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Review Article

Arthropod Derived Venoms: Natural Source of Anti-HIV Drug Molecules: A Review

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Abstract

Present review article describes venom derived toxins from various arthropods and their therapeutic uses against various virus pathogens of human diseases. Arthropods mainly bees, wasps, hornets, scorpions, spiders, ticks and marine arthropods synthesize toxins which possess unique functional groups and display target specific receptor binding on pathogen surface. These toxins exhibit cytolytic activity against moat of microbial pathogens and kill them by penetrating their cell membrane and inhibit major cellular functions through channel binding and receptor interactions. They inhibit virus entry into host cells, and obstruct HIV virus replication. These highly selective, powerful short toxin peptides show multiple biological activities and are of great therapeutic value. These could be used for creation of new target-specific novel antiviral medications of great therapeutic value. This is possible by utilizing the structural and functional diversity of toxin peptides through the application of bio-informatics tools, methodologies, and approaches. These low cost novel toxin-antibiotics can be used to manage various viral infections.

Keywords: Arthropods; Animal Venom Toxins; Defense Molecules; Anti-HIV Therapeutics

Abbreviations

ACP: Anticancer Peptides; AMP: Antimicrobial Peptide; ChTx: Charybdotoxin; CMV: Cytomegalovirus; CTL: Cytotoxic T Cells; DBP: Disulfide-Bridged Peptide; DENV: Dengue Virus; EBV: Epstein-Barr Virus; H5N1: Influenza Virus; HBV: Hepatitis B virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; MAPK: Mitogen-activated Protein Kinase; MeV: Measles Virus; NDBP: Non-disulfidebridged Peptide; SARS-CoV: Severe Acute Respiratory Syndrome/Coronavirus; VSV: Vesicular Stomatitis Virus; WHO: World Health Organization; YFV: Yellow Fever Virus; RFP: Red Fluorescent Protein

Introduction

HIV infection is very serious health problem throughout globe. Its cases are increasing day by day in spite of the fact that so many medications are applied for combating the disease. Both incidence rate and infection rate is on acceleration path. Human immunodeficiency viruses (HIV) are terrible viruses that compromise an individual's immune system. HIV is a retrovirus that causes a slowly progressing disease. It belongs to the Lentivirus genus and has two species. HIV spreads through bodily fluids such as blood, breast milk, semen, and vaginal secretions from an infected individual [1]. It cannot be transmitted by sharing meals, hugs, or kisses. Additionally, it can pass from a mother to her child. Acquired immune deficiency syndrome (AIDS) is the most advanced stage of HIV infection, which lowers the immune system and causes various cancers and other opportunistic diseases.

HIV primarily targets immunological surveillance cells found in the white blood cells of the body. The virus prevents receptor binding and distorts cells' ability to distinguish between their own and non-self powers. HIV targets CD4 cells, which are white blood cells. HIV virus replicates once it enters the CD4 cell. After HIV destroys the CD4 cell, fresh HIV copies seek out more CD4 cells to infiltrate and recommence the cycle. It causes an acute infection; the virus mutates and avoids the immune system's production of cytotoxic

T cells (CTL). It spreads quickly among the population of infected cells as a result of its fast reproduction within the host cell. Viral mutations have the potential to mediate viral escape from the CTL response, which results in the immune system gradually failing [2].

Consequently, the weakened immune system of the diseased patient makes them more susceptible to infections, malignancies, and other illnesses including tuberculosis. A virus can infiltrate cells and spread throughout the body very quickly. AIDS patients exhibit flu-like symptoms at this point, including fever, sore throats, and exhaustion. Patients face weight loss, fever, diarrhea, headache, sore throat, coughing, and swollen lymph nodes, exhaustion, and recurrent infections. HIV-positive individuals risk developing tuberculosis (TB), cryptococcal meningitis, serious bacterial infections, and malignancies such lymphomas and Kaposi's sarcoma if they do not receive appropriate therapy. HIV exacerbates other illnesses, including mpox, hepatitis B, and hepatitis C. HIV infection becomes asymptomatic after a few weeks and quickly advances to full bloom AIDS disease.

Antiretroviral medications have been shown to be effective in preventing complications and secondary infections; however, the fast replication of HIV viruses and their increasing quantity do not aid in the resolution of the infection [3]. Hence, there is a heavy demand of new novel anti-HIV drugs all around the world. Animal venoms are a rich source of bioactive molecules which could be used as alternative medicine to treat a variety of human diseases including virus generated [4]. Arthropod venoms possess diverse group of toxin molecules with different structure and function. Hence, toxins from bees, wasps, scorpions and spider venom derived peptides could be used as therapeutic agents. These toxins block the HIV replication cycle by selectively binding to the chemokine receptor CXCR4 and promote cell-mediated antiviral defense and prevent HIV-1 replication [5]. Although there are a number of HIV treatment options available based on toxin templates and their fusion products, analogues which can restrict HIV growth and reproduction inside host cells. They have been shown high efficacy against several enveloped and non enveloped viruses. People are still waiting for a vaccine, which still remains unattainable due to the HIV virus's rapid changes in genome. HIV vaccines are being tested, however as of yet, no reliable vaccine has been created so far.

Antiviral potential

Tick saliva toxins

Tick saliva also contains defensins against microbes, mainly viruses. It plays an important role in tick innate immunity [6]. These also possess Serine Protease inhibitors (PIs)which are important vaccine targets. Tick saliva serine protease inhibitors (serpins) facilitate tick blood meal feeding through inhibition of protease mediators of host defense pathways. Ticks possess immunosuppressant peptide, and, immunoreactive proteins and antimicrobial peptides. Serpin from the saliva of the tick *Ixodes ricinus* displays high affinity for human leukocyte elastase of act as immunosuppressor (Iris). Iris also displays pleotropic effects because it interferes with both the immune response and hemostasis of the host [7]. T22 [Tyr5,12, Lys7] polyphemusin II) inhibits the activity of human immunodeficiency virus (HIV). T22 inhibits HIV-1 replication through specific binding to the chemokine receptor CXCR4, which acts as a co-receptor for entry of T-tropic HIV-1 strains. Prodigiosin showed in vitro antiviral activity in cells infected with *Bombyx mori* nucleopolyhedrovirus (BmNPV) with specific modes of action [8]. The hemolymph of Lonomia oblique larvae contains an antiviral protein. This antiviral protein requires for expression in the baculovirus/Sf9 cell system [9].

