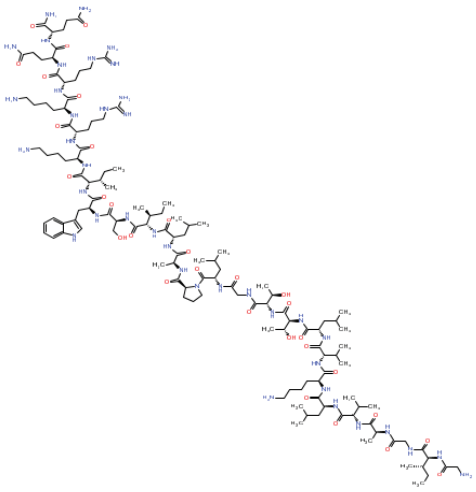


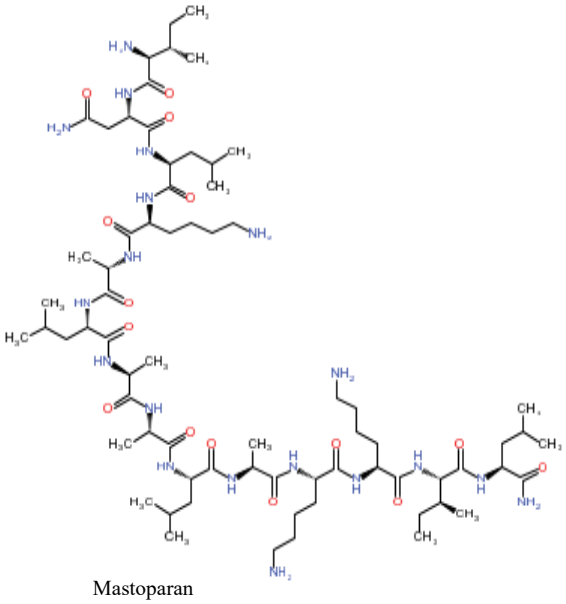
Phospholipase A



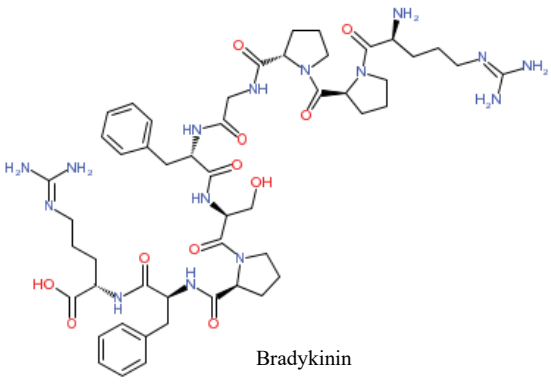
Hyaluronidase



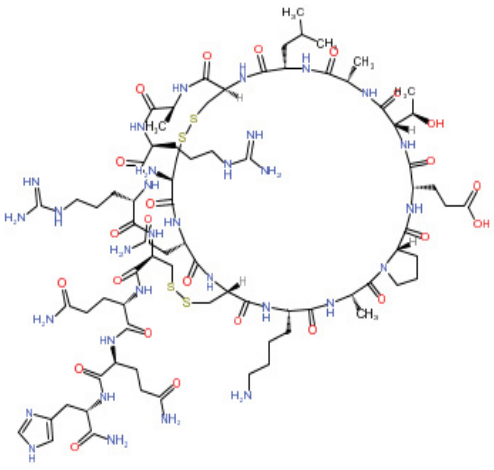
Melittin



Mastoparan



Bradykinin



Apamin

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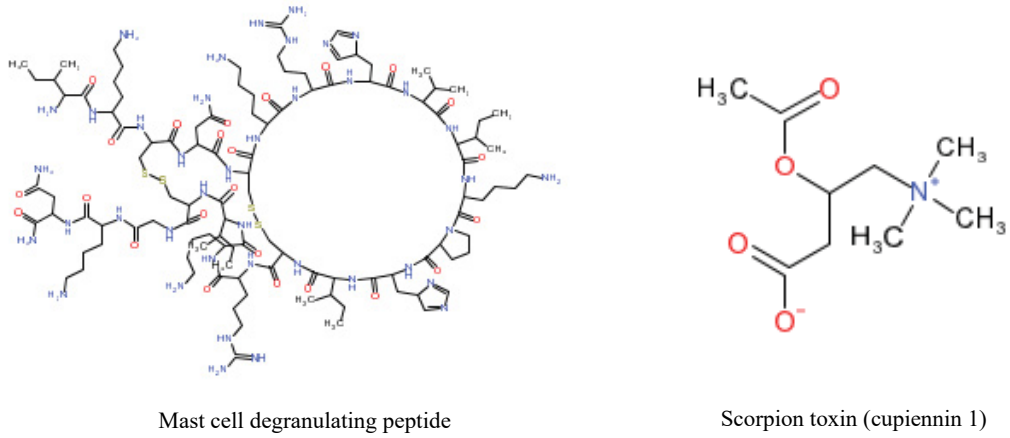

