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Review Article

THERAPEUTICS APPROACHES OF INVERTEBRATE ANIMAL TOXINS: A REVIEW

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ABSTRACT

The present review article describes invertebrate venoms and various toxins secreted by them. Animal venoms are stores of novel peptides which exhibit a wide variety of biological effects and actively interact with pathogen and parasites. Animal toxins selectively bind to ion channels and receptors and display show hemolytic, cytolytic, proteolytic, anti-diabetic, antimicrobial and analgesic activity. These generate allergic and inflammatory responses in victims. These disrupt cell membranes and inhibit bacterial growth and kill them. Animal toxins inhibit virus entry into host cells and obstruct virus replication. These were also found highly effective against protozoan and fungal pathogens. By using bioinformatics tools, methods and approaches, both structural and functional diversity of toxin peptides could be harnessed to develop highly effective broad-spectrum drugs for therapeutics. Animal venoms are an inexhaustible source of bioactive molecules, which could be used for the development of immune diagnostics, various pharmaceuticals for therapeutics and bio-insecticides. Present article tries to explore the exceptional specificity and high potency of animal toxins for drug development.

Keywords: Invertebrates, Animal toxins, Ion channel blockers and therapeutic effects

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INTRODUCTION

In the animal kingdom, a large diversity of venom-bearing animal species exists. These belong to both invertebrates and vertebrates. Animal venoms are the natural depository or source of various bio-molecules, mainly toxins and enzymes. These venom toxins were evolved during long evolutionary periods as selective and targeted molecules. More specifically, these are used in self-defense, for paralyzing prey and deterring predator from the territory. These successfully control angiogenesis and inhibit cell proliferation *in vitro* cancer cell cultures. These toxins displayed anticancer effects and inhibit the growth and proliferation of tumor and cancerous cells [1]. A number of toxins purified from anemones, centipedes, bees, or wasps, hornets, snails, spider and scorpion and sea, fish, toads, fry, and the snake has been isolated and screened for their anticancer effects. These successfully showed inhibition of cancer cell invasion, cell cycle arrest, proliferation, migration, induction of apoptosis activity and neo-vascularization and blocking signaling pathways [2]. Animal toxins could be used as therapeutic molecules, mainly in drug development.

Animal venom glands are natural depositories of diverse toxin molecules which possess large numbers of chemical structures with a variety of action on cancer-affected cells. Similarly, snake venom toxin successfully inhibits cell growth at very low IC50 value 4.5 *μg*/ml (*Vipera lebetina*). Snake toxin-induced apoptosis in ovarian cancer cells via inactivation of nuclear factor kβ and inhibits DNA binding activities of toxin [3]. Snake venom toxin combined with salicylic acid and states3, these have significantly increased inhibition of cell growth. These act as signal transducers [4].

Source of information

For writing this comprehensive research review on invertebrate animal toxins/peptides/proteins, various databases were searched. For the collection of relevant information, specific terms such as medical subject headings (MeSH) and key text words, such as "animal venom toxins and its therapeutic uses" published till 2022 were used in MEDLINE. *Most specially* for retrieving all articles pertaining to the use of animal venoms for various therapies, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the venom toxins/proteins were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporating 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, Swiss rot, Google searches" From this common methodology, discoveries and findings were identified and summarized in this final review.

Cytolytic or neurotoxic effects

Cnidarians possess nematocysts which also inflict toxins to target their prey. They target different animals, such as insects, crustaceans and vertebrates. Sea anemones possess proteins and peptides which show cytolytic or neurotoxic activity. Potency of these toxins varies with the structure and site of action [5, 6]. Sea anemones toxins bind to voltage-gated Na^+ and K^+ channels and acid-sensing ion channel toxins. Few cytolysins act as Kunitz-type protease inhibitors activity and Phospholipase A2 activity. Similarly, *Palythoa caribaeorum* venom toxins show cytolytic activity against U251 and SKLU-1 cancer cell lines. Cnidarian venoms *show* cytotoxic and hemolytic effects (table 1) [7].

Hemolytic activity

Sea Anemone *Entacmaea quadricolor* contain venom toxins in nematocysts that show haemolytic effects [8]. The *A. equina* mucus matrix shows hemolytic activity on rabbit erythrocytes, cytotoxic activity against the tumor cell line K562 (human erythromyeloblastoid leukemia) and antibacterial lysozyme-like activity [9]. *H. crispa* contain actinoporins which show potential hemolytic activity, it is employed as offensive and defensive chemicals by corals as armaments [10]. Actinoporin show consistent different hemolytic activity in all their representatives [11]. Sea anemones *H. crispa* is a pore-forming toxin belongs to actinoporins that show hemolytic activity [12]. Pocilopotoxin-Spi1 toxin (α-PCTX-Spi1) isolated from *Stylophora pistillata* shows hemolytic activity (table 1) [13].

Anti-parasitic activity

Sea-Anemone *Stichodactyla helianthus* contains *collision* I and II from (St I and St II) and Actiniaequina (EqtII) contain equinatoxin II

[14]. Sea-anemone also contains cytolysins which have Kunitz-type protease inhibitors activity. These toxins efficiently kill Giardia cells and show anti-parasite specificity with anti-Giardia antibodies (table 1) [15, 16].

α-amylase inhibitor activity

Sea Anemone *Heteractis magnifica* contain magnificamide a 44 amino acid peptide (4.77kDa) Da) [17]. It shows major α-amylase inhibitory activity on cytoplasmic membranes and ion channels. More especially, pancreatic Sea Anemone *Metridium senile* contain peptide toxins TXMs 9a-1 [18, 19].