Both mucosa and serosa membranes found in midgut act as natural barrier of pathogens, these secrete mucus and that assist in making innate immune defense. Red fluorescent protein (RFP) isolated from the midgut of the silkworm larvae secret an antiviral red fluorescent protein that was found effective against the BmNPV. It was also found active against against*, Klebsiella pneumonia, Bacillus subtilis* and, *Phytophthora meadii* [10]. PEF (protein-enriched fraction) isolated from the larvae of the housefly similar protein-enriched fraction with strong antiviral activity against influenza virus was isolated from midgut of housefly larvae.

This prevents the virus from entering the cells. PEF has great potential as a resource for health products [11] (Table 1). BmSP-2 is an insect digestive enzyme that functions as an antiviral factor against BmNPV at the site of virus infection [11]. Rbv protein is isolated from the hemolymph of *Lonomia oblique*; it shows powerful antiviral activity against measles, influenza, and polioviruses [12]. This protein acts as a constitutive agent, creating innate immune defenses. These effects may be mediated by changes in the GTP pool of treated cells [13]. Seroins are proteins isolated

from *Bombyx mori* with strong antiviral activity. Seroins could be used as effective candidates for transgene-based disease-resistant silkworms [14]. Melittin and phospholipase A2 (PLA2) are the main components of bee venom. Bee and wasp venom also contain anticancer peptides (ACP), most of which are small cationic and hydrophobic peptides with antioxidant, antimicrobial, neuroprotective or antitumor effects [15].

Scorpion venom

Arachnids mainly scorpions use their venom as defensive and offensive tool to kill or immobilize their prey. Venom infliction defends them from potential competitors and predators. Scorpion venoms are highly poisonous and display multiple clinical effects after envenomation and results in death of patients in lack of proper treatment. Scorpions show rich molecular diversity of venom proteins and peptides enzymes such as hyaluronidase, phospholipase, serotonin, histamine, enzyme inhibitors and mucopolysaccharides [16]. Scorpion venom also contains metals, and biogenic amines and so many unknown substances of great therapeutic value. Scorpion venom also contains α-toxins which, rapidly deactivate the receptor affinity of sodium channels [17] and bind to receptor site 3 of vertebrate voltage-gated Na+ channels in a membrane-dependent manner [18].

Scorpion venom consists of many peptides that can disrupt ion channels and modulate their functional properties. These peptides have different physiological and pharmacological effects. Scorpion also posses *β*-Toxins which are disulfide-bridged peptides, these specifically bind to receptor site 4 on vertebrate Na^+ channels and create a more negative membrane potential [19]. Most interestingly, small molecules and peptides found in scorpion venom had very high therapeutic potential [20]. The family Buthidae is famous for the most venomous and medically important scorpion species. Important members are *Androctonus bicolor, Androctonus crassicauda* and *Leiurus quinquestriatus*. They are very toxic because their venom consists of small molecule peptides, nucleotides, amino acids, ions, neurotransmitters and salts [21]. Once produced, the venom causes toxic and pharmacological effects on the victim.

Mucroporin-M1, derived from scorpion venom, was found to be active against RNA viruses (measles viruses, SARS-CoV and H5N1, and HIV-1). Kn2-7 a scorpion venom peptide inhibits the replication and multiplication of HIV-1 particle [22]. Kn2-7 could inhibit all members of HIV-1 subtype B pseudotyped virus (PV) with CCR5-tropic and CXCR4-tropic NL4-3 PV strain. Furthermore, it also inhibited a CXCR4-tropic replication-competent strain of HIV-1 subtype B virus. It directly interacts with HIV-1 envelope [23]. It is a promising candidate for the development of an anti-HIV-1 therapeutic agent [32]. Few Cationic peptides have shown anti-infective and anti-tumor activity [24]. A short peptide T22 T-cell-tropic (T-tropic) [Tyr5,12, Lys7] with polyphemusin II) found highly active against human immunodeficiency virus (HIV). It inhibits HIV-1 infection by specifically binding to the chemokine receptor CXCR4, which acts as a co-receptor for the entry of T-tropic HIV-1 strains. Similarly, *H. lepturus* venom components showed considerable virucidal activity against HIV infection. *H. lepturus* venom inhibits the growth and replication of Human Immunodeficiency Virus 1 (HIV-1) [25].

Leiurus quinquestriatus hebraeus, venom contains Charybdotoxin (ChTx) and scyrratoxin. These possess a CS-α/β motif that can block K+ channels [26,27]. These toxins have been successfully used as molecular scaffolds for gp120-CD4 interaction assays. Because amino acid residues Phe43 and Arg59 of CD4 have been shown to be important for CD4 binding to gp120, we added the corresponding amino acid residues to our new compounds [28].

ChTx a mimetic peptides possess CD4M and TXM1 scaffold, these contain 33 and 32 amino acid residues. When CD4 CDR2 loop sequence 40QGSF43 was inserted into the equivalent position of the β-loop of ChTx, this important modification enhances the target specificity of toxin peptide. Thus, Phe28 of CD4M or Phe27 of TXM1 of CD4 serves as Phe43. The remaining sequences are similar in the two analogues except for two positions: Arg20 of TXM1 (Arg25 of ChTx) is replaced by Lys of CD4M, and TXM1 has Gly1 as the N-terminal residue instead of Val1-Ser2 residues of CD4M. Thus, the charged N-terminus of the Gly1 residue of TXM1 is in a similar position to the charged side chain of Arg59 of CD4 [28]. In modified CD4M (Lys of CD4M) was able to inhibit the binding of gp120 to CD4 and showed a lower IC50 value of 20 μM [27]. Similarly, TXM1 competed with CD4 for gp120 binding, causing a CD4-like enhancement of gp120 binding to antibody 17b [39].Subsequently, other CD4 mimetics with gp120 affinity were successfully generated by randomization of phage epitopes in the β-turn loop in a ChTx-based scaffold [28].

Similarly, scyllatoxin a 27 amino acid miniprotein named as CD4M3 showed scaffold-based mimetics. This constructed mini

toxin potentially inhibited the binding of CD4 to gp120 with an IC50 value of 40 μM [29]. Further, modifications in CD4M3 and derivation of a new compound (CD4M9), showed increased the affinity for gp120 with IC50 values of 0.1–1.0 μM. Furthermore, this new toxin molecule CD4M9 was found to inhibit the infection of CD4+ cells when exposed to other HIV-1 strains [27]. Thus CD4M9, an effective mimetic that potentially interacts and show CD4-like properties.

The chemokine receptor CXCR4 plays an important role as the receptor for the normal physiological function of stromal cell-derived factor 1alpha (SDF-1alpha) and the coreceptor for the entry of human immunodeficiency virus type 1 (HIV-1) into the cell [30]. However, for increasing the antiviral efficacy new family of unnatural chemokines was prepared synthetically and modularly modified (SMM). These chemokines, derived from the native sequence of SDF-1alpha or viral macrophage inflammatory protein II (vMIP-II) bind many residues on CXCR4 TM and extracellular domains that are important for HIV-1 entry. It will help in generation of development of selective HIV-1 inhibitors [30]. The beta-chemokines MIP-1alpha, MIP-1beta and RANTES inhibit infection of CD4+ T cells by primary, non-syncytium-inducing (NSI) HIV-1 strains at the virus entry stage, and also block env-mediated cell-cell membrane fusion. CD4+ T cells from some HIV-1-exposed uninfected individuals cannot fuse with NSI HIV-1 strains and secrete high levels of beta-chemokines. Expression of the beta-chemokine receptor CC-CKR-5 in CD4+, non-permissive human and non-human cells renders them susceptible to infection by NSI strains, and allows env-mediated membrane fusion. CC-CKR-5 is a second receptor for NSI primary viruses [5].

Similarly, a new toxin constructed molecule CD4M33 much ably inhibited CD4-gp120 binding in various viral strains and inhibited HIV-1 cell fusion. This molecule also expressing CD4, CCR5 or CXCR4 co-receptors at levels similar to those of CD4 in bioassays. Its three-dimensional structure was further analyzed in complex with gp120 [31]. Subsequently, another analogue was developed, called F23, which differs from CD4M33 in the presence of a biphenylalanine substitution at position 23 (Phe23 (Bip23)). Scorpiontoxin mimics of CD4 in complex with human immunodeficiency virus gp120 crystal structures, molecular mimicry, and neutralization breadth. F23 mimics CD4 better than CD4M33. Furthermore, F23 showed increased neutralization against phylogenetically related primate lentivirus isolates [45]. Structural and thermodynamic analyses showed F23 to be a better molecular mimic of CD4 than CD4M33. F23 also showed increased neutralization breadth, against diverse isolates of HIV-1, HIV-2, and SIVcpz [31].

AMPs from scorpion venom are NDBPs, its analogues exhibit strong antiviral activity. Some of these compounds act by directly disrupting the viral envelope, thereby reducing the infectivity of the virus [32]. AMPs block the entry of virus particles into cells by occupying cellular receptors used by viral [32]. Contrary to this few AMPs do not compete with viral glycoproteins for binding to cellular receptors. Instead, they penetrate the lipoprotein membrane of cells and remain in the cytoplasm or organelles, preventing viral infection by altering the profile of the host cell to improve defense against the virus or by blocking the expression of viral genes in the host cell. To prevent infection of others, cells may be shut down [33].

These natural bioactive molecules derived from Scorpion venom were found highly effective against retroviruses such as HIV/SIV. More specifically, DBPs found in scorpion venom bind to the HIV gp120 glycoprotein due to molecular mimicry of the host cell CD4+ receptor of lentiviruses. This protein form complexes with CD4 receptor and acts as a neutralizing human antibody. As a result, they abolish the gp120-CD4 interaction that is essential to initiate the conformational changes of the viral envelope that lead to the entry of the virus into the host cell [34]. These CD4-mimicking scorpion toxins contain approximately 30 amino acid residues with three or four disulfide bridges characterized by a cysteine-stabilized α/β motif (CS-α/β), in which a β-turn exists between two β-strands. The CDR2 loop of CD4 is similar to these peptides [35]. Paradoxically, these bioactive molecules have diverse mechanisms of action and are of very high biotechnological applications. These could be used as drug templates for creation of new medicines for therapeutics of so many human diseases including virus infection [36].

Honey bee venom

Bee venom toxins have biological effects, mainly antiviral activity [37]. Bee venom and its components, namely melittin (MLT), phospholipase A2 (PLA2) and apamin, have shown inhibitory effects against important disease-causing viruses such as influenza A virus (PR8), vesicular stomatitis virus (VSV), respiratory syncytial virus (RSV) and herpes simplex virus (HSV) *in vitro* and *in vivo* [38]. Bee peptide melittin has been shown to be effective against several viruses, including coxsackievirus, enterovirus, in-

fluenza A virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), Junín virus (JV), respiratory syncytial virus (RSV), vesicular. stomatitis virus (VSV and tobacco mosaic virus) [39]. The mastoparan-derived peptide MP7-NH2 inactivates viruses and stimulates cell-mediated antiviral defense. MP7-NH2 primarily inactivates enveloped viruses [40] (Table 1) (Figure 1).

Category	*Scientific name*	Toxin	Active against	Mode of action
Insect	*Vespula lewisii*	MP7-NH_2	HSV	Viral envelope disruption
Insect	*Apis mellifera*	Melittin	HIV	CXCR4 and CCR5 tropic inhibition HIV-1 infectivity
Insect	Synthetic (from melittin)	Hecate	HSV	Cellular target
Insect	Bee venom	$bvPLA_2$	HIV	Virion entry blocking into host cell
Insect	Synthetic (from $bvPLA_2$)	p3bv	HIV	HIV glycoprotein fusion inhibition to CXCR4 cell receptor
Insect	*Calliphora vicina*	Alloferons 1 and 2	IAV/HSV	Immunomodulatory activity
Insect	*Hyalophora cecropia*	Cecropin A-magainin 2	HIV	Virion entry blocking into host cell
Insect	*Vespula lewisii*	MP7-NH_2	HSV	Viral envelope disruption
Insect	*Vespula sp*	Melittin	JV	Melittin hampered multiplication of Junín virus in Vero cells infected
Insect	Bee venom	Apamin	Bovine viral diarrhea virus (NADL)	apamin potentiated its anti-viral activity.
Insect	Bee venom Apis mellifera	Mastoparan	broad-spectrum antiviral activity	Dislodging the membrane
Insect	Bee venom Apis mellifera	Melittin	HSV-1 (MP, syn20, FFV3, tsB5, and amb 1511-7)	Strong anti-viral activity.
Insect	Bee venom Apis mellifera	Mixture of melittin, apamin, and mastoparans	coxsackievirus, enterovirus, influenza A viruses, (HIV), (HSV-1), Junín virus (JV), (RSV), (VSV), and TMV,	triggered molecular fusion and stops virus spread
Scorpion	venoms	Hyaluronidase phospholipase A2	H5N1, and HIV-1	bind to receptor site 3 of vertebrate voltage-gated Na+ channels in a membrane-dependent manner
Scorpion	venom	Mucroporin-M1, derived from	measles viruses, SARS-CoV and H5N1, and HIV-1	inhibits the replication and multiplication of HIV-1 particle
Scorpion	*Leiurus quinquestriatus hebraeus* venom	Charybdotoxin (ChTx) and scyrratoxin	Measles viruses, SARS-CoV and H5N1, and HIV-1	CS-α/β motif that can block K+ channels ChTx a mimetic peptides possess CD4M and TXM1 scaffold
Scorpion	*Leiurus quinquestriatus hebraeus* venom	Scyllatoxin CD4M3	HIV-1	Binding in various viral strains and inhibited HIV-1 cell fusion showed scaffold-based mimetics.
Scorpion	*H. lepturus* venom	CD4M33	Anti - HIV	AMPs from scorpion venom are NDBPs, its analogues exhibit strong antiviral activity.
Tick	Ixodes ricinus	Salivary toxin iris	Anti-virus	high affinity for human leukocyte elastase of act as immunosuppressor (Iris).
Spider venom	*Alopecosa nagpag* (An1a)	An1a	Restricts zika virus (ZIKV)	showed antiviral activity against anti-dengue serotype-2 virus (DENV2 virus) and ZIKV contamination via way of means of inhibiting the NS2B–NS3 protease.

Spider venom	Selenocosmia huwena	huwentoxin-IV 4.1-kDa toxin,	measles viruses, SARS-CoV and H5N1, and HIV-1	Membrane disruption
Spider venom	*Lachesana tarabaevi*)	Latarcin (LATA,	HIV-1	Membrane disruption
Insect	insect Podisus maculiv-entris)	fusion of LATA-PAP1-THAN THAN, a loop-struc-ture peptide	CHIKV	protein inhibited CHIKV replication inside the Vero cells
Insect	*Phytolacca americana*)	ribosome-inactivating protein (RIP) from is an antiviral protein	CHIKV	protein inhibited CHIKV replication inside the Vero cells
Horseshoe crab	*Tachypleus tridentatus*	Polyphemusin	HIV	Chemokine receptor, CXCR4/viral co-receptor attachment

Table 1: Anti-HIV activity of arthropods toxins.

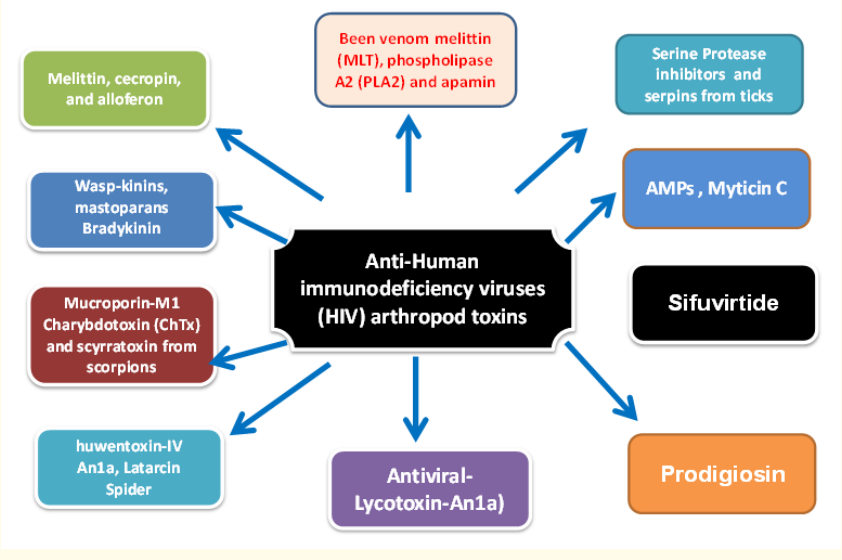

Figure 1: Major arthropod toxins which show anti-HIV activity.

Honey bee venom also showed antiviral activity, both Melittin and phospholipase A2 a aluminum hydroxide as an adjuvant utilized in immune therapy in COVID-19 were found highly effective against HIV 1 virus. It was found effective against SARS-CoV-2 infection. It also shows effectiveness against invasion of the host cells by the SARS-CoV-2 virus [41]. Melittin had no satisfactory anti-viral activity against BVDV but apamin potentiates anti-BVDV efficacy of melittin [41]. Mellitin is also found in melittin is able to obstruct HSV-1 attachment onto Vero cells in a dose-dependent manner and to hinder HSV-1 penetration into cells [42]. Melittin has been demonstrated to exert marked anti-herpetic activity against HSV-1 M and HSV-2 G [43]. Melittin is able to mitigate infectivity of influenza A virus infection [44].

Three honey bee peptides melittin, apamin, and mastoparans in mixture confirmed effectiveness towards diverse viruses. Its analogues inhibits herpes simplex virus-1 (HSV-1)-triggered mobileular fusion and virus spread [44]. The melittin itself on HIV-1-inflamed lymphoma cells [45], wherein melittin is carried in a nanoparticle assemble designed for use as a topical vaginal virucide. Melittin was found effective against group of viruses which include coxsackievirus, enterovirus, influenza A viruses, human immunodeficiency virus (HIV), herpes simplex virus (HSV), Junín virus (JV), breathing syncytial virus (RSV), vesicular stomatitis virus (VSV), and tobacco mosaic virus (TMV) [46].

Bee venom also contains so many biologically active molecules which show anti-proliferative, anti-bacterial, and anti-inflammatory effects. Bee venom possesses two primary constituents, melittin (MEL) and phospholipase A2 (PLA2), which inhibit the replication of variety of enveloped and non-enveloped viruses [5]. Secreted phospholipases A(2), a new class of HIV inhibitors found to block virus entry into host cells. Inhibition by sPLA(2)s is not a virucidal effect nor a cytotoxic effect on host cells, but it prevents the intracellular release of the viral capsid protein, and successfully block viral entry into cells before virion uncoating and independently of the coreceptor usage [47]. Similarly, secreted phospholipases A2 (sPLA2) from snake venoms have potent anti-human immunodeficiency virus (HIV) activity. These sPLA2s block HIV-1 entry into host cells through a mechanism linked to sPLA2 binding to cells [47].

Wasp venom

Mastoparan is a tetradecapeptide found in the venom of the wasp *Vespula lewisii* [48], which forms an amphipathic helical structure that inserts into the lipid bilayer of bacteria, erythrocytes, mast cells and other cells, forming pores [49]. A mastoparan analog, mastoparan-7, shows broad-spectrum antiviral activity against enveloped viruses from five different families (Rhabdoviridae, Poxviridae, Flaviridae, Paramyxoviridae and Herpesviridae) *in vitro* (Table 1). Structural studies show that the amphipathic α-helix of mastoporan inserts into the viral lipid envelope, forming pores that lead to its disruption. Similarly, melittin, isolated from venom of Apis mellifera obstruct the replication of murine retroviruses, tobacco mosaic virus and herpes simplex virus [50]. Melittin remedy of T cells reduces degrees of intracellular Gag and viral mRNAs, and reduces HIV lengthy terminal repeat (LTR) interest. Hecate, an analog of melittin, selectively reduces the biosynthesis of virus-specific proteins. Besides, HIV LTR interest is likewise decreased in human cells stably transfected with melittin and cecropin genes.

HIV virions generally infect host cells in the genital mucosa by infecting macrophages and are called M-tropic viruses. After migrating to lymph nodes, they infect T lymphocytes and transform into T-tropic viruses. Based on HIV tropism, phospholipase A2 from honeybee venom bvPLA2 blocked the replication of both M-tropic and T-tropic HIV virions, whereas a small peptide p3bv derived from bvPLA2 blocked only the replication of T-tropic viruses and acted as a ligand for the HIV-1 coreceptor CXCR4, [52] (Table 1). AMPs isolated from invertebrates have shown increased antiviral activity in human diseases. Such peptides include the molecules melittin, cecropin, and alloferon [53] (Table 1). Melittin, isolated from the venom of the honeybee (*Apis mellifera*), is an amphipathic peptide consisting of 26 amino acid residues arranged in two α-helical segments. Melittin incorporated into nanoparticles showed virucidal activity against HIV-1 in the cell line VK2, an epithelial vaginal cell line, and also inhibited HIV infection in TZM-bl reporter cells (a HeLa cell line expressing the HIV receptor). Among other antiretroviral mechanisms, melittin complemented the inhibition of reverse transcription by azidovudine [54].

Mastoparans

Mastoparan derivative shows broad-spectrum antiviral activity *in vitro* against five families of enveloped viruses directly via disruption of their lipid envelope structure [30]. Mastoparans are low molecular weight α-helical polycationic amphiphilic linear tetradecapeptide amides present in the venom of the wasp *Vespula lewisii* [55] (Table 1). They are rich in hydrophobic leucine, isoleucine, and alanine, as well as basic residues that maintain electrostatic interactions with the negatively charged phospholipid head groups of biological membranes [68]. Wasp venoms are represented by mastoparans. They are based on the histamine-releasing principle. Wasp venoms are represented by mastoparans. They are based on the histamine-releasing principle. Mastoparan is antibacterial in nature, induces mast cell degranulation, and exhibits hemolytic activity [56]. These peptides are amphipathic and therefore interact with different types of cell membranes through different mechanisms depending on their primary sequence. Nonlytic mastoparan interacts with a variety of cell lineages and may cause minimal membrane rearrangements, but does interact with cell membrane receptors, especially those coupled to G proteins. The high affinity of these receptors makes the mastoparan molecule a highly attractive lead compound for the development of a new generation of drugs that modulate the activity of G protein-coupled cell signaling systems. Mastoparan stimulates insulin secretion from βTC3 and INS-1 cells [49] (Table 1).

Mastoparan peptides are inserted into the membrane bilayer and thus directly interact with G proteins on the cytoplasmic surface, attacking transmembrane signaling induced by an increase in cytoplasmic Ca2+ and also by an increase in the intracellular second messenger inositol-1,4,5-triphosphate (IP3). These peptides cause activation of G protein-mediated mechanisms, stimulation of phospholipases A2, C, and D, and mobilization of Ca2+ from mi-

tochondria and sarcoplasmic reticulum. They also activate ryanodine receptors and regulate various enzymes, including rat brain Na+-K+-ATPase, inducing mitochondrial permeability transition and cell death by necrosis and apoptosis [57]. Mastoparan induces apoptosis, which is initiated by the release of Ca2+ from intracellular stores via PLC and IP3. It also causes disruption of cell membrane integrity [58]. Mastoparan affects intracellular free Ca++ concentration in human astrocytoma cells [59], inhibiting NMDA receptor-mediated responses and blocking neurotransmission [60]. In chronic hornet venom-induced hypertension, functional activity of Ca2+-dependent K+ channels is increased in the basilar artery [61]. Mastoparan, an activator of gastrointestinal and mast cells, selectively stimulates PLD2 in intact cells, independently of gastrointestinal, ADP-ribosylation factor-1 (ARF-1), protein kinase C and calcium [62]. PLD is involved in the exocytosis of secretory granules in mast cells and neutrophils [63]. Mastoparan, found in wasp venom, potently stimulates exocytosis in a variety of mammalian cells. It causes the secretion of histamine from mast cells, serotonin from platelets, catecholamines from chromaffin cells, and prolactin from the anterior pituitary gland.

Wasp-kinins

Hornet venom contains a variety of bradykinin-related peptides from different species. Vespicelkinins are polypeptides (9-18 amino acid residues) containing a bradykinin-like sequence at the C-terminus. Hornets contain two kinins, bradykinin (BK) and lysylbradykinin (Table 1), which are produced in human plasma kallikrein and tissue kallikrein, respectively. They are important mediators of inflammatory responses, potent pain generators, and increase vascular permeability and vasodilation. The nonapeptide bradykinin contained in vespid kinins exhibits potent pharmacological and long-lasting effects. Kinins such as threonine-bradykinin (Thr6-BK) and megascoriakinin (Thr6-BK-Lys-Ala), as well as glycosylated vespid kinins, are neurotoxic. Vespid kinins have been experimentally implicated in muscle contraction and relaxation, leukocyte activation with subsequent release of cytokines, prostaglandins, leukotrienes, and reactive oxygen species, and blockade of cholinergic transmission in the insect central nervous system.

Bradykinin is a non-peptide that is also found in bodily secretions such as urine, saliva and sweat. It is also present in various tissues such as the heart, blood vessels, blood, kidneys, colon and liver [65]. Bradykinin is a potent endothelium-dependent vasodilator and a mild diuretic with blood pressure lowering effects. It also causes contraction of non-vascular smooth muscle of the bronchi and intestine, increases vascular permeability and is involved in pain mechanisms. In addition to vespid kinins, vespid venom contains a number of hydrophobic peptides, mastoparans and chemotactic peptides as important peptidergic components. The first major component of the venom is mastoparm. Mastoparan family peptides are tetradecapeptide amides that cause degranulation of mast cells, releasing histamine from the cells, and act on adrenal chromaffin cells to release catecholamines and adenylate. Some mastoparans cause hemolysis and release of serotonin from platelets. The second major component, a new cytotrophic peptide, is a tridecapeptide amide with chemotactic activity for polymorphonuclear leukocytes and monocytes. Some peptides of this family also cause histamine release from mast cells. Mastoparan adopts a random coil conformation in aqueous solution, but changes its conformation to an alpha helix in methanolic solutions and in the presence of lysophosphatidylcholine (Table 1) [64].

Spider venom toxins

Spider venom possesses diverse biologically active components with high selectivity and specificity. Spider venoms are complex mixtures of salts, small organic molecules, peptides, enzymes, proteins, polyamines and acids which display multiple biological effects in animals and human beings. Venom from big spiders such as tarantula is dangerous to humans [65]. More than 500 bioactive peptides which possess mol weight less than 10 kDa have been isolated from 60 spider species (20 families) [66]. Spider toxin consists of C1 x5-19 C2 G/Px2 C3X6-19C4 sequences wherein X is any amino acids residues and association of the di-sulphide bond is C1-C3, C2-C4.

Most of the spider peptides incorporate six or 8 cysteine residues to shape 3 to 4 disulfide bridges and also have distinct disulfide bond motifs. Spiders produce venom with a predominance disulphide containing peptides. Most of these disulfide-containing peptides showed neurotoxic and cytolytic properties. *Alopecosa nagpag* spider venom (An1a) showed antiviral activity against antidengue serotype-2 virus (DENV2 virus) [67]. It acts like a NS2B-NS3 protease inhibitor [67]. An1a also restricts zika virus (ZIKV) contamination via way of means of inhibiting the ZIKV NS2B–NS3 protease. Spider toxins have enough potential to control flavivirus infection [67].

Similarly, a short peptide huwentoxin-IV 4.1-kDa toxin, was isolated Chinese hen spider, Selenocosmia huwena. This is composed of 35 residues with three disulfide bridges: Cys-2-Cys-17, Cys-9-Cys-24, and Cys-16-Cys-31 [68]. It specifically inhibits the neuronal

tetrodotoxin-sensitive (TTX-S) voltage-gated sodium channel [69]. Similarly, 4.1-kDa toxin Latarcin (LATA, from the venom of the spider *Lachesana tarabaevi*) peptide with the N-terminus of the PAP1 (a ribosome-inactivating protein (RIP) from *Phytolacca americana*) is an antiviral protein. A fusion of LATA-PAP1-THAN THAN, a loop-structure peptide, isolated from the insect *Podisus maculiventris*) protein inhibited CHIKV replication inside the Vero cells [70].

Invertebrate AMPs and antiviral activity

AMPs isolated from marine invertebrate *Theonella mirabilis* showed antivirus activity against herpes simplex virus, human immunodeficiency virus, influenza virus, hepatitis C virus (HCV), and SARS-CoV-2 [71]. *Theonella mirabilis* antmicrobial peptide showed virucidal activity against human immunodeficiency virus 1 (HIV-1). This peptide does inhibition of formation of virus membrane, makes disruption and does viral inactivation [72]. Similarly, tachyplesin from the *Tachypleus tridentatus* horseshoe crab exhibited a potent antiviral activity against herpes simplex virus [73]. Myticin C, derived from hemocytes of the *Mytilus galloprovincialis* mussel, has shown an antiviral action against fish rhabdovirus, ostreid herpesvirus, and human herpes simplex viruses 1 and 2, affecting the intracellular phase of viral replication. Venom of the Alopecosa nagpag spider synthesizes a defense peptide named Av-LCTX-An1a (Antiviral-Lycotoxin-An1a) that possess anti-dengue serotype-2 virus (DENV2) *in vitro.* An1a also restricts zika virus (ZIKV) infection by inhibiting the ZIKV NS2B–NS3 protease.

Conclusion

Arthropod venom toxins are considered as great candidates for drug development. But there is growing demand for new drugs and natural therapeutic products for multi resistant viral pathogens. There is a shortage of novel drugs which could stop progression of HIV, dengue, chikungunya and Zika viruses – or worldwide pandemics, such as influenza and SARS or Corona virus. Till date no single treatment available for HIV. Virus once adhered to the host genome it replicates very fast and makes millions of copies which again target healthy blood cells and rapidly decrease the immune resistance of the body. Venom toxin components from bees, wasps, spiders, and scorpions were found to inhibit replication of HIV 1 virus. More specifically, dimeric PLA2s potentially inhibit HIV-1 replication inside host cells. PLA2s adhere on the viral membrane and act as antiretroviral regimens. It destroys lipid bilayer and causes destabilization of the virus. In addition, it shows syncytium formation and viral adsorption and shows synergistic effects with HIV NRTIs such as Lamivudine and Tenofovir. It targets virus cells and save normal body cells which are targeted by The HIV1. There are other toxin based drugs which also showed improved effects than the existing therapies. A through screening of animal origin venoms is needed for exploration of therapeutic validation of venom toxins, and their clinical development for novel antivirus drugs.

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The author declares no competing financial interests.

Bibliography

1. Galvin SR and Cohen MS. "The role of sexually transmitted diseases in HIV transmission". *Nature Reviews Microbiology* 2 (2004): 33-42.

2. Batorsky R., *et al*. "The route of HIV escape from immune response targeting multiple sites is determined by the cost-benefit trade off of escape mutations". *PLOS Computational Biology* 10.10 (2014): e1003878.

3. Cohen MS., *et al*. "Prevention of HIV-1 infection with early antiretroviral therapy". *The New England Journal of Medicine* 365 (2011): 493-505.

4. Yaacoub C., *et al*. "Bee Venom and Its Two Main Components-Melittin and Phospholipase A2-As Promising Antiviral Drug Candidates". *Pathogens* 12.11 (2023): 1354.

5. Dragic T., *et al*. "HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5". *Nature* 381.6584 (1996): 667-73.

6. Zhou W., *et al*. "Antiviral activity and specific modes of action of bacterial prodigiosin against *Bombyx mori* nucleopolyhedrovirus in vitro". *Applied Microbiology and Biotechnology* 100 (2016): 3979-3988.

7. Prevot PP., *et al*. "Exosites Mediate the Anti-Inflammatory Effects of a Multifunctional Serpin From the Saliva of the Tick *Ixodes Ricinus*". *FEBS Journal* 276.12 (2009): 3235-3246.

8. Carmo AC., *et al*. "Expression of an antiviral protein from *Lonomia oblique*hemolymph in baculovirus/insect cell system". *Antiviral Research* 94 (2012): 126-130.

9. Manjunatha GKS., *et al*. "Identification of In-Vitro Red Fluorescent Protein with Antipathogenic Activity from the Midgut of the Silkworm (*Bombyx Mori L.*)". *Protein and Peptide Letters* 25 (2018): 302-313.

10. Wang F., *et al*. "In vitro anti-influenza activity of a protein-enriched fraction from larvae of the housefly (*Muscadomestica*)". *Pharm Biology* 51 (2013): 405-410.

11. Nakazawa H., *et al*. "Antiviral activity of a serine protease from the digestive juice of *Bombyxmori* larvae against nucleopolyhedrovirus".*Virology* 321 (2004): 154-162.

12. Greco KN., *et al*. "Antiviral activity of the hemolymph of *Lonomia obliqua* (Lepidoptera: Saturniidae)". *Antiviral Research* 84 (2009): 84-90.

13. Liao HJ, *et al*. "Reversal of the antiviral activity of ribavirin against Sindbis virus in *Aedes. albopictus* mosquito cells". *Antiviral Research* 22 (1993): 285-294.

14. Singh CP., *et al*. "Characterization of antiviral and antibacterial activity of *Bombyx mori* seroin proteins". *Cell Microbiology* 16 (2014): 1354-1365.

15. Carpena M., *et al*. "Bee Venom: An Updating Review of Its Bioactive Molecules and Its Health Applications". *Nutrients* 12 (2020): 3360.

16. Petricevich VL. "Scorpion venom and the inflammatory response". *Mediators Inflammatory* (2010): 903295.

17. Catterall WA. "Cellular and molecular biology of voltage-gated sodium channels". *Physiological Reviews* 72.4 (1992): S15-S48.

18. Marcotte P., *et al*. "Effects of Tityus serrulatus scorpion toxin γ on voltage-gated Na^+ channels". *Circulation Research* 80.3 (1997): 363-369.

19. Ding J., *et al*. "Scorpion venoms as a potential source of novel cancer therapeutic compounds". *Experimental Biology and Medicine (Maywood)* 239 (2014): 387-393.

20. Silva EC., *et al*. "Cloning and characterization of cDNA sequences encoding for new venom peptides of the Brazilian scorpion *Opisthacanthus cayaporum*". *Toxicon* 54 (2009): 252-261.

21. Sample CJ., *et al*. "A mastoparan-derived peptide has broad-spectrum antiviral activity against enveloped viruses". *Peptides* 48 (2013): 96-105.

22. Chen Y., *et al*. "Anti-HIV-1 activity of a new scorpion venom peptide derivative Kn2-7". *PLoS One* 7 (2012): e34947.

23. Couto J, *et al*. "Anti-plasmodial activity of tick defensins in a mouse model of malaria". *Ticks Tick Borne Disease* 9 (2018): 844-849.

24. Zabihollahi R., *et al*. "Venom Components of Iranian Scorpion *Hemiscorpius lepturus* Inhibit the Growth and Replication of Human Immunodeficiency Virus 1 (HIV-1)". *Iranian Biomedical Journal* 20.5 (2016): 259-265.

25. Miller C., *et al*. "Charybdotoxin, a protein inhibitor of single Ca2+-activated K+ channels from mammalian skeletal muscle". *Nature* 313.6000 (1985): 316-318.

26. Chicchi GG., *et al*. "Purification and characterization of a unique, potent inhibitor of apamin binding from *Leiurus quinquestriatus hebraeus* venom". *Journal of Biological Chemistry* 263.21 (1988): 10192-7.

27. Drakopoulou E., *et al*. "Engineering a CD4 mimetic inhibiting the binding of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein gp120 to human lymphocyte CD4 by the transfer of a CD4 functional site to a small natural scaffold". *Letters in Peptide Science* 5.2 (1998): 241-245.

28. Li C., *et al*. "Phage randomization in a charybdotoxin scaffold leads to CD4-mimetic recognition motifs that bind HIV-1 envelope through non-aromatic sequences". *Journal of Peptide Research* 57.6 (2001): 507-18.

29. Choi WT., *et al*. "Unique ligand binding sites on CXCR4 probed by a chemical biology approach: implications for the design of selective human immunodeficiency virus type 1 inhibitors". *Journal of Virology* 79.24 (2005): 15398-15404.

30. Huang CC., *et al*. "Scorpion-toxin mimics of CD4 in complex with human immunodeficiency virus gp120 crystal structures, molecular mimicry, and neutralization breadth". *Structure* 13.5 (2005): 755-768.

31. Chen Y., *et al*. "Anti-HIV-1 activity of a new scorpion venom peptide derivative Kn2-7". *PLoS One* 7.4 (2012): e34947.

32. Li Q., *et al*. "Virucidal activity of a scorpion venom peptide variant mucroporin-M1 against measles, SARS-CoV and influenza H5N1 viruses". *Peptides* 32.7 (2011): 1518-1525.

33. Kwong PD., *et al*. "Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody". *Nature* 393.6686 (1998): 648-659.

34. Hong W., *et al*. "Inhibitory activity and mechanism of two scorpion venom peptides against herpes simplex virus type 1". *Antiviral Research* 102 (2014): 1-10.

35. Ojeda PG., *et al*. "Chlorotoxin: structure, activity, and potential uses in cancer therapy". *Biopolymers* 106.1 (2016): 25-36.

36. Uddin MB., *et al*. "Inhibitory effects of bee venom and its components against viruses *in vitro* and *in vivo*". *Journal of Microbiology* 54 (2016): 853-866.

37. Lee WR., *et al*. "The protective effects of melittin on Propionibacterium acnes-induced inflammatory responses in vitro and in vivo". *Journal of Investigative Dermatology* 134 (2014): 1922-1930.

38. Sarhan M, *et al*. "Potent virucidal activity of honeybee *Apismellifera*" venom against Hepatitis C Virus". *Toxicon* 188 (2020): 55-64.

39. Goswami S and Chowdhury JP. "Antiviral attributes of bee venom as a possible therapeutic approach against SARS-CoV-2 infection". *Future Virology* (2023): 10.2217/fvl-2023-0127.

40. Cortegiani A., *et al*. "A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19". *Journal of Critical Care* 57 (2020): 279-283

41. Baghian A and Kousoulas KG. "Role of the Na^+,K^+ pump in herpes simplex type 1-induced cell fusion: melittin causes specific reversion of syncytial mutants with the syn1 mutation to syn^+ (wild-type) phenotype". *Virology* 196.2 (1993): 548-556.

42. Yasin B., *et al*. "Evaluation of the inactivation of infectious Herpes simplex virus by host-defense peptides". *European Journal of Clinical Microbiology and Infectious Diseases* 19.3 (2000): 187-194.

43. Baghian A., *et al*. "An amphipathic alpha-helical synthetic peptide analogue of melittin inhibits herpes simplex virus-1 (HSV-1)-induced cell fusion and virus spread". *Peptides* 18 (1997): 177-183.

44. Wachinger M., *et al*. "Influence of amphipathic peptides on the HIV-1 production in persistently infected T lymphoma cells". *FEBS Letter* 309 (1992): 235-241.

45. Memariani H., *et al*. "Melittin: a venom-derived peptide with promising anti-viral properties". *European Journal of Clinical Microbiology and Infectious Diseases* 39.1 (2020): 5-17.

46. Fenard D., *et al*. "A peptide derived from bee venom-secreted phospholipase A2 inhibits replication of T-cell tropic HIV-1 strains via interaction with the CXCR4 chemokine receptor". *Molecular Pharmacology* 60.2 (2000): 341-347.

47. Hirai Y., *et al*. "A new mast cell degranulating peptide "mastoparan" in the venom of *Vespula lewisii*". *Chem Pharm Bull (Tokyo)*. 27.8 (1979): 1942-1944.

48. Leite NB., *et al*. "The effect of acidic residues and amphipathicity on the lytic activities of mastoparan peptides studied by fluorescence and CD spectroscopy". *Amino Acids* 40.1 (2011): 91-100.

49. Marcos JF., *et al*. "Inhibition of a plant virus infection by analogs of melittin". *Proceedings of the National Academy of Sciences (PNAS)* 92.26 (1995): 12466-12469.

50. Bachis A., *et al*. "M-tropic HIV envelope protein gp120 exhibits a different neuropathological profile than T-tropic gp120 in rat striatum". *European Journal of Neuroscience* 32.4 (2010): 570-578.

51. Fenard D., *et al*. "Secreted phospholipases A (2), a new class of HIV inhibitors that block virus entry into host cells". *Journal of Clinical Investigation* 104.5 (1999): 611-618.

52. Wickline SA., *et al*. "Nanoparticulate-based contraceptive/anti-HIV. Composition and methods". 2012. Patent US20120100186 A1. Washington University (2012).

53. Moreno M, Giralt E. "Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: melittin, apamin and mastoparan". *Toxins (Basel)* 7.4 (2015): 1126-1150.

54. de Azevedo RA., *et al*. "Mastoparan induces apoptosis in B16F10-Nex2 melanoma cells via the intrinsic mitochondrial pathway and displays antitumor activity *in vivo*". *Peptides* 68 (2015): 1139.

55. Higashijima T., *et al*. "Mastoparan, a Peptide Toxin from Wasp Venom, Mimics Receptors by Activating GTP-binding Regulatory Proteins (G Proteins)". *The Journal of Biological Chemistry* 263.14 (1988): 6491-6494.

56. Rocha T., *et al*. "Myotoxic Effects of Mastoparan from *Polybia paulista* (Hymenoptera, Epiponini) Wasp Venom in Mice Skeletal Muscle". *Toxicon* 50 (2007): 589-599.

57. Rivers DB., *et al*. "Venom from the Ectoparasite Wasp *Nasonia vitripennis* Increases Na+ Influx and Activates Phospholipase C and Phospholipase A2 De- pendent Signal Transduction Pathways in Cultured Insect Cells". *Toxicon* 40 (2002): 9.

58. Hirata Y., *et al*. "Identification of a 97-kDa mastoparan-binding protein involving in Ca (2+) release from skeletal muscle sarcoplasmic reticulum". *Molecular Pharmacology* 57 (2000): 1235-1242.

59. Hirata Y., *et al*. "Mastoparan binds to glycogen phosphorylase to regulate sarcoplasmic reticular Ca2+ release in skeletal muscle". *Biochemistry Journal* (2003);371 (Pt 1): 81-8.

60. Karst H., *et al*. "Philanthotoxin inhibits Ca2+ currents in rat hippocampal CA1 neurons". *European Journal of Pharmacology* 270 (1994): 357-360.

61. Chahdi A., *et al*. "Mastoparan Selectively Activates Phospholipase D2 in Cell Membranes". *The Journal of Biological Chemistry* 278 (2003): 12039-12045.

62. Jones D., *et al*. "Phospholipase D and Membrane Traffic: Potential Roles in Regulated Exocytosis, Membrane Delivery and Vesicle Budding". *Biochimica et Biophysica Acta* 1439 (1999): 229-244.

63. Duncan AM., *et al*. "Kinins in Humans". *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology* 278 (2000): R897-904.

64. Akef HM. "Anticancer, antimicrobial, and analgesic activities of spider venoms". *Toxicology Research (Camb).* 7.3 (2018): 381-395.

65. Vassilevski AA., *et al*. "Molecular diversity of spider venom". *Biochemistry (Mosc)* 74.13 (1999): 1505-1534.

66. Ji M., *et al*. "An Antiviral Peptide from *Alopecosa nagpag* Spider Targets NS2B-NS3 Protease of Flaviviruses". *Toxins (Basel)* 11.10 (2019): 584.

67. Liang S. "An overview of peptide toxins from the venom of the Chinese bird spider *Selenocosmia huwena* Wang [=Ornithoctonus huwena (Wang)]". *Toxicon* 43.5 (2004): 575-585.

68. Peng K., *et al*. "Function and solution structure of huwentoxin-IV, a potent neuronal tetrodotoxin (TTX)-sensitive sodium channel antagonist from Chinese bird spider *Selenocosmia huwena*". *Journal of Biological Chemistry* 277.49 (2002): 47564-47571.

69. Rothan HA., *et al*. "Inhibitory effects of a peptide-fusion protein (Latarcin-PAP1-Thanatin) against chikungunya virus". *Antiviral Research* 108.1 (2014): 173-180.

70. Sukmarini, L. "Antiviral Peptides (AVPs) of Marine Origin as Propitious Therapeutic Drug Candidates for the Treatment of Human Viruses". *Molecules* 27 (2022): 2619.

71. Ford PW., *et al*. "Papuamides A-D, "HIV-inhibitory and cytotoxic depsipeptides from the sponges *Theonella mirabilis* and *Thenonella swinhoei* collected in Papua New Guinea". *Journal of the American Chemical Society* 121 (1999): 5899-5909.

72. Manohar M., *et al*. "Silver Nanoparticle Conjugated Marine Invertebrate Antimicrobial Peptides (AgNPs-Amps) against Gram-Negative ESKAPE Pathogens". *International Journal of Research and Analytical Reviews* 6 (2019): 264-287.

73. Mengyao Ji., *et al*. "An Antiviral Peptide from *Alopecosa nagpag* Spider Targets NS2B-NS3 Protease of Flaviviruses". *Toxins* 11.10 (2019): 584.