Mast cell degranulating peptide

Scorpion toxin (cupiennin 1)

Figure 1: Chemical structure of different venom toxins.

Table 1: General physiological action of some important insect venom components.

Arthropod category	Genus/Species	Toxic component	Chemical nature	Nature of cellular activity	Physiological target
Wasps	*Vespula lewisii*	Mastoparan	Peptide	Cytolytic	Membrane phospholipids, cell lysis
Honey bee	*Apis mellifera*	Melittin	Peptide	Cytolytic	Cell membrane, pore formation
		Apamin	Peptide	Cytotoxic	Ca^{2+} dependent K^+ channel, SK channels
		MCD	Peptide	Cytotoxic	Mast cells, releases histamine
Vespa, fire ants, bees	Several species of *Vespa, Vespula, Polybia, Polistes*, *Solenopsis invicta*	Phospholipase A1	Protein	Cytotoxic	Membrane glycerophospholipids
Wasps, bees, centipedes	Many species of *Apis, Polybia, Agelaia, Bombus, Scolopendra* genera	Phospholipase A2	Protein	Cytotoxic	Same as PLA_1
Bees, wasps, ants, fleas, scorpions, spiders, hornets	First isolated from *Dugesiella hentzi*, many members of *Apis, Vespa, Scorpio*, *Solenopsis*	Hyaluronidase	Glycoprotein	"Spreading factor"	Hyaluronan, chondroitin sulfate, dermatan sulfate
Ants	*Ectatomma tuberculatum*	Ectatomin	Peptide	Cytolytic	Membrane receptors
	Paraponera clavata	Poneratoxin	Peptide	Neurotoxic	Voltage gated sodium channels
	Pachycondyla goeldii	Ponericin	Peptide	Cytotoxic	Cell membrane (pore formation)
Wasps, bees and ants	Several species of *Vespa*, *Apis* and *Pogonomyrmex*	kinin	Peptide	Neurotoxic	Central nervous system (CNS)
Hornets	*Vespa crabro*	Crabrolin	Peptide	Cytotoxic	Mast cell, RBCs
Bumblebees	*Megabombus pennsyluanicus.*	Bombolitin	Peptide	Cytotoxic	Cell membrane penetration
Scorpions	*Leiurus quinquestriatus hebraeus*	Chlorotoxin	Peptide	Neurotoxic	Voltage gated chloride channels
Scorpions	*Pandinus imperator*	Scorpine	Peptide	Neurotoxic	Voltage sensitive ion channels
Blister beetle	*Cantharis vesicatoria*	Cantharidin	Fatty terpenoid	Cytotoxic	Outer layer of skin, desmosomal plaque
Centipede	*Scolopendra subspinipes mutilans*	SsmTx-I	Peptide	Neurotoxic	Voltage gated potassium channel

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inhibits the EGF-induced MMP-9 expression through blocking the PI3K/Akt/mTOR and NF-κB pathway. In addition, melittin effectively suppresses the EGF-induced FAK phosphorylation through the inhibition of mTOR/p70S6K/4E-BP1 pathway [153].

Apamin

Apamin inhibits IFN-γ- and TNF-α- induced inflammatory cytokines and chemokines through the suppression of STAT and NF-κB signaling pathway in human keratinocytes [154].

Hyaluronidase

In a non-canonical signal pathway, hyaluronidase (HYAL-2) serves as a receptor for TGF-β to signal with downstream tumor suppressors, namely SMAD4 and WWOX to control gene transcription. Cell death occurs when SMAD4 responsive element is overly driven by the HYAL-2–WWOX–SMAD4 signaling complex. In case of rats subjected to traumatic brain injury, over accumulation of a HYAL-2–WWOX complex occurs in the nucleus which causes neuronal death. Hyaluronan induces the signaling of HYAL-2–WWOX–SMAD4 and relocation of the signaling complex to the nucleus. When the signaling complex is overexpressed, WWOX-expressing cells face bubbling cell death [155].