The transient receptor potential ankyrin-repeat 1 (TRPA1) is an important player in pain and inflammatory pathways [20-22]. It shows anti-inflammatory effects in experimental mice [23, 24]. Sea anemone *Heteractis crispa* Kunitz-type peptides showed anti-inflammatory and anti-histamine effects [25]. Ueq 12-1 is a unique peptide potentiator of the TRPA1 receptor that produces anti-inflammatory effects *in vivo*. Sea anemone *Urticina eques* contains a bioactive peptide named α-AnmTxUeq 12-1. It consists of 45 amino acids, including 10 cysteine residues with (table 1) [26].

Neuroprotective activity

Cnidarians have been known since ancient times for the painful stings they induce to humans. The effects of the stings range from skin irritation to cardiotoxicity and can result in the death of human beings [27]. α-AnmTXMs 9a-1 has been isolated from the venom of sea anemone *Metridium senile.* It potentiates the response of TRPA1 to endogenous agonists, followed by persistent functional loss of TRPA1-expressing neurons. It imposes potent analgesic and anti-inflammatory effects in mice. The sea Anemone *Heteractis crispa* contains Kunitz-peptides shows neuroprotective activity against 6-hydroxydopamine [28]. Sea anemone *Heteractis crispa* venoms have Kunitz-type peptides, which are also known as the "analgesic cluster" of the HCGS peptide subfamily (table 1) [29].

Anti-helminthic activity

Nematostella vectensis nematocyst venom proteins are metallopeptidases belong to Tolloid family and a cysteine-rich protein. These show anti-helminthic activity [30]. AnewKunitz-type protease inhibitor InhVJ was isolated from the sea anemone *Heteractis crispa* (*Radianthus macrodactylus).* It also shows similarity to serine protease [31] (fig. 2). Sea anemone *Anthopleura dowii* Verrill venom toxins act like proteases. These also synthesize neurotoxins which potentially inhibit potassium (K+) or sodium (Na+) channels, proteases, phospholipases A2, and the activity of other polypeptides [32]. These also activate TRPV1 channels [33]. The Sea Anemone *Bunodactisverrucosa* venom contains metalloproteinases and neurotoxins, which activate TRPV1 channels [34]. These also affect basal cell metabolism and biosynthesis of antibiotics (table 1) [35].

Anti-diabetic activity

Sea Anemone *Heteractis magnificamucus*, contain Magnificamide, a α-Defensin-Like Peptide target, mainly on cytoplasmic membranes and ion channels. It is a rich source of pancreatic α-amylase inhibitors, which maintain the glucose level in the blood and can be used for the treatment of prediabetes and type 2 diabetes mellitus. The main function of magnificamide is the inhibition of α-amylases, and also acts as a potential drug candidate for the treatment of type 2 diabetes mellitus (table 1) [36].

Immunomodulating activity

Sea *Anemone Stichodactyla helianthus* immunomodulates CCR7-effector memory T (TEM) lymphocytes. This also acts as potent immunomodulators for the treatment of autoimmune diseases [37]. Similarly, ShK-186, a synthetic analog of ShK is used as a therapeutic agent for autoimmune diseases (table 1) (fig. 2) [38].

Channel inhibitors

Jellyfish is scyphozoans which possess venoms which is rich sources of toxin peptides and protein. Jellyfish use stings to capture prey or deter predators. A toxin aurelin from *Aurelia aurita* and phospholipases from *Nemopile manomurai* phospholipases display high lethality after stinging. These toxins mainly cell membrane-and show thrombin-like activity and cause hemolysis [39]. Different Jellyfish species *Stomolophus meleagris, Aurelia aurita*, *Nemopile manomurai* shows channel inhibition. Preproaurelin is an 84-residue signal peptide that has 22 amino acids is much similar to defensins blocks K+channel belongs to ShKT domain family (table 1, fig. 2) [40].

Other major toxin components from Jellyfish are C-type lectin, phospholipase A_2, potassium channel inhibitor, protease inhibitor, metalloprotease, hemolysin and other toxins. Presence of the compounds makes the sting more toxic [41]. Jellyfish envenomations shows dermatological symptoms and cause inflammation [42]. This venom-induced inflammation may be caused due to inhibitory effects of matrix metalloproteinase (MMP) inhibitors for venom-induced inflammation were explored at a cellular level (table 1) [43].

Cnidarians, mainly hydra, jellyfish, and sea anemones organisms, inflict deadly toxins for hunting prey and for territorial defense [44]. Zoanthid *Protopalythoa variabilis* are neurotoxic peptides, hemostatic and hemorrhagic toxins, membrane-active (pore-forming) proteins, protease inhibitors, mixed-function venom enzymes, and auxiliary venom proteins. Most of them belong to ShK/Aurelin family [45]. Sea anemones secrete α-actitoxin-Ate1a (Ate1a) which selectively inhibit voltage-gated potassium channel 18 BDS-I and II, and selectively which target Kv3.4 channels (table 1) (fig. 2).

PhcrTx1 toxin characterized from the sea *Anemone phymanthus crucifer*, is ASIC inhibitor, it shows lower potency on *kV* channels [46]. Sea *Anemone anthopleuradowii* Verrill venom contains neurotoxins which act as potassium (K+) or sodium (Na+) channels inhibitors [47]. These neurotoxins act upon a diverse panel of ion channels, such as voltage-gated sodium and potassium channels. These mainly target sodium channels and modify those21. Four different types of neurotoxins with different structures and modes of action have been isolated from sea anemones (table 1) [48].

These toxins consist of cysteine-rich peptides which are capable of binding to different extracellular sites of this channel protein. These specially targets voltage-gated Na (+) channels which perform conduction of electrical impulses in sea anemones, Sea *Anemone* type 1 peptides known to be found active on Na*(v)* 1. x channels. These peptides are 46-49 amino acid residues long*;* contain three disulfide bonds and their molecular weights range between 3-5 Kda [49]. Sea Anemone *Anthopleura immaculate* contain three peptide toxins (Am I-III) with crab toxicity Type 1 sea *Anemone* sodium channel toxins, both Am I (27 residues) and II (46 residues) are potent neurotoxins [50]. Sea Anemone *Heteractis crispa* contain neurotoxin RTX-VI that modulates the voltage-gated sodium channels (NaV). The RTX-VI molecule consists of two disulfide-linked peptide chains and is devoid of Arg13, for the NaV channels. *System* (NaV1.2, NaV1.6) and insect (BgNaV1, VdNaV1) sodium channels [51]. A neurotoxin (BDS)-like antimicrobial peptides (AMPs)-Crassicorin-I and its putative homolog (Crassicorin-II) that was isolated from the pharynx extract of an anthozoan sea anemone (*Urticina crassicornis*). Crassicorin-I shows functional linkage between AMPs and neurotoxins in a basally branching metazoan (table 1) [52].

The Sea Anemone *Stichodactyla haddoni* contains peptide toxins, SHTX I-III with crab-paralyzing activity. SHTX I (new toxin, 28 residues), II (analogue of SHTX I, 28 residues) and III (Kunitz-type protease inhibitor, 62 residues) are potassium channel toxins and SHTX IV (48 residues) is a member of the type 2 Sea Anemonesodium channel toxins [53]. Indeed, cnidarians are considered is the largest phylum of toxic animals [54]. *Stichodactyla helianthus* contains potassium channel blocker shookits analogue ShK-186 for the treatment of autoimmune diseases [55]. These toxic products, particularly peptide toxins, could be used as a promising target for biomedicine research.

Allergic and immune hypersensitivity

Myrmeciapilosulais an Australian ant, its venom contains Pilosulin 3, pilosulin 1 and Pilosulin 4.1. Among which, pilosulin 1 and Pilosulin 4.1 are minor allergens. Its sting causes allergy and imposes immune hyper sensitivity and sometimes fatal anaphylaxis [56]. Fire ant

stings induce eosinophil recruitment and production of Th2 cytokines [57]. Fire antsirritates skin, severe pain, cross-reactive to oter ants and non-sensitive individuals through sera from sensitive individuals [58]. An *Ectomomyrmex spp. sting causes* hypersensitivity with many incidents of allergic reactions and generates a high level of specific IgE. It mediates type I hypersensitivity in patients [59]. Similar systemic hypersensitive reactions can pose life-threatening complications are also seen in red Imported Fire Ant (RIFA) *Solenopsis invicta* Buren (Insecta: Formicidae). It shows immediate effects due to the presence of major (>95%) toxic alkaloids [60]. Fire ant stings also are capable of causing serum sickness, nephrotic syndrome, seizures, worsening of pre-existing cardiopulmonary disease, and anaphylaxis (fig. 2).

Proteolytic activity

The crude venom from invertebrates, mainly sea anemones, show high proteolytic activity on azocasein an optimal pH 8.0 and 37 °C. In the presence of protease inhibitors as aprotinin, leupeptin and EDTA, the azo-caseinolytic activity was reduced by 45%, 29% and 9%, respectively (table 1) (fig. 2) [61].

Anti-angiotensin converting enzyme activity

The anti-angiotensin I converting enzyme activity of box jellyfish, *Chiropsalmus quadrigatus* Haeckel contain venom hydrolyzate. Angiotensin I converting enzyme (ACE) show inhibitory activity (fig. 2) [62].

Histamine-releasing activities

A pilosulin-like toxin peptide 1-6, isolated from the predatory ant *Odontomachus monticola* displays hemolytic, and histamine-releasing activities (fig. 2) [63].

Fibrinogenolytic activity

Ant *Odontomachus bauri* crude venom degrades the fibrinogen α-chain faster than the α-chain, while the fibrinogen α-chain remained unchanged. It is due to the presence of serine proteases (table 1) (fig. 2) [64].

Anti-angiogenic activity

Sea Anemone *Anemonia viridis* contains a low molecular weight protein that shows anti-angiogenic activity. It also limits the proliferation of endothelial cells proliferation and angiogenesis. It shows trypsin activity inhibition like a Kunitz-type inhibitor. It interacts with integrin protein of membrane due to presence of an Arginine Glycin Aspartate (RGD) motif [65]. This inhibitor stops formation of new blood vessels or anti-angiogenesis effects [66]. It prevents HT-29 colorectal cancer cell migration [67]. Sea Anemone secretions are actinoporins Sticholysins I and II (Sts, StI/II), which interact with biological membranes of cells and form pores. Sticholysins I and II also show anti-tumor effects [68]. Few important cnidarians species such as *Palythoa caribaeorum* venom contains compounds which show ant-cancer activity [69]. *Palythoa caribaeorum* possess PLA2 activity that shows specific cytotoxicity against U251 and SKLU-1 cancer cell lines [70]. These cause cell swelling, impairment of ionic gradients and cell death. A marine-derived compound PE displays anti-angiogenesis and. anti-tumor activities. PE shows inhibition of VEGFR2 signaling, and anti-tumor activity and increased apoptosis of both endothelial cells and tumor cells (table 1) (fig. 2) [71].

Anti-proliferative activity

Melittindisplays anti-proliferative activity [72] and inhibits angiogenesis [73]. Its recombinant form is used for making immunotoxins by fusion of genes [74]. Melittin also binds to anti-asialo glycoprotein receptor (ASGPR) a single-chain variable fragment antibody (Ca) shows anti-invasive activity in hepato cellular carcinoma cells [75]. More specifically, CTLA-4-targeted scFv-melittin fusion protein acts as a potential immunosuppressive agent showed selective cytotoxicity assist in organ transplants [76]. Melittin coupled to avidin, when released induces immediate cell lysis [77] and stop cancer cell latency [78]. Asterosaponin 1 is isolated from starfish *Culcitano vaeguineae*. It was found active against malignant glioblastoma. It more efficiently kill glioblastoma cells and is used in anti-tumor chemotherapy [79]. It also shows potential anti-proliferative and pro-apoptotic activity of in A549 human lung cancer cells. Asterosaponin 1 inhibits the proliferation of A549 cells through induction of ER stress-associated apoptosis, making asterosaponin 1 a candidate new anticancer drug for lung cancer therapy (table 1) (fig. 2) [80].

Amphibians are reservoirs of biologically active toxin molecules with antitumor activity. Toads, *Bufo Bufo gargarizans* possess toxins in their skin and poison glands. Their toxins are bufadienolides, such as bufalin, cinobufagin, resibufogenin, and telocinobufagin. These are major active compounds derived from the toad skin. Among all these cinobufacini (e. g. bufalin and cinobufagin) shows inhibit of cell proliferation, induction of cell differentiation, induction of apoptosis, disruption of the cell cycle, and inhibition of cancer angiogenesis.

Cinobufacini have effective anticancer activity with low toxicity and few side effects [81]. Arenobufagin, is used in Chinese medicine for cancer therapy. It inhibits cell growth in several cancer cell lines. It shows anti-angiogenic activity. Arenobufagin inhibited vascular endothelial growth factor (VEGF)-induced viability, migration, invasion and tube formation in human umbilical vein endothelial cells (HUVECs) *in vitro*. More specifically, arenobufagin is a specific inhibitor of VEGF-mediated angiogenesis (table 1) (fig. 2) [82].

Snake venom-based drugs are widely used to treat various types of cancer. Caspian cobra venom toxins showed cytotoxic effects against human cancer cell lines [83]. *Leaven* is a snake venom disintegrin which generates anti-angiogenic effects by inhibiting vascular endothelial growth factors (VEGF) [84]. A toxin-derived drugs from snakes effectively check cancer cell proliferation, migration, invasion, and neovascularization and induce apoptotic activity. CrTX toxin was found effective against viper *Crotalusdurissusterrificus*, in human lung adenocarcinoma A549 cells (table 1) (fig. 2).

Inducing cell apoptosis due to activation of P38MAPK and caspase-3, and by cell cycle arrest mediated by increased wt p53 expression. In addition, CrTX displayed anti-angiogenic effects *in vivo* [85]. Snake venom-derived drug cerivastatin also reduces the proliferation and invasion of aggressive breast cancer cells [86]. DisBa-01, a low molecular weight recombinant protein, specifically interacted with alpha(v)beta3 integrin and shows potent anti-metastatic and anti-angiogenic properties. It causes hemostasis and thrombosis (table 1) (fig. 2) [87].

Similar effects, and anti-angiogenic effect with the integration are seen in Lebetin 2 isolated from *Macrovipera lebetina* exhibits [88]. Dabmaurin-1 exhibits anti-angiogenic effects *in vitro with* similar anti-integration properties. Contortrostatin (CN), a disintegrin from southern copperhead snake venom, possesses anti-angiogenic activity both *in vitro* and *in vivo* [89]. A cryptic plasminogen-derived domain, kringle 5, inhibits endothelial cell growth [90]. Phospholipases type A2 (PLA2s) are the most abundant proteins found in Viperidae snake venom. It exerts neurotoxicity, myotoxicity, hemolytic activity, antibacterial, anticoagulant, and anti-platelet effects; some venom PLA2s show antitumor and anti-angiogenic activities by mechanisms independent of their enzymatic activity (table 1) (fig. 2) [91].

Ant venom toxins inhibit angiogenesis and apoptosis [92]. Ant venom (SAV*) Pachycondyla sennaarensis* shows anti-neoplastic activity HepG2, MCF-7, and LoVo in different cancer cell lines. Its shows the differential dose-dependent antineoplastic effect with an increased level of significant cytokines, including Interleukin (IL)-1β, IL-6, and IL-8 and transcription factor, nuclear factor-kappa B (NF-kB) [93]. Mastoparan is an α-helical and amphipathic tetradecapeptide obtained from the venom of the wasp *Vespula lewisii* (fig. 1). This peptide kills cancer cells by causing irreparable membrane damage and cell lysis, or by inducing apoptosis [94]. It shows strong tumor cell cytotoxicity and induces caspase-dependent apoptosis in melanoma cells through the intrinsic mitochondrial [95]. Melittin (MEL), isolated from bee venom is one of the major amphipathic 26-residue peptide that shows anti-arthrosclerosis effects [96]. This is also a good candidate for cancer therapy [97]. Melittin induces apoptotic cell death in cervical cancerous cellsand

shows an inhibitory effect on the proliferation of cancer cells. [98]. α-mangostin is a major active compound with potential anticancer activity in *T. laeviceps cerumen* in Thailand [99] (fig. 1). Propolis is a complex resinous honeybee product it shows antimicrobial, anti-inflammatory and anti-tumor properties. *A. mellifera propolis* contains cardanol and cardol, both display potential anti-cancer bioactivity and could be used for future development of anti-cancer drugs [100, 101]. *Apis mellifera* BV, venom glands possesses melittin (MEL) and phospholipase A2 (PLA2). Both showed cytotoxic effect on human colon carcinoma cells (HCT116), and synergistic effect on other cancer cells [102]. Venom anti-cancer peptide 1, VACP1 was derived from the wasp venom of *Vespa ducalis* SMITHVACP1. It more potently suppressed cell proliferation and induced the cell apoptosis of OS cells by inducing the activation of the p38 MAPK and JNK signaling pathways [103]. Spider venom shows anticancer activity in a variety of human malignancies, including lung cancer. Anti-cancer peptide toxin LVTX-8, from the spider *Lycosa vittata* LVTX-8 shows strong cytotoxicity and anti-metastasis towards lung cancer. LVTX-8 anticancer peptide with high efficiency and acceptable specificity, LVTX-8 may become a potential precursor of a therapeutic agent for lung cancer in the future [104]. A proteinaceous toxin, named Latroeggtoxin-V, isolated form *Latrodectus tredecimguttatus*. Black widow spider selectively acts on breast cancer line MDA-MB-231 cells. It is not only arresting their cell cycle, inhibiting their proliferation and migration, but also inducing their apoptosis. Latroeggtoxin-V belongs to the ATPase inhibitor protein family and used in the anticancer drug development (table 1) (fig. 2) [105].

Fig. 1: Showing animal toxins peptides

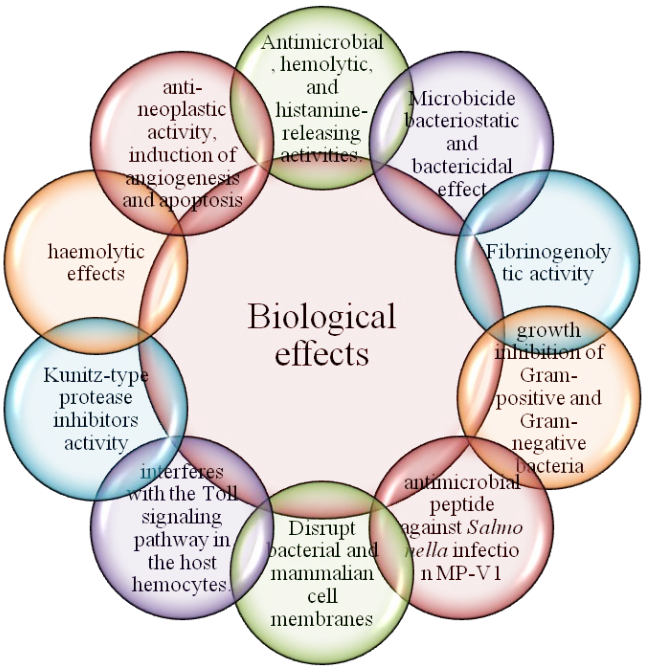

Fig. 2: Showing biological effects of animal venom toxins

Table 1: Showing animal peptide toxins ant and its biological effects

S. No.	Animal species	Peptides	Biological activities	Reference
1.	*Palythoa caribaeorum*	Sticholysin I and II	PLA_2 activity, cytotoxicity	[4]
2.	*Entacmaea quadri color*	Cytolysins	Haemolytic effects	[7]
3.	*Lasioglossum laticeps*	Lasiocepsin	Antimicrobial peptide	[13]
4.	*Urticin aeques*	Ueq 12-1	Analgesic activity	[14]
5.	*Urticina grebelnyi*	Ugr 9-129 amino acid peptides	Analgesic activity	[15]
6.	*Urticina eques*	α-AnmTxUeq 12-1	Anti-inflammatory activity	[16]
7.	*Rhizostoma pulmo*	collagen peptides	Antioxidant activities	[17]
8.	*Bunodactis verrucosa*	metalloproteinases	Anti-helminthic activity	[27]
9.	*Metridium senile*	τ-AnmTXMs 9a-1	Analgesic and anti-inflammatory effects	[41]
10.	*Odontomachus monticola.*	Pilosulin-like peptides	Antimicrobial, hemolytic, and histamine-releasing activities.	[53]
11.	*Odontomachus bauri*	serine proteases	Fibrinogenolytic activity	[54]
Insect venom	*Cnidopus japonicas*	linear polypeptides (Cys-free)	Analgesic effects	[58]
12.	*Platymeris biguttatus*	S1 proteases, redulysins, Ptu1-like peptides	Shows neurotoxic, hemolytic, antibacterial, and cytotoxic effects	[59]
13.	Sea anemone	Cytolysins, α-AnmTxUeq 12-1	Voltage-gated Na^+ and K^+ channels toxins, acid-sensing ion channel toxins, Kunitz-type protease inhibitors activity and toxins with Phospholipase A2 activity	[61]
14.	*Chiropsalmus quadrigatus*	hydrolysate. Angiotensin I converting enzyme	Inhibitory activity	[62]
15.	*Anemonia viridis*	linear polypeptides (Cys-free)	Cytotoxic and anti-proliferative activities	[63]
16.	*Pelagia noctiluca*	Sticholysin I and IIv	Anticancer and nitric Oxide (NO) inhibition activities	[74]
17.	*Pachycondyla sennaarensis*	Serine proteases	Anti-neoplastic activity, induction of angiogenesis and apoptosis	[86]
18.	*Neoponera goeldii*	Ponericins	Haemolytic, antibacterial, insecticidal activity	[86]
19.	*Myrmecia pilosula*	Pilosulin 3, pilosulin 1 and Pilosulin 4	Allergenic activities	[87]
20.	*Macropis fulvipes*	macro pin (MAC-1)	Antimicrobial peptides	[88]
21.	*Macropis fulvipes*	AcKTSPI-Kd, microbial serine proteases Kazal-type serine protease inhibitors	Antibacterial activity against Gram-positive bacteria	[90]
22.	*Panurgus calcaratus*	Panurgines	Antimicrobial peptides (AMPs), antifungal activity, and low hemolytic activity against human erythrocytes	[91]
23.	A. *baumannii*	Agelaia-MPI and Polybia-MPII	Antibacterial activity against both Gram-positive and Gram-negative bacteria	[93]
24.	*Vespula vulgaris*	Mastoparan V1 (MP-V1)	Antimicrobial peptide against *Salmonella* infection MP-V1	[94]
25.	*Equmenine* wasp	Antimicrobial α-helical peptides	antimicrobial peptide	[95]
26.	eumenine wasp	eumenine mastoparan-EM1 and eumenine mastoparan-EM2 peptides	Kazal-type serine protease inhibitors exhibit thrombin, elastase, plasmin, proteinase K, or subtilisin A inhibition activity	[96]
27.	*Laches anatarabaevi*	Cytolytic peptides	Antibacterial activity against Gram-negative and Gram-positive bacteria	[100]
28.	*Polistes dominulus*	EMP-EM peptides	Disrupt bacterial cell membranes and mammalian cell membranes	[105]
29.	*Microplitis mediator*	VRF1, a metalloprotease homolog venom protein	Interferes with the Toll signaling pathway in the host hemocytes.	[106]
30.	*Polybia paulista*	Polybia-CP	Antibacterial activity	[105]
31.	*Tetramorium bicarinatum*	Dermaseptin-, defensin-, ICK-, pilosulin- and ponericin-like antimicrobial peptides	Antimicrobial activity	[105]
32.	*B. verrucosa*	Metalloproteinases and neurotoxins	Antimicrobial activity	[105]
33.	*Hydra*	Hydramacin-1	Antimicrobial activity	[105]
34.	*Hydra*	Arminin 1a-C	Antimicrobial peptide	[105]
35.	*Pseudopolybia vespiceps*	Mastoparan	Antimicrobial activity against bacteria	[105]
36.	*Opistophtalmus carinatus*	Opistoporin 1 and parabutoporin	Pore-forming and hemolytic peptides	[105]
37.	*Polybiapaulista*	Polybia-MPI, anoplin (GLLKRIKTLL-NH_2)	Antifungal activity	[106]
Cnidarians	*Fusarium culmorum*	polybia-CP, Hefutoxin 1	Antifungal activity	[107]
38.	*T. stigmurus*	Polybia-CP	Antifungal efficacy	[108]
39.	*Orancistrocerus drewseni*	OdVP2 and OdVP2L	Antifungal activities	[109]
40.	*Palythoa caribaeorum*	Actinoporins	Pore-forming toxins	[110]
41.	*Ectatomma tuberculatum*	Ponericin peptides	Antibacterial activity, growth inhibition of Gram-positive and Gram-negative bacteria	[111]
42.	*Heteractis crispa*	Kunitz-type peptides	Anti-inflammatory effects	[114]
43.	*H. crispa*	Actinoporins	Hemolytic activity	[115]
44.	*Apis dorsata*	Mast cell degranulating peptide (MCD), apamin, or the small peptides melittin (MLT)	Anti-HCV activity against hepatitis C virus (HCV	[118]
45.	*Nasonia vitripennis*	Mastoparan	Anti-trypanosomal	[119]
46.	*Bombyx mori*	Bacterial prodigiosin	Antiviral activity	[121]
47.	Scorpion	mucroporin-M1, Kn2-7	Antiviral activity	[126]
48.	Tick	Defensins	Antimicrobial peptides	[126]

Antimicrobial peptides

The macropin (MAC-1) is antimicrobial peptides (AMPs) isolated from the venom of the solitary bee *Macropis fulvipes* having the sequence Gly-Phe-Gly-Met-Ala-Leu-Lys-Leu-Leu-Lys-Lys-Val-Leu-NH2MAC-1 exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria [106]. AcKTSPI-Kd showed antibacterial activity against Gram-positive bacteria (table 1). It also acts as an inhibitor of microbial serine proteases, Kazal-type serine protease inhibitors [107]. Three antimicrobial peptides (AMPs), named penguins (PNGs), were isolated from the venom of the wild bee *Panurgus calcaratus*. The dodecapeptide of the sequence LNWGAILKHIIK-NH_2 (PNG-1) belongs to the category of α-helical amphipathic AMPs. All three peptides exhibited antimicrobial activity against Gram-positive bacteria and Gram-negative bacteria, antifungal activity, and low hemolytic activity against human erythrocytes (table 1) (fig. 2) [108].

Mastoparan peptide isolated from the venom of the social wasp *Pseudopolybia vespiceps* shows antimicrobial activity against bacteria (*Staphylococcus aureus* and *Mycobacterium abscessus* subsp. *massiliense),* fungi (*Candida albicans* and *Cryptococcus neoformans*) and *in vivo S. aureus* infection. These antimicrobial peptides display pore-forming ability in membrane and could be used as antimicrobial drugs. Polybia-MPII proved to be highly effective, with a lower haemolysis rate compared with peptides of the same family (fig. 1). Mastoparan V1 (MP-V1), a mastoparan from the venom of the social wasp *Vespula vulgaris*, is a potent antimicrobial peptide against Salmonella infection MP-V1 [109]. Cationic Polydim-I exhibits powerful antimicrobial activity against different and diverse microorganisms [110]. Wasp venoms contained such antimicrobial α-helical peptides as the major peptide component [111]. Polydim-I provoked cell wall disruption and exhibited non-cytotoxicity towards mammalian cells (table 1) (fig. 2).

This is isolated from *Polybia dimorpha* Neotropical wasp and shows anti-mycobacterial activity [112]. Antimicrobial peptides (AMPs) have been isolated from scorpion and spider venom [113]. These have shown strong antimicrobial activity against pathogenic bacteria. Insect-derived Kazal-type serine protease inhibitors exhibit thrombin, elastase, plasmin, proteinase K, or subtilisin A inhibition activity. Both eumenine mastoparan-EM1 and eumenine mastoparan-EM2 peptides exhibited potent antibacterial activity (table 1) (fig. 2) [114].

Pin2 [14] and Pin2 [17] have the potential to be used as alternative antibiotic and anti-tuberculosis agents with reduced hemolytic effects [115]. Lasiocepsin is a unique 27-residue antimicrobial peptide isolated from *Lasioglossum laticeps* (wild bee) venom, shows antibacterial and antifungal activity [116]. Cardiolipin, found at the poles of bacterial cells, showed membrane-permeabilizing activity that is not limited to the outer membranes of Gram-negative bacteria (fig. 2).

The peptide interacts with phospholipids initially through its N terminus, and its degree of penetration is strongly dependent on the presence of cardiolipin. Venom of the social wasp *Vespula vulgaris* contains mastoparan V1 (MP-V1 a potent antimicrobial peptide that was found active against Salmonella infection. Eumenine wasps *Anterhynchium flavor* marginatum micado venom contains antimicrobial α-helical peptides as the major peptide component. These were found active against E. coli. Mastoparan-EM1 and EM2 are mast cell degranulating peptides which found in social wasp venoms [117]. The paper wasp *Polistes dominulus* venom toxins show resistance to polymicrobial disease of vineyards. Endoparasitoid wasp, *Microplitis mediator* secrete VRF1, a metalloprotease homolog venom protein that modulates egg encapsulation in its host, the cotton bollworm, *Helico verpaar migera.* This end parasitoid wasp venom protein interferes with the Toll signaling pathway in the host hemocytes (fig. 2) [118].

Similarly, another protein Edin expresses in the fat body of hosts and regulates the increase of plasmatocyte numbers and the mobilization of sessile hemocytes in *Drosophila* larvae. Insect venom is a rich source of peptides that could be used for drug design and innovative therapeutic discoveries. The predatory giant ant *Dinoponera quadriceps* secretes a complex mixture of bioactive peptides in its venom. It contains five classes' e. g., dermaseptin-, defensin-, ICK-, pilosulin-and ponericin-like antimicrobial peptides. Its synthetic templates sDq-2562 and sDq-3162 are ponericin-like dinoponera toxins. The most effective peptide, the 28-residue sDq-3162 displayed a significant bacteriostatic and bactericidal effect with minimal inhibitory concentrations. Similarly, venom peptide bicarinalin, from the ant *Tetramorium bicarinatum*, shows strong antimicrobial activity with a broad spectrum of activity against Helicobacter pylori. It significantly decreases the density of *H. pylori* on gastric cells. It shows both curative and preventive use. It significantly decreases the density of H. pylori on gastric cells. It shows both curative and preventive use. It shows low cytotoxicity against human lymphocytes at a very low concentration (fig. 4). Bicarinalin action is much similar to melting and other humanitarian antimicrobial peptides such as pilosulin or defensing [119]. In addition, the venom showed antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* as well as anti-parasitic activity on *Toxoplasma gondii* infection *in vitro* table 1).

Sea Anemone *B. verrucosa* contain putative toxin, mainly metalloproteinases and neurotoxins. These also showed antimicrobial effects Hydramacin-1 a toxin isolated from Hydra was found potently active against Gram-positive and Gram-negative bacteria including multi-resistant human pathogenic strains. Arminin 1a-C is also an antimicrobial peptide (AMP) is also isolated from metazoan marine *Hydra* [120].

Antibacterial activity

Venoms from ant species *Paraponera clavata*, *Ectatomma quadridens* and *Ectatomma tuberculatum* possess ponericin peptides which showed growth inhibition of Gram-positive and Gram-negative bacteria Lasiocepsin is a unique 27-residue antimicrobial peptide, isolated from *Lasioglossum laticeps* (wild bee) venom, shows antibacterial. Similar antibacterial activity is reported in synthetic fire ant venom alkaloids trans-2 methyl-6-(cis-6-pentadecenyl) piperidine against *Staphylococcus aureus* and *Escherichia coli in vitro*] (table 1) (fig. 2).

Polybia-CP isolated from wasp *Polybia paulista* shows potent antibacterial activity against both Gram-positive and Gram-negative bacteria. This is a membrane-active peptide and passes through membrane of bacteria. It shows strong in action against drug resistant bacteria. The wasp *A. baumannii* MPs Agelaia-MPI and Polybia-MPII had better action against MDR (multidrug-resistant). Anoplin a decapeptide and 19 analogs showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* ATCC 33591 (MRSA), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), vancomycin-resistant *Enterococcus faecium* (ATCC 700221) (VRE Opistoporin 1 and parabutoporin) isolated from scorpion *Opistophtalmus carinatus* were found most active in inhibiting growth of Gram-negative bacteria. Opistoporin 1 and parabutoporin are pore-forming and hemolytic peptides were isolated from scorpion *Opistophtal muscarinatus* and show moderate hemolytic activity than melittin. Bee venom is used against different types of cancer as well against the challenging (table 1) (fig. 2) [121].

Bee venom and its components, i.e. melting (MLT), phospholipase A2 (PLA2), and apartments, showed inhibitory effects against viruses, i.e. Influenza A virus (PR8), Vesicular Stomatitis Virus (VSV), Respiratory Syncytial Virus (RSV), and Herpes Simplex Virus (HSV) *in vitro* and *in vivo.* Similarly, melting also showed antiviral and inflammatory responses *in vitro* and *in vivo*. Honey bee peptide melittin curbs infectivity of a diverse array of viruses, including coxsackievirus, enterovirus, influenza A viruses, human immunodeficiency virus (HIV), herpes simplex virus (HSV), Junín virus (JV), respiratory syncytial virus (RSV), vesicular stomatitis virus (VSV), and tobacco mosaic virus (TMV). Honey bee venom contains mast cell degranulating peptide (MCD), apamin, or the small peptides melittin (MLT) showed anti-HCV activity against hepatitis C virus (HCV). It disrupts HCV replication life cycle. It also act as a good therapeutic agent (table 1) [122].

Mastoparan-derived peptide MP7-NH2 could inactivate viruses of multiple types and whether it could stimulate cell-mediated antiviral

activity. MP7-NH2 potently inactivated a range of enveloped viruses. Melittin and phospholipase A2 (PLA2) are the most abundant components of bee venom. These showed antioxidant, antimicrobial, neuroprotective or antitumor effects. Bee venom toxins show broad spectrum antiviral activity (table 1) (fig. 2) [123].

Scorpion-venom-peptide-derived mucroporin-M1 is microbicidal to HIV-1, it shows mild activity to three RNA viruses are measles viruses, SARS-CoV, and H5N1 to HIV-1. More specifically, Kn2-7 scorpion venom peptide derivative shows most potent anti-HIV-1 activity. Kn2-7 inhibit HIV-1 by direct interaction with viral particle and may become a promising candidate compound for further development of a microbicide against HIV-1. Besides this, some body fluids of invertebrate organisms also exhibit antiviral activity (table 1) (fig. 2) [124].

Tick defenses are antimicrobial peptides that play a major role in the innate immunity of ticks by providing a direct antimicrobial defense against viruses. Cationic peptides showed anti-infection and anti-tumoral activity. [Tyr5, 12, Lys7]-Polyphemus in II) has been shown to have strong anti-human immunodeficiency virus (HIV) activity. T22 inhibits the T cell line-tropic (T-tropic) HIV-1 infection through its specific binding to a chemokine receptor CXCR4, which serves as a co-receptor for the entry of T-tropic HIV-1 strains (table 1) (fig. 2) [125].

Mode of action

Animal toxins bind ligand-gated ion channels, including acid-sensing ion channel (ASIC) toxins. These toxins break glycerophospholipids, and make pores in cell membrane and disturb most of the cellular functions, such as membrane permeability, metabolism enzyme activity and cell signaling. These toxins mainly act on voltage-gated sodium and potassium channel toxins. Voltage-gated ion channels activate non-selective pores within membranes, by which the ions can pass using the electrochemical gradient across the membrane itself. When this mechanism is altered, the transmission of signals through the neurons and muscles is critically disturbed and imposes disorders including paralysis. These toxins bind at three sites in the sodium channel, and regulate their functioning. By controlling the opening and closing of the sodium channel, the toxins control the electrical signals that encode and propagate vital information across long distances. The activity of the sodium channel toxins shows these toxins act as pain blockers. Pharmacological applications and produce insecticides. Animal venom toxins show target specificity to various receptors present on cell membranes; these also bind and inhibit various ion channels. No doubt, toxin peptides from various animal groups could become the source of anticancer drugs and best therapeutic candidates for the treatment of microbial diseases [126].

CONCLUSION

Animal venoms are large living depositories of diverse peptides and proteins which are used in self-defense and to immobilize the prey by them. These are low molecular weight toxin peptides interact to voltage-gated sodium and potassium channels. These toxins fire membranes and form and accelerate active passage of ions which pass using the electrochemical gradient across the membrane itself. These toxins show diverse biological activity such and cytolytic, hemolytic, proteolytic, allergic, inflammatory, histamine-releasing activities, fibrinolytic and Kunitz-type protease inhibitor and pancreatic α-amylase inhibitor activity. These show diverse therapeutic activity such as anti-pathogenic effects against microbes such as viruses, bacteria, protozoan and fungal species. These show anti-helminthic, analgesic, anti-diabetic and immune-modulating activity of great of pharmacological and biotechnological interest. These pore-forming toxins show action much similar to actinoporins and cause cytolysis of human myelogenous leukemia and cancer cell lines, anti-angiogenesis and anticancer activity. These could be used for generation of new, highly effective drug molecules for the treatment of various human diseases. These toxins could be used as a natural source for development of alternative medicine. Animal venoms are an invaluable and almost inexhaustible source of bioactive molecules, some of which have found use as pharmacological tools, human therapeutics, and bioinsecticides.

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CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Babenko VV, Mikov AN, Manuvera VA, Anikanov NA, Kovalchuk SI, Andreev YA. Identification of unusual peptides with new Cys frameworks in the venom of the cold-water sea anemone *Cnidopus japonicus*. Sci Rep. 2017;7(1):14534. doi: 10.1038/s41598-017-14961-1, PMID 29109403.
2. Mariottini GL, Pane L. Cytotoxic and cytolytic cnidarian venoms. A review on health implications and possible therapeutic applications. Toxins (Basel). 2013;6(1):108-51. doi: 10.3390/toxins6010108, PMID 24379089.
3. Mariottini GL, Pane L. Mediterranean jellyfish venoms: a review on Scyphomedusae. Mar Drugs. 2010;8(4):1122-52. doi: 10.3390/md8041122, PMID 20479971.
4. Lazcano Perez F, Zavala Moreno A, Rufino Gonzalez Y, Ponce Macotela M, Garcia Arredondo A, Cuevas Cruz M. Hemolytic, anticancer and antigiardial activity of *Palythoa caribaeorum* venom. J Venom Anim Toxins Incl Trop Dis. 2018;24:12. doi: 10.1186/s40409-018-0149-8, PMID 29692802.
5. Ben Ari H, Paz M, Sher D. The chemical armament of reef-building corals: inter- and intra-specific variation and the identification of an unusual actinoporin in *stylophora pistilata*. Sci Rep. 2018;8(1):251. doi: 10.1038/s41598-017-18355-1, PMID 29321526.
6. Leychenko E, Isaeva M, Tkacheva E, Zelepuga E, Kvetkina A, Guzev K. Multigene family of pore-forming toxins from sea anemone *Heteractis crispa*. Mar Drugs. 2018;16(6):183. doi: 10.3390/md16060183, PMID 29794988.
7. Tejuca M, Anderