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Review Article

Animal Venom Toxins: Potential Source of Antiviral Agents to Counter Pathogen Attack

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Abstract

Present review article explains antivirus activity of animal venom toxins against various virus pathogens of important human diseases. Venom toxins are highly specific defense molecules, which are secreted from basic glandular structures and used as arsenals to protect territory, food and mate selection. Few venomous animals secrete antimicrobial peptides which exhibit a wide variety of biological effects i.e. kill microorganisms by penetrating the cell membrane and inhibiting cellular functions through toxin-channel interactions. They inhibit virus entry into host cells, and obstruct virus replication. Short toxin peptides act as highly specific potent bioactive molecules and lessen inflammation, regulate glutamate release, modify neurotransmitter levels, block ion channel activation, decrease the number of protein aggregates, and increase the levels of neuro-protective factors. These highly active natural peptides could be used as antibiotics to control virus pathogens and could be used for the development of novel therapeutic agents. By using bio-informatics tools, methods and approaches, both structural and functional diversity of toxin peptides could be used to discover target specific new antiviral drugs for therapeutic purposes. No doubt animal toxins are excellent molecules which exert target specific effects and could become an important treatment options for COVID-19, if viral inactivation is being done in a complete downstream process. It will require *in silico* molecular modeling studies of novel toxin templates, and their testing in different animal models to determine safety and to explore therapeutic of new drugs.

Keywords: Animal Venoms; Natural Toxin Peptides; Receptor-drug Interaction; Therapeutic Uses

Introduction

Animal venom toxins are a highly specific defense molecule which have been evolved during long evolutionary period and exists in diverse animal groups. Venomous animals found worldwide except cold geographical regions. In these animals some basic glandular structures were modified during long evolution in presence of various ecological factors to ensure survival in highly competitive environment and to make quick defense. Animal venoms are complex mixtures of highly specialized toxic short peptides enzymatic in nature which exert severe patho-physiological effects [1]. Venom also possesses non-proteinaceous active ingredients. From a zoogeographical estimate there are more than 100000 species of animals exist, but till date bio-informatics data of more approximately 21500 animal species is available on various data base. However, less than 0.01% of these toxins have been identified and characterized. So far studies have been done thousands of natural toxin peptides have been identified and characterized in venoms isolated from various animal species of sponges, coelenterates, annelids, mollusks, and arthropods such as scorpions, spiders, bees and wasps. Venom toxins have been also isolated from fish,

amphibians and snakes. Venomous animals, such as cone snails, spiders, snakes, assassin bugs, centipedes and scorpions are rich sources of remarkably potent and selective ion channel inhibitors [2]. Moreover, marine animals such as fish, amphibians, reptiles and invertebrates show chemical and biological diversity of toxins that can be used to explore new drugs of high therapeutic potential [3].

Animal protein and peptides are showed broad spectrum antimicrobial potential [4]. Animal-secreted toxins are enzymatic in nature and exert action on body cells, tissues and organ system and impose multiple human health risks [5]. Venom toxins after infliction show extreme pain, inflammation, swelling, and fire neurons, hemolysis, regulate glutamate release, modify neurotransmitter levels, affect muscle contraction and block ion channels [6]. These toxins interact and act on several major portals consist of ion channels, pumps, transporters and ligand gated ionotropic receptors. These interact with group of portals consists of G-protein-coupled and tyrosine kinase receptors. After interaction venom toxins, alter second messengers towards pathological levels. These also affect sub-cellular organelles such as mitochondria, nucleus, protein- and RNA-synthesis machineries, cytoskeletal networks and exocytic vesicles. Venom toxin peptides target mainly ion channels, membrane receptors and components of the hemostatic system with high selectivity and affinity [7] (Table 1). They massively disturb the intracellular ion homeostasis.

Toxin/s	Source	Name of species	Antiviral effects	Therapeutic target
Ara-A (vidarabine	sponge	*Tethya crypta*		
manzamine A	sponge	Manzamine Alkaloids Acanthostrongylophora sp.	Dengue virus	Reduce DENV-1, DENV-2, and DENV-3 serotypes in LLC-MK2 cells infection
PhcrTx2	Sea anemone	Phymanthus crucifer	anti-virus	inhibited glutamate-gated currents in snail neurons
Equistatin		anemone *Actinia equine*	anti-virus	Inhibitor of replication
Cytolysins	Sea anemone	Actinia equina	anti-virus	Kunitz-type protease inhibitors activity
Histidine-rich Scorpion -derived Peptide	Scorpion	*Euscorpiops validus*	HSV-1.	Suppress HSV-1 infection , Inhibitory Activity against HSV-1
Peptide Smp76	Scorpion	*Scorpio maurus palmatus*	Dengue virus (DENV) and Zika virus (ZIKV)	Inhibits Viral Infection by Regulating Type-I Interferon Response
Mucroporin and mucroporin-M1	Scorpion	*Lychas mucronatus*	SARS-CoV and influenza H5N1 and measles, MeV, HBV,HIV1	Virucidal activity by directly binding to virus membranes.
Kn2-7 Bmkn2	Scorpion	*Mesobuthus martensii*	HIV-1 HIV-1	Antimicrobial and anticancer agents
Hp1090, Hp1033, Hp1239	Scorpion	Heterometrus petersii	HCV, HSV-1,	Antimicrobial and anticancer agents
Aplysiatoxin , debromoaplysiatoxin	Marine Cyanobacterium	*Trichodesmium erythraeum.*	Anti-Chikungunya	exhibited significant anti-CHIKV
Heparan sulfate (HS)	ubiquitous glycosaminoglycan	HS-octa inhibited infection of viruses	RSV, human para influenza virus 3 (hPIV3), HSV	serves as a cellular attachment site for a number of significant human pathogens

Cys rich disulfide toxins	cold-water sea anemone	*Cnidopus japonicus*	cytotoxic	Antibacterial and anti-viral activity
Mastoparans	Wasp and honey bee venom	*Apis Melifera L Vespa tropica, Polistes flavus*	Membrane active amphipathic peptide	Antibacterial and anti-viral activity
Melittin	Was and honey bee venom	*Apis Melifera L Vespa tropica, Polistes flavus*	HSV-1, RSV	Inhibit virus replication and entry
Bradykinin	Wasp venom	Inflammatory	Act through G protein-coupled receptors	Antimicrobial and anti-cancer
Adiapin, apamin	Wasp and honey bee venom	*Apis melifera* L	anti-microbial and anticancer	Active against gram negative and gram positive bacteria
Mast cell degranulating peptide	Was and honey bee venom	Polycationic peptide	Activation of G protein	Antmicrobial and anticancer
Phospholipse A2	Wasp and honey bee venom	Polycationic peptide	cytotoxic	Antmicrobial and anticancer
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
κM-conotoxin RIIIJ	marine gastropod cone snails	*Conus radiates*	Channel inhibitor	Bind to Kv1.1/1.2 channels as prevalent neuronal Kv complex
Tunicate	*Tridemnum solidum*	Didemnins A, B and C	HSV-1 and 2; coxsackie virus A-21 and equine rhinovirus	Protein, DNA and RNA synthesis inhibition
Frog	*Phyllomedusa*	Dermaseptin S_4	HSV-2	Viral envelope disruption
Frog	*Litoria chloris*	Caerin 1.9	HIV	Viral envelope disruption
Frog	*Litoria genimaculata*	Maculatin 1.1	HIV	Viral envelope disruption
Ophidian	*Trimeresurus stejnegeri*	TSV-LAO	HIV-1	Syncytium formation inhibition and HIV-1 p24 antigen reduction
Ophidian	*Bothrops jararaca*	BjarLAAO-I	DENV-3	Infected cells reduction
Ophidian	*Crotalus durissus terrificus*	PLA_2 -Cdt	DENV, YFV	Virus envelope cleavage and protein destabilization

Ophidian	*Bothrops leucurus*	*Bl*K-PLA$_2$; *Bl*D-PLA$_2$	DENV	Viral RNA levels reduction
Ophidian	*Naja kaouthia* (*Naja siamensis*)	Immunokine	HIV	CCR5 and CXCR4 receptors interaction
Marine sponge	*Sidonops microspinosa*	Microspinosamide	HIV	Cytopathic effect inhibition
Marine sponge	*Siliquariaspongia mirabilis* and *Stelletta clavosa*	Mirabamides A-H	HIV	Viral glycoprotein fusion neutralization to the cell receptors
Marine sponge	*Homophymia* sp.	Homophymine A	HIV	Virion entry inhibition
Marine sponge	*Theonella* sp.	Papuamides A and B	HIV	Virion entry inhibition
Marine sponge	*Theonella swinhoe*	Theopapuamide A	HIV	Virion entry inhibition
Marine sponge	*T. swinhoe* and *T. cupola*	Koshikamides F, H	HIV	Virion entry inhibition
Marine sponge	*Siliquariaspongia mirabilis*	Theopapuamide B	HIV	Viral envelope disruption
Marine sponge	*Siliquariaspongia mirabilis*	Celebesides A–C	HIV	Virion entry inhibition
Marine sponge	*Callipelta* sp.	Callipeltin A	HIV	Virion entry inhibition
Marine sponge	*Neamphius huxleyi*	Neamphamide A	HIV	Virion entry inhibition
Horseshoe crab	*Tachypleus tridentatus*	Polyphemusin	HIV	Chemokine receptor, CXCR4/viral co-receptor attachment
Fish	*Pleuronectes americanus*	Pa-MAP	HSV	Viral envelope interaction

Table 1: Showing various antiviral toxin peptides secreted by invertebrates and vertebrates.

More specifically, venoms of cnidarians and arachnids generate pore-forming proteins (PFPs) that could puncture the plasma membrane of target cells [1]. Few PFPs mainly actinoporins and latrotoxins isolated from spider venom of Latrodectus genus bind sphingomyelin found in membrane [1]. These highly specific insect-toxins are used as toxic arsenals for hunting insects [1]. It shows fundamental correlation between structure, pathophysiology and ecological evolution of short toxin peptides and its long inherent association of venomous animals to their prey. It connects much longer evolutionary relationship between predation and biological economy [8]. Hence, a broader study of evolutionary ecology is being required to understand the biological relevance of venom systems and its impact on body of prey.

Toxin peptides evolved through convergent evolution allowed enormous modifications in venom systems multiple times. These were selectively refined, restructured according to environmental need (ecological adaptability) geared up numerous changes in operational neurobiology and genetics of animals to shaped them as highly specific potent bioactive molecules [9]. This structural and functional diversity in toxin peptides could become a good source for discovery of new drugs [3]. These highly active natural peptides could be used as antibiotics. However, to find most appropriate therapeutic toxins its molecular, biochemical, and pharmacological aspects must be explored [9]. These are environmentally safe and are species specific [10]. For instance, Captopril® (Enalapril), Integrilin® (Eptifibatide) and Aggrastat® (Tirofiban) are drugs based on snake venoms, venoms are complex mixtures of enzymatic and

non-enzymatic components with specific pathophysiological functions. Hence, there is a need to study toxin knowledge-based physiological effects of toxin-like proteins/peptides in experimental animals (TLPs) [8] (Table 1).

Toxin based drugs mainly cationic peptides may decrease the number of protein and cellular aggregates, make pores in pathogen membrane, inhibit virus replication and increase the levels of neuroprotective factors [6]. Phospholipase A2 isolated from the venom of *Crotalus durissus terrificus* found active against dengue virus, Yellow fever virus and other enveloped viruses by disrupting the viral envelope (Table 1). It inhibits E protein shell on the virus surface [11]. No doubt animal toxins are excellent molecules which can stop virus entry in host cell and more efficiently obstruct virus replication by maintaining specific effects because of induction of immune functions of host body. Thus virus inactivation becomes possible in downstream process [12]. Animal toxins are highly active bio-molecules and can be used to prepare novel drugs that may work as new treatment options for COVID-19 [13]. This article signifies use of toxin peptides as much potent antiviral therapeutic agents (Table 1).

Use of bio-informatics tools

There is a larger scope of highly active toxin peptides and non peptide molecules to transform them into target specific drugs. New highly potent anti-viral drugs could be possible only by using bio-informatics tools and biological researches. Till date venom specific bio-informatics data of more than 21000 animal species is available on various data base [14]. For prediction of molecular targets of toxin computational techniques can be used [14]. These modern bioinformatics tools can be used to find natural inhibitors of virus invaders after studying receptor-toxin interaction *in silico* [14]. Besides this, protein-protein interactions of these virus inhibitors should check in animal models after treatment with antiviral agents in laboratory [15]. Further, for development of much potent antiviral agents [16] combination of transcriptomics and proteomics is highly useful [17]. Venomics can be used to recognize toxin transcript sequences among processed natural toxin peptide sequences [17].

Computational approaches can be used to consolidate venomics data, as well as algorithms to analysis of toxin nucleic acid and protein sequences, toxin three-dimensional structures and toxin functions venoms [17] (Figure 1). From venom secreted toxins new putative toxin structures can be generated by using biological tools and transcriptomic library (Figure 2). These modern tools can be used to tackle specific challenges associated with the identification and annotations of toxins. These could also analyze basic sequence similarity, consensus and conserve sequences among vast array of toxins which are highly divergent (Figure 1 and 2). These will also help in exploring pattern of molecular evolution of different venoms and their toxins [18]. In addition, for accurate prediction of toxin specificity recent bioinformatics and molecular modeling approaches should apply. These properties could be used to make rational drug design and their potential. In addition, for studying biological safety issues and challenge well designed clinical trials are to be completed. Therefore, for finding new promising drugs which could show maximum efficacy and lesser side effects both prophylactic and post-exposure studies are to perform (Figure 2).

Future drugs, target specific best therapeutic molecules

Animal venoms comprise a diversity of peptide toxins that manipulate molecular targets such as ion channels and receptors, making venom peptides attractive candidates for the development of therapeutics to benefit human health [19]. For exploration and discovery of highly potent and specific antiviral drugs characterization, and optimization of venom peptides is highly essential [19].

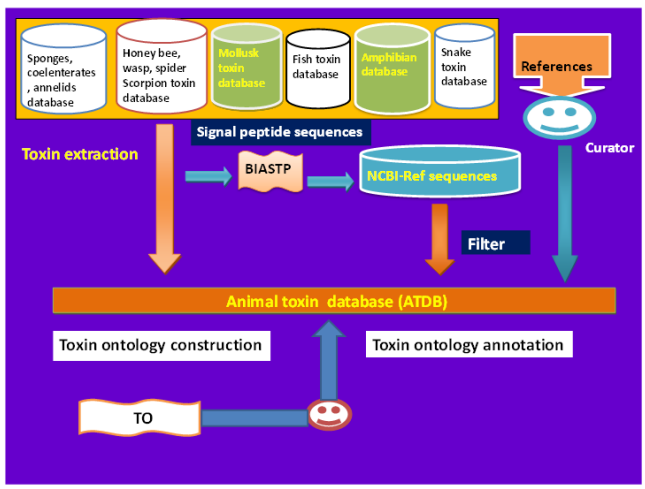

Figure 1: Structural and functional information of animal toxins in database and its use in ontology construction.

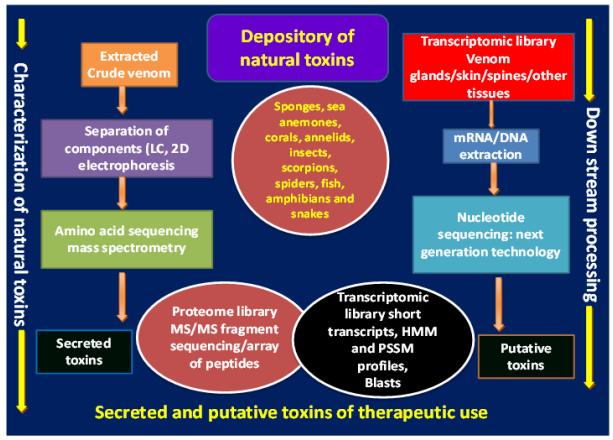

Figure 2: Showing naturally secreted toxins and methods to generate putative toxin structures by using biological tools and transcriptomic library.

However, for obtaining highly active target specific antiviral drug molecules that can work at multiple combinations of transcriptomics and proteomics must be used with downstream processing. From researches, low molecular weight cationic or amphipathic in nature and easy in delivery have been proved valuable therapeutic leads [20]. Enzymatic toxins that may bind to membrane lipid domain and act upon it could be more suitable interacting toxin/s and their molecular targets to combat virus pathogens [5]. More specifically, for engineered toxins safety potentials and target specific applications are to be established [21]. At present viral safety issues remain a great challenge because of its highly contagious nature. Hence, for finding most appropriate solutions biological and therapeutic effectiveness of short toxin peptides must be checked for receptor-toxin interaction inside human body cells. It should be testified for obstruction of virus entry into body cells, stop initiation of infection, control proliferation and invasion of virus. For establishment of their mechanism of action, and the role of different cell surface molecules elicited during viral binding and entry into the target cell target specific screening and its immediate and delayed effect on normal body cells must be studied in experimental animals [22] (Table 1).

Drug delivery

For delivery of toxin based drugs they should be tagged to some specific ligand or nanomaterials device for its delivery across or transport across biological Barriers. Nanomaterials offer unique physico-chemical properties that have linked benefits for drug delivery as ideal tools for viral treatment. Currently, different types of nanomaterials namely nanoparticles, liposomes, nanospheres, nanogels, nanosuspensions and nanoemulsions [23]. Nanomaterials are used for drug delivery as ideal tools for viral treatment. Currently, different types of nano-materials namely nanoparticles, liposomes, nanospheres, nanogels, nanosuspensions and nanoemulsions [23]. In addition, various types of nanoparticles such as chitosan based nanomers, dendrimers, carbon nanotubes, niosomes, beta cyclodextrin carriers, cholesterol mediated cationic solid lipid nanoparticles, colloidal drug carriers, liposomes, and micelles are used for various antiviral therapeutic applications [24]. More specifically drug molecule can be combined with a non-invasive carrier molecule. This second molecule assists in synergistic inhibition of viruses and delays or prevents resistance, and decrease dosages of toxic drugs. New approaches, such as liposomes carrying antiviral drugs and computer-aided drug design, have shown exciting results and may fulfill promising future prospects [25].There is an immense need of physiological and therapeutic optimization of existing drug delivery methods and their carriers to deliver therapeutic amount of drug into the various organs systems of the body for treatment of various virus generated diseases. More specially, nano-sized drug carriers/vehicles and noninvasive therapeutic alternatives of conventional methods are essentially required for better therapeutics of various virus generating diseases. Besides this, there is an urgent need to design nontoxic bio-compatible drugs and noninvasive drug delivery methods to check post treatment clinical fatalities in patients [24] (Figure 1).

Source of information

For writing this comprehensive research review on animal toxins and its anti-viral activity, various databases were searched. For mining relevant information specific terms such as medical subject headings (MeSH) and key text words, such as “animal venoms”, “biological and pharmaceutical effects”, “mode of action”, “drug development” published till 2020 were used. Thus, the abstracts of published studies with relevant information on the animal venom

toxins information centers were identified. These terms were used individually and in combination to ensure an extensive literature search. For updating the information about subject and incorporation of recent knowledge, relevant research articles, books, conferences proceedings' and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including SCOPUS, Web of Science, and *EMBASE*, Pubmed, Swissprot, Google searches" From this common methodology, discoveries and findings were identified and summarized in this final review.

Anti-virus potential of venom toxins

Sponges

Sponges are sessile, filter feeding marine animals and are richest sources of pharmacologically active compounds. Most of them are secondary metabolites which are produced in associations to symbiotic microorganisms. Sponges use these bioactive components against various foreign invaders such as viruses, bacteria, or eukaryotic organisms [26]. Most of these marine natural products are secondary metabolites, which are mainly used to maintain and modulation of cellular communication and defense. Few of them found to be promising pharmaceutical agents for the treatment of human immunodeficiency virus (HIV) and herpes simplex virus (HSV) [27]. One important antiviral nucleoside Ara-A (vidarabine) has been isolated from sponge *Tethya crypta* that successfully inhibit viral DNA polymerase and DNA synthesis of herpes, vaccinica and varicella zoster viruses [27]. Few other marine bioactive agents such as manzamine A were found active against HIV [28], and other pathogens [26]. Microspinosamide, a cyclic depsipeptide isolated from the marine sponge *Sidonops microspinosa* is strong HIV-inhibitor [29] (Table 1).

Sea anemones

Marine coelenterates such as sea anemones *Carybdea alata* produce venom and inflict them for defense and predation [30]. Sea anemones secrete proteinaceous more diverse toxin molecules with different molecular scaffolds toxins act on a large variety of ion channels and multiple exert pharmacological effects [31]. A toxin peptide PhcrTx2 isolated from family Phymanthidae [32]. Sea anemone *Bunodosoma caissarum* (Cnidaria, Anthozoa) generate BcsTx1 and BcsTx2 [33] type 1 potassium toxins that act upon voltage-gated K+ channels (KV) [20]. Equistatin, isolated from the sea anemone *Actinia equine* [34] and two novel γ-hydroxybutenolide sesterterpenes from the Mediterranean coral *Cladocora cespitosa* showed a protease inhibitor activity [35]. Other marine compounds such as sesterterpenoids cladocorans, their diastereomers and analogues showed PLA_2 inhibitory activity [36]. Anthozoan orders Alcyonacea and Gorgonacea secrete active compounds which possess useful therapeutic attributes [37]. Few cnidarian compounds, i.e terpenoids (monoterpenoids, diterpenoids, sesquiterpenoids are more promising bioactive compounds produced by cnidarians [38] (Table 1).

Antimicrobial activity of hymenopterans insects

Mastoparans isolated from wasp venoms are host-defense peptides that penetrate lipid bilayers. Its analogs might interact with the lipid components of virus membrane and thereby reduce infectivity of enveloped viruses [39]. Mastoparan is a α-helical and amphipathic tetradecapeptide obtained from the venom of the wasp *Vespula lewisii*. This peptide exhibits a wide variety of biological effects, including antimicrobial activity, increased histamine release from mast cells, induction of a potent mitochondrial permeability transition and tumor cell cytotoxicity [40]. It shows strong antimicrobial activity against numbers of pathogens [41]. Melittin a venom peptide also heavily interact with the lipid membrane and form pores in it [40]. Melittin operates through various cellular events, actions orientation, and aggregation state. Both melittin and its analogs interrupt specific intracellular events, and selectively cut down biosynthesis of some viral proteins mainly in herpes virus-1 [42] and inhibit proliferation of HIV-1-infected lymphoma cells [43]. Melittin selectively inhibit reverse transcriptase activity and growth of HIV-infected cells [44]. Melittin heavily act on virus transcription and cut down the Levels of all HIV-1 transcript classes and suppressed them in a dose-dependent manner [45] (Wachinger., *et al*. 1998). Melittin interferes with viral gene expression and cellular signal transduction and involves in intracellular immunization against HIV. It interferes in the process of activation of phospholipase A2 and decrease activities of calmodulin and protein kinase C in virus cells [46-48] (Figure 1). It stops HIV transcription act as an inhibitory factor and induce interferon-induced therapeutic functions [45]. Melittin suppresses cell fusion mediated by HSV-1 syncytial mutants by interfering with the activity of the Na^+ K^+ ATPase, a cellular enzyme involved in the membrane fusion process [49]. Both Melittin and phospholipase A2 and apamin showed inhibitory effects against virus pathogens mainly against Influenza A virus (PR8), vesicular stomatitis virus (VSV),

respiratory syncytial virus (RSV), and herpes simplex virus (HSV) both *in vitro* and *in vivo* [49,50] (Table 1).

Insects mainly wasps (*Vespa tropica*) venoms possess antimicrobial peptide (AMPs) which showed broad spectrum antimicrobial activity and act through diverse mechanisms [51]. Anoplin is an antimicrobial peptide (AMPs) is a promising candidate for battling multi-resistant bacteria [52]. Moreover, anoplin-4 is a novel anoplin analogue shows enzymatic stability and used for treatment of different pathogen induced infection [53]. These AMPs are widely distributed in different wasp venom and might provide templates or the development of novel peptides antibiotics [54]. These could be used as peptide antibiotics [54]. The peptides alloferon 1 and 2 have shown activity against the influenza virus, through the same mechanism and induce effector immune functions (Chernysh, *et al.* 2002). A synthetic peptide T22 ([Tyr5, 12, Lys7]-polyphemusin II), in association to promiscuous peptide tachyplesin and the peptide polyphemusin, identified in hemocytes of horseshoe crab *Tachypleus tridentatus* and *Limulus polyphemus* showed potent antiviral activity against HIV-1 and HIV-2 *in vitro* [56,57]. This inhibitory activity is due to specific binding to a chemokine receptor CXCR4, which serves as a co-receptor for the entry of HIV-1 into T cells [58]. Ant venom glands also secrete proteinaceous and alkaloidal toxins which showed cytolytic, haemolytic, allergenic antimicrobial and pain-producing pharmacologic activities [59] (Table 1; Figure 1).

Scorpion venom

Large numbers of toxins have been isolated from scorpion venom and are characterized for their biophysical and biological properties. Most of them have shown antiviral activity against various virus pathogens. BmKDfsin4 is a unique multifunctional defensin from scorpion inhibits hepatitis B virus replication *in vitro* [60]. It also shows potassium ion channel Kv1.3-blocking activities. Similarly, scorpion venom peptide Smp76 isolated from *Scorpio maurus palmatus* is a potential new antiviral agents that inhibits Dengue virus (DENV) and Zika virus (ZIKV) infection by regulating type-I interferon response. It acts as a potent natural AMPs that enhance immunity by functioning as immunomodulators [61]. Similar activity is reported in recombinant Smp76 (rSmp76) and effectively inhibit DENV and ZIKV infections in a dose-dependent manner in cell line cultures and primary mouse macrophages. This recombinant rSmp76 up regulate the expression of IFN-β by activating interferon regulatory transcription factor 3 (IRF3) phosphorylation, and enhance type-I IFN response [62]. It strongly suppresses Chikungunya virus infection [62]. Scorpion venom peptide variant mucroporin-M1 shows virucidal activity against measles, SARS-CoV and influenza H5N1 viruses. Mucroporin-M1 exerts severe effects on viruses by directly binding to virus membranes [63]. The peptide Eval418 shows very high virus clearance activity in an HSV-1 plaque reduction [64] (Figure 1). Egyptian scorpion species also produce virocidal AMPs which were found effective against hepatitis C virus [65] (Table 1).

Spider venom toxins

Spiders show wide diversity; throughout the world its 48,409 species are known [66]. Spider venom is a complex mixture and contains over 400 venom peptides/species. Venoms from spiders are a complex mixture of molecules with enormous diversity. The chemicals they contain, such as small polypeptides, acylpolyamines, free acids, biogenic amines, glucose, free amino acids, inorganic salts, and ions, may have pharmacological actions, as neurotransmitters, modulators, and/or blockers of ion channels and pore formers in plasma membranes. Spider venom toxin peptides interact with ligand gated channels and modulate the activity of neuronal ion channels and receptors located on cell membrane Liu., *et al*. Spider toxins are useful source of pharmacological peptides [67]. In addition, high molecular weight molecules, including enzymes and other proteinaceous neurotoxins, can be found in these venoms [68,69] (Table 1).

Spider venom toxins also show wider antimicrobial potential against communicable disease pathogens [70]. Venom toxins isolated from fishing spiders *Dolomedes mizhoanus* and *Dolomedes sulfurous* are potent neurotoxins these mainly target ion channels and impose pharmacological effects [71]. These spider neurotoxins are linear short peptides [72]. Most spider venoms are dominated by disulfide-rich peptides that typically have high affinity and specificity for particular subtypes of ion channels and receptors [73]. Peptide toxins isolated from Tarantula *Haplopelma hainanum* (*Ornithoctonus hainana*) impose pathophysiological effects like cardiovascular disorders, chronic pain, inflammation, and erectile dysfunction [73]. Spider toxins are abundant and variable, factors [74] that work together to generate diverse bioactivities [8] (Table 1).

Molluscs

Molluscs mainly tunicates secrete peptides such as didemnins

and depsipeptides which show very strong antiviral and antitumor activity [75-77]. Teretoxins secreted by members of Terebridae family which show strong antivirus activity [78] (Table 1).

Fish toxins

Fish venoms are natural depository of highly active bioactive components and could become a good source for discovery of novel drugs and physiological tools. Bioactive components from fish venoms reveal such as cardiovascular, neuromuscular, cytotoxic, inflammatory, and nociceptive activities. Fish venoms also contain antimicrobial peptides (AMPs) which act on the membrane of microbial cells and cause cell lysis. *Pyridoxine* is a cationic AMP which *shows* antimicrobial potential to be used as a novel antibiotic [79]. Similarly antimicrobial activity is also reported in Hepcidin 1 isolated from *S. marmoratus*. Piscidin, Moronecidin, NK-*lysine* and β-*defense* kill pathogen infection in aquaculture [79]. These show broad pharmacological activities [80] and could be used novel antibiotic to treat virus infection [79]. Venom toxins isolated from different fish venoms such as stonefish, soldier fish, lionfish, weaver fish, and stingrays inhibit activity of various physiological enzymes such as proteases [81,82] hyaluronidase and phospholipase C activity [83,84]. Additionally, natterins, a novel family of toxins found in toadfish venom shows kininogenase activity have been found in toadfish venom [85] (Table 1).

Fish venom toxins after infliction impose various biochemical and pathological changes [86-88]. These also showed angiotensin processing activities [89]. *N. robusta* venom also contains hyaluronidase activity [90] while *S. argus* possesses phospholipase C activity and causes hemolysis much similar to PLA2 found in some terrestrial venoms [91,92]. Catfish venom contains very high hyaluronidase and lipase *activity, but* lesser activities of phospholipase A2, lactate dehydrogenase (LDH), cholinesterase (CE), alkaline phosphatase (ALP), and aspartate transaminase (AST), and *last activity* of *proteins* and 5-*nucleotides* (5'-NT) [92]. Fish toxin peptides act upon major portals mainly ion channels, pumps, transporters and ligand gated ionotropic receptors and disturb the intracellular ion homeostasis [5]. These also interact to G-protein-coupled and tyrosine kinase receptors, bind second messengers and alter its messages and impose pathological changes [5]. Fish venom toxins interact to subcellular organelles such as mitochondria and nucleus. These strongly affect protein- and RNA-synthesis machineries, cytoskeletal networks and exocytic vesicles and impose big human health risks [5]. Several large proteinaceous toxins, such as stonustoxin, verrucotoxin, and Sp-CTx, form pores in cell membranes, resulting in cell death and creating a cascade of reaction s(Table 1).

Amphibians

Frogs and toads possess poison glands and secrete important pharmaceutical compounds i.e. biogenicamines, bufodienolides, alkaloids, steroids, peptides, and lactones. These natural substances show diverse pharmacological effects such as antitumor, antivirus, anti-infection, and analgesic [93]. AMPs isolated from frog venom have shown high therapeutic efficacy *in vitro* and *in vivo* [94]. Antimicrobial peptides buforin II isolated from the skin of a Korean frog, *Rana rugosa* [95] kills microorganisms by penetrating the cell membrane and inhibiting cellular functions [96]. Frog venom components could be used for the development of novel therapeutic agents [97] (Table 1).

Snake venom

Snake venoms secrete more potent toxic components myotoxin crotamine, mambalgin which show antiviral activity against Dengue virus, Yellow fever virus and *Measles virusi* [98]. Crotoxin (CX) and its subunits crotapotin (CP) and phospholipase A2 (PLA2-CB isolated from *Crotalus durissus terrificus* inhibit the Hepatitis C virus (HCV) life cycle in virus infected Huh 7.5 cells [99]. PLA2-CB a small toxin peptide inhibits HCV entry and replication [99]. Phospholipase A2, from *Bothrops leucurus* venom shows replication inhibition activity against Dengue virus (DENV) [98]. Sarafotoxins toxins from *Atractaspis aterrima* [100] (Terrat Y., *et al*. 2013) and three-finger toxins (3FTx) are most abundantly secreted and potently toxic components which make venom highly poisonous arsenal [101]. Protein-protein interaction (PPI) inhibitors show strong antiviral activity [102]. L-amino acid oxidase and peptide derivatives isolated from *Bothropoides mattogrosensis* pitviper venom showed strong an antimicrobial activity [103,104] (Table 1).

Currently, no definitive treatment or prevention therapy exists for COVID-19. This large depository of natural toxins of potential bioactive proteins could be used for development of novel drug molecules to control virus pathogens' more specifically Covid-19 infection [15]. These low molecular weight short animal toxins could be predicted for their most appropriate action in virus targets molecular modeling studies be performed *in silico* and test *in* real time experimental research in different animal models to [15] (Figure 1 and 2).

Conclusion

Animal toxins isolated from different animals i.e. sponge, tunicates, crabs, cnidarians, scorpions, spiders, wasps, bees, fish, amphibians and snakes isolated from marine sponge, tunicates, crabs, cnidarians, scorpions, spiders, wasps, bees, fish, amphibians and snakes showed very high antiviral efficacy against enveloped viruses. There is a question mark over ability of anti-viral agents as no one among them is proved to be an appropriate solution of unprecedented rise of this pandemic. From various researches animal venom toxins were found active against number of virus microbial infection. Many of these proteins are part of humoral responses generated in the insects and mammals and play an important role in immune defense and reactions developed by the host to bring off infections. These have shown high structural and physiological competence in comparison to synthetic drugs AMPs showed highly antimicrobial activity and much efficiently kill infectious agents. Hence, these highly active antimicrobial peptides could be used as antibiotics after testing them in clinical controlled trials. Venom toxins can be used as templates for development of highly active pharmaceutical drugs. However, for obtaining novel drugs to control pandemic viruses activity finding, receptor interactions stability downstream processing of toxins and its genes is highly important, for quick solutions bioinformatic tools mainly transcriptomics and proteomics data should be analyzed.

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Disclosure of Conflict of Interest

The authors declare no competing financial interests.

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