Ectatomin

Ectatomin can get efficiently inserted into the plasma membrane, where it can form channels. Ectatomin was found to inhibit L-type calcium currents in isolated rat cardiac myocytes [117]. In these cells, ectatomin induces a gradual and irreversible increase in ion leakage across the membrane that can lead to cell death.

Mast Cell Degranulating Peptide

Mast cell degranulating peptide is the most potent peptide of naturally occurring mast cell secretagogues. It is found to stimulate the GTPase activity of G proteins (G_0/G_i) in a concentration dependent manner [156].

Scorpion Toxin (Chlorotoxin)

Chlorotoxin can directly bind to ERα and change the protein secondary structure of its LBD domain, hence inhibiting the ERα signaling pathway. Vasodilator stimulated phosphoprotein (VASP) is a target gene of ERα signaling pathway. Chlorotoxin can inhibit breast cancer cell proliferation, migration, and invasion via ERα/VASP signaling pathway [157].

Spider Toxin (ω-agatoxin-1a)

Phorbol-12 myristate-13 acetate - promoted calcium influx can be inhibited by spider toxin such as ω-agatoxin-1a which is a calcium channel blocker specific for Cav2.1 channels [158].

Therapeutic Potential of Venom in Chronic Diseases

In cancer

Insect venom can play a promising role to tackle the growing burden of cancer, as they are packed with target specific bioactive components. Many of the insect venom principles show affinity towards membrane phospholipids expressed on cancer cell and membrane receptors. They exert cytotoxicity and cell lysis. This property can be useful in targeting cancer cells and development of novel target specific drugs. Mastoparan, one key component of wasp venom, mediates cancer cell cytotoxicity and death by binding with anionic phospholipids expressed on the membrane of cancer cells. This interaction leads to pore formation and leakage of vital cell organelles out of the cell. It also affects the mitochondrial membrane permeability transition causing swelling and ruptures outer and partially inner mitochondrial membranes [63]. Mastoparan induces release of LDH from leukemia cells, suggestive of the fact that it is an anti-cancer peptide (ACP) with lytic property [159]. Report has shown that peritumoral mastoparan administration in murine melanoma model delayed tumor growth by activating apoptosis [160]. Similar potential is seen in case of bee venom peptides. Melittin acts as a surfactant, binds with membrane phospholipids and disrupts the bilayer leading to exocytosis. It inhibits calcium binding protein calmodulin and restricts the growth of leukemic cells [161]. It shows anti-tumor potential by blocking COX-2 and VEGFR-2 mediated MAPK signaling pathway [162]. Solenopsin, isolated from fire ant *S. invicta* shows anti-angiogenic property and inhibits PI3K signaling [163]. Huh et al. reported that bee venom can downregulate vascular endothelial growth factor (VEGFR-2) signalling pathway, in turn inhibits tumour proliferation, angiogenesis and metastasis. A potent anti-cancer agent isolated from Chinese blister beetle (*Mylabris phalerata*), called cantharidin can arrest cell cycle in G2/M phase and induces apoptosis in T 24 and HT 29 cell lines (Huan et al., 2006). It also suppresses pro-tumor autophagy and induces cell death in triple negative breast cancer cell lines [164]. BmHYA1, a hyaluronidase from *Buthus martensi* showed anti-proliferative activity by reducing expression of CD44 variant in breast cancer cell line [165]. Various potent anti-cancer agents are also reported in the venom of scorpion *Buthus martensii Karsch*, such as BmK AGAP, BmKCT, that targets cancer signaling pathways, viz., Bcl-2, NFκB, MAPK pathways and inhibits Na_V and chloride current in cancer cell lines (Zhao et al., 2011; Fu et al., 2007; Fan et al., 2010)·

In Rheumatoid Arthritis (RA)

RA is a chronic auto-immune disorder characterised by inflammation, joint pain, redness and ankylosis, which can lead to deformities and permanent disability. Hydrolysis of glycerophospholipids by PLA2 releasing lysophospholipids,

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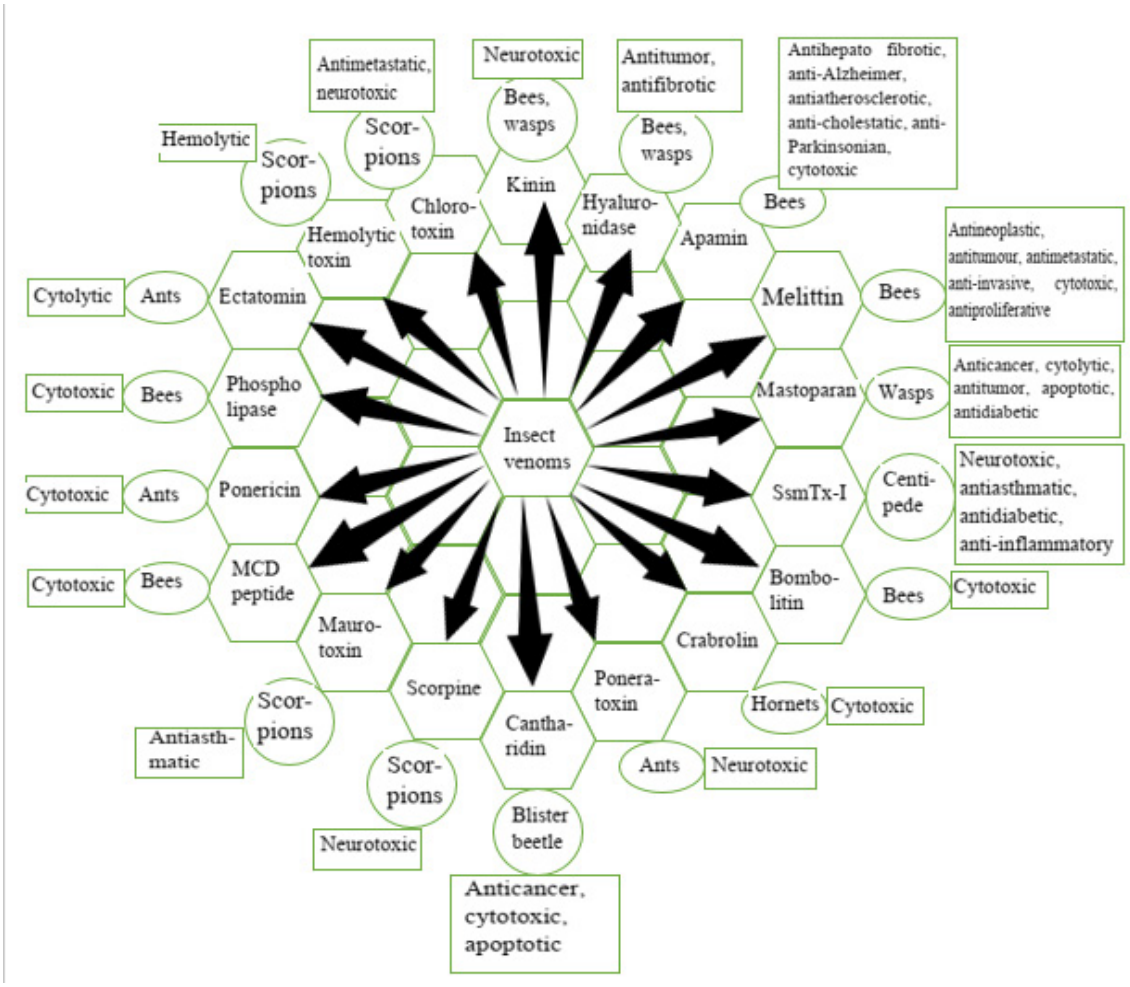

Figure 2: Biological activity of bioactive components present in insect venoms.

precursor of eicosanoids. Eicosanoid level elevation in circulation is related to patho-physiologicial conditions as pain, inflammation etc. Blocking the voltage sensitive ion channels (such as Na_V, Ca_V, acid sensitive ion channels) and receptors (e.g., purinergic receptors) associated with nociception can reduce the pain and inflammatory condition of RA. Analgesic effects of bee venom components (melittin and apamin) are already reported in a number of research works [166-168]. These bio-actives can inhibit enzymatic activity of sPLA2 and reduce inflammation [169,170]. Nipate et al. in 2015, evaluated anti-arthritic, anti-inflammatory property of Indian honey bee (*Apis dorsata*) venom in FCA and CIA-induced rat arthritic model. Random clinical trials on using bee venom acupuncture in treating RA showed improvement of joint pain and swelling in RA patients [171]. Huwentoxin-I and Huwentoxin-IV toxins isolated from *Ornithoctonus huwena,* inhibits voltage sensitive sodium channels ($Na_V1.7$) and tetrodotoxin- sensitive channels [172]. These channels are directly related to depolarisation of nerve fibres associated with nociception. μ-scoloptoxin-Ssm6a, a toxic principle isolated from *S. subspinipes mutilans*, inhibits $Na_V1.7$ channels portraying anti-nociceptive potential against formalin-induced pain in rat model, which is many fold higher than morphine [173]. SsmTx-I is another active component from *S. mutilans* that showed anti-inflammatory property by blocking voltage gated potassium channels $K_V2.1$ in murine model system [147].

In diabetes

Type I diabetes, also called diabetes mellitus is an autoimmune disorder characterized by impairment of insulin action and secretion and hyperglycemia whereas, type II diabetes, known as diabetes insipidus is related to dietary habits and resistance towards insulin action as well as hyperglycemia. Active toxic component of wasp venom, mastoparan has been reported to increase insulin release on glucose augmentation from pancreatic islet cell of human [174]. SsmTx-I, from *Scolopendra subspinipes mutilans*, can specifically blocks voltage gated potassium channels ($K_V2.1$) found in pancreatic β cells and stimulates insulin secretion [147]. Hassan et al. in 2019 reported that bee venom components also possess the property to suppress plasma

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glucose level and increases insulin level in albino rat model system. Active toxic component GxTX-1 from the venom of tarantula *Plesiophrictus guangxiensis*, inhibits delayed rectifier potassium current in β cells and increased glucose stimulated secretion of insulin (Herrington et al., 2006).

In asthma

Asthma is a chronic disorder characterized by inflammation, narrowing of lungs airways and excessive mucous production. It can be life threatening by making the patient experience difficulty in breathing and shortness of breath. This pathophysiological condition is related to infiltration of CD4 T cells that expresses IL-2 and IL-17 cytokines responsible for inflammatory condition of asthma. This proliferation of type 2 helper T cells (T_h2) occurs due to exposure to allergens. Bee venom reportedly decreased the levels of T_h2 cytokines and serum IgE levels in ovalbumin induced asthma in mice (Choi et al., 2013). Maurotoxin isolated from *Scorpio maurus palmatus* has been found to inhibit intermediate conductance channel, K_{Ca} channel, in human T lymphocyte cells in concentration dependent manner [175]. T lymphocyte cell activation is modulated by K_{Ca} channels [176], hence blocking these channels can reduce expression of inflammatory cytokines.

Other Chronic and Genetic Disorders

A potent toxin GsMtx-4, isolated from venom of tarantula *Grammostola spatulate*, has shown inhibitory actions on mechanosensitive ion channels as well as supressed arterial fibrillation, indicating anti-arrhythmic property [177]. Another toxic component PhKv isolated from the venom of Brazilian spider *Phoneutria nigriventer*, has shown remarkable ability to reduce nociception by blocking AchE activity and inactivating cholinergic transmission in mice model [178]. This property might play important role in treating Alzheimer disease. PhTx4-5-5 toxin from the venom of same spider species showed neuro-protective activity by inhibiting glutamate excitotoxicity responsible for cell death in neurons of mice [179]. Bee venom and its component apamin can significantly increase striatal dopamine level and decreasing MPTP-induced neuron cell loss. Thus it acts as neuro-protective agent against Parkinson disease [180]. It is also excellent in reducing the serum nitrate, TNFα levels and suppressing multiple sclerosis symptoms in experimental encephalomyelitic rat model [181]. Apamin also exhibits anti-atherosclerotic property in lipopolysaccharide- induced atherosclerotic mice model by inhibiting macrophage apoptosis and suppressing expressions of members of Bcl2 family, Cyctochrome C, caspase 3 and PARP [182]. Proulx et al. in 2019 reported that apamin can boost nicotinic excitation improving cognitive function and attention acquisition in transgenic mice model system, which is indicative of a novel anti-Alzheimer agent. FrPbAII and Parawixin 10 are two toxins isolated from venom of Brazilian spider *Parawixia bistriata* have shown remarkable neuroprotective abilities in treating retinal glaucoma in rat [183,184].

Venom- a Future Prospective of Drug Discovery

Despite being a source of paramount of bioactive principles with diverse physiological properties and actions, only a few drugs have been developed from insect venoms that are under clinical and pre-clinical trials. Most of the toxin based approved drugs are derived from the venoms of snake, frog, cone snail and puffer fish (viz. Haemocaogulase® from

Table 2: Cellular Regulatory pathways of different venom toxins.

Sl. No.	Venom	Insect (s)	Regulation of cell signaling	Reference
1	Phospholipase A2	Wasp, bee, scorpion, centipede	Arachidonic acid pathway ↑	[148]
2	Mastoparan	Wasp	G protein-coupled signaling ↓	[149]
3	Bradykinin	Wasp, ant	ERK/MAP kinase pathway ↑	[151]
4	Melittin	Bee	PI3K/Akt/mTOR pathway ↓; NF-κB pathway ↓; mTOR/ p70S6K/4E-BP1 pathway ↓	[153]
5	Apamin	Bee	NF- κB signaling pathway ↓; STAT signaling pathway ↓	[154]
6	Hyaluronidase	Bee, wasp, ant, flea, scorpion, spider, hornet	HYAL-2–WWOX–SMAD4 signaling ↑	[155]
7	Ectatomin	Ants	Ion leakage across membrane ↑; L-type calcium currents in myocytes ↓	[117]
8	Mast cell degranulating peptide	Bee	G protein-coupled signaling ↑	[156]
9	Scorpion toxin (Chlorotoxin)	Scorpion	ERα signaling pathway ↓	[157]
10	Spider toxin (ω-agatoxin-1a)	Spider	Calcium influx activity ↓	[158]
11	Centepede toxin (κ-SLPTX-Ssm2a)	Centepede	K_v channel activity ↓	[35]

(↑upregulation and ↓ downregulation)

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Table 3: Therapeutic potential of whole venom or venom bioactive components in chronic diseases.

Venom component	Experimental model	Physiological role	Therapeutic potential	References
Melittin	Hodgkin Lymphoma (HL) cell lines KM-H2 and L-428	Plays synergistic role with cisplatin	Anti-neoplastic	[185]
Melittin	Human hepatocellular carcinoma cell lines: SMMC-7721 and BEL-7402	Activates CaMKII-TAK1-JNK/p38 and inhibits IkBa kinase- NFkB	Anti- timour	[186]
Melittin	Caki-1, Caski, SK-BR-3 cell lines	Inhibits matrix metalloproteinase-9 (MMP-9) gene expression by blocking activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB)	Anti- metastatic	[187]
Melittin	human breast carcinoma MCF-7 cell line	Downregulation of cluster of differentiation (CD)147 and (MMP-9) expressions	Anti-invasive and anti-metastatic	Wang et al., 2016
Melittin	Human peripheral blood leukocytes	Inhibits neutrophil O2- production.	Anti-inflammatory	[188]
Melittin-like peptide 101	*In vitro*: LNCaP-LN3, DU-145, C3 cell lines	Peptide 101-immunoconjugates showed more affinity towards cell binding and cell killing, delaying tumor growth	Cytotoxic, anti- tumor	[189]
	***			
Melittin	Human HCC cells (BEL-7402)	Apoptosis and growth arrest, up-regulates Fas expression	Anti-proliferative	[190]
Melittin	human acute T lymphocyte leukemia cell line 6T-CEM	Apoptosis, cell death	Cytotoxic, anti-proliferative	[191]
Ad-rAFP-Mel (Recombinant adenovirus carrying melittin gene)	*In vitro*: BEL-7402 cell line In vivo: BALB/c-nu/nu athymic mice (male)	Reduced rate of tumorigenicity and detection of significant anti-neoplastic effect	Anti-neoplastic	[192]
Melittin	Murine leukemic lymphocyte cell lines (L1210 and L5178Y) and human promyelocytic leukemic granulocyte cell line (HL-60)	Calmodulin inhibition, inhibition of cell growth and clonogenicity	Anti-proliferative	[193]
Melittin	Ras transformed cells	Hyper-activation of PLA2 and enhanced Ca2+ influx	Anti-neoplastic	[194]
Bee venom (whole)	Patients with sepsis from Intensive Care Unit	Decreases generation of inducible Nitic Oxide (NO) synthase and TNFa	Anti-arthritic	[195]
Bee venom (Water soluble sub fractionated part)	J774A.1 (mouse macrophage cell line), A549 (human airway epithelial cell line), U937 (human myelomonocytic cell line)	Inhibits COX2 activity, pro-inflammatory cytokines: TNF-a and IL-1b	Anti-arthritic	[196]
Bee venom (whole)	Male Lewis rats, Charles River CD strain male rats	Suppression of adjuvant arthritis and carrageenan induced paw edema in time and dose dependent manner	Anti-arthritic	[197]
Bee venom (Apis mellifera)	Albino rats (male)	Decreases plasma glucose level and increases plasma insulin level	Ant-diabeteic	[198]
Adolapin	Rats	Anti-inflammatory activity in carrageenan, prostaglandin (PG) and adjuvant-induced paw edema by cyclo-oxygenase, PG synthesis inhibitory activities	Anti-arthritic	[199]
Bee venom	Lewis rats (male and female)	Depression of cytochrome p450 level and Ethylmorphine N-demethylase activity	Anti-arthritic	[200]
Bee venom (whole) (Apis mellifera)	Sprague-Dawley rats (male)	Decrease in erosions of articular cartilage and infiltration of inflammatory cells in adjuvant-induced hind paw arthritis	Anti-arthritic	[201]

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Apamin	AML12 cell line	Suppresses epithelial mesenchymal transition induced by TGF-b1 and inhibits smad dependent/ independent signalling pathways	Anti- hepato fibrotic	[202]
Apamin	HaCaT (human keratinocyte cell line)	Inhibits NF-kB and JAK/STAT signaling pathways; suppresses inflammatory chemokines and cytokines	Anti-inflammatory	[203]
Apamin	Transgenic TgCRND8 mice	Improves cognitive function and attention acquisition	Anti-Alzheimer agent	[204]
Apamin	*In vitro*: THP-1 (human monocyte cell line) *In vivo:* C57BL/6 mice (male)	Inhibits apoptosis of macrophages by suppressing levels of Bcl-2 family, cytochrome-c, caspase-3 and PARP	Anti-atherosclerotic	[182]
Apamin	*In vivo:* HSC-T6 (rat hepatic stellate cell line) *In vitro*: C57BL/6 mice (male)	Attenuates IL-6, IFN-γ, TNF-α, IL-1β expressions and inhibits HSC activation by Smad signaling pathway	Anti-cholestatic	[203]
Apamin	C57/Bl6 mice (male)	Decreases MPTP-induced dopamine neuron cell loss and increases striatal dopamine levels	Anti-parkinsonian agent	[180]
Solenopsin (Solenopsis invicta)	Transgenic zebrafish Fli-EGFP (embryos)	Inhibits PI3K activation and delayed angiogenesis	Anti-angiogenic	[163]
Cantharidin (Lytta vesicatoria)	CCRF-CEM (leukemia cell line) and its sub-lines: CEM/ADR5000, CEM/ VLB100, CEM/E1000	Induces apoptosis of multidrug resistant cells by p53 dependent mechanism	Anti-cancer	[205]
Cantharidin (Mylabris phalerata)	T 24 (human bladder carcinoma) and HT 29 (human colon carcinoma) cell lines	Arrests cell cycle at G2/M phase and induces apoptosis	Cytotoxic, anti-cancer	[206]
Cantharidin	In vitro: MDA-MB-231, MDA-MB-468 (human breast cancer cell lines) *In vivo:* BALB/c nude mice	Reduces cell viability in dose dependent manner, induces apoptosis, suppresses pro-tumor autophagy	Apoptotic	[207]
Scorpion venom (Heterometrus bengalensis Koch)	U937 and K562 (human leukemia cell lines)	Arrests cell cycle, induces apoptosis by membrane blebbing and DNA damage	Anti-proliferative	[208]
Chlorotoxin	Various human and animal cell lines	Tumour-specific binding with glioma cells, inhibits cell invasion	Anti-metastatic	[209]
Maurotoxin (Scorpio maurus palmatus)	B82 (mouse fibroblast cells) and Ovary cells of Chinese hamster	Inhibition of intermediate conductance subclass of KCa channels	Anti-asthmatic	[175]
Hyaluronidase BmHYA1 (Buthus martensi)	MDA-MB-231 (Breast cancer cell line)	Reduces CD44 variant expression	Anti-tumor	[165]
Hyaluronidase (Tityus serrulatus)	C57BL6/6 mice	Reduces bleomycin induced pulmonary fibrosis by decreasing collagen deposition and TGFb expression	Anti-fibrotic	[210]
Mastoparan	*In vito*: Jurkat, THP-1 (human leukaemia cell line), and HOPC (murine myeloma cells line)	Induces cell death in concentration dependent manner, reduces tumour growth and acts synergistically with chemotherapeutic drug (gemcitabine)	Anti-cancer	[159]
	In vivo: T41 mammary carcinoma induced immune competent mice			
All-D Mastoparan M	Colo 225, KB, Hep-2, H226Br and HeLa cell lines	Inhibits tumor growth by direct lysis of cancer cells	Cytolytic, anti-tumor	[211]
Mitoparan and analogues	U373MG and ECV304 cell lines	Causes DNA fragmentation, modulates mitochondrial membrane permeability, initiates apoptosis	Apoptotic	[212]

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Mastoparan	In vitro: B16F10, B16F10-Nex2, A2058, SiHa, Jurkat, MCF-7, MDA-MB-231, U87, SK-BR-3, Melan-a cell lines *In vivo*: C57BL/6 mice (male)	Increases ROS level and decreases pro-caspases-3, 9 and 12, leading intrinsic pathway of cell death	Anti-tumor, apoptotic	[160]
Mastoparan	Sprague-Dawley rats (male) Human pancreatic islet cells	Many fold increase in mastopran-induced insulin release over glucose augmentation	Anti-hyper glycemic, anti-diabetic	[174]
SsmTx-I (Scolopendra subspinipes mutilans L. Koch)	Sprague–Dawley rats	Blocks voltage sensitive potassium channel (Kv 2.1)	Anti-asthmatic, anti-diabetic, anti-inflammatory	[147] Herrington et al., 2006
Ssm6a (S. subspinipes mutilans)	*In vitro*: HEK293T cell line *In vivo:* mice model	Blocks voltage gated sodim channel (NaV1.7) and pain reliving effectiveness is manyfold higher than morphine	Antinociceptive, analgesic	[173]
Scolopendrasin VII (S. subspinipes mutilans)	U937 and Jurkat cell lines	Reduces viability of cancer cells, induces necrosis by interacting with membrane phosphatidylserine	Anti- cancer	[213]
Centipede venom (*Scolopendra viridicornis*)	*In vitro*: Hep 3B, HBL-100, IMR-32, HEL 92.1.7, ACHN *In vivo:* Swiss albino mice	Substantially decreases tumor growth	Anti-tumor	[214]
S. subspinipes mutilans extract	A375 cell line	Arrests cell cycle and promotes cell death, decreases Bcl-2, increases Bak, Bax and Bad expressions	Apoptotic	[215]
Psalmotoxin 1 (Psalmopoeus cambridgei)	Rats	Blocks ASIC1a (acid sensing ion channel), opioid activity similar to morphine	Antinociceptive	[216]
β-TRTX-Gr1b (Grammostola spatulata)	Rats	Interacts with Cav channels, relieves pain	Analgesic	[217]
GsMtx-4 (Grammostola spatulata)	Rabbit	Inhibits mechanosensitive channels, suppresses atrial fibrillation	Antiarrhythmic	[177]

****In vivo*: LN3 or DU-145 human CaP cell xenografts established in Athymic BALB/c nu/nu (nude) male mice

Bothrops atox moojeni, ABT-594 from *Epipedobates tricolor*) [23]. There are ample of active insect-venom components yet to be explored and documented, that may play crucial role in discovery of potential modern drugs for the treatment of chronic diseases, including cancer. Furthermore, emphasis is given only on more stable venom peptides while selecting for drug designing, such as, presence of Disulphide Bridge in the core peptide. This provides the venom peptides or proteins, the ability to withstand proteolytic digestion and penetration through physiological shuttles or barriers, e.g., blood-brain barrier [218]. Attention is also required on the mode of delivery and bio-availability of the designed drugs. Oral administration of toxin derived drugs designed from large molecular weight proteins is more likely to be a poor option due to the chance of getting digested by proteolytic enzymes. An alternative to improve stability of venom derived drugs is replacement of disulphide bond configuration with diselenide bonds by incorporating Selenocysteine residues [219,220]. Being isosteric in nature with disulphide bonds and less reactive towards biological reductions, diselenide bonds architecture is of highly stable nature [221,222]. Another issue associated with venom derived drug discovery is that their half-life is poor in human gastric juice and serum. This creates a limitation regarding high drug clearance by liver and kidney [223,224]. It can be overcome by using carrier proteins or conjugation with non-immunogenic polyethylene glycol (PEG) [225,226]. Some of insect venom derived drugs under clinical or pre-clinical trials are listed in table 3.

Conclusion

Exploring venomics is like exploring the treasure house of novel therapeutics. Despite large number of research works completed on insect venom and their therapeutical potentials, few works have been published on practical application as bio-available drugs. Thorough optimization on some issues, such as, their mode of action, route of delivery, side effects and safety, can lead to find out plausible compositions of highly selective target- specific drugs. This area needs more focus and attention to meet success in combating chronic diseases as well as cancer.

Declaration of Competing Interest

The authors declare no conflict of interest.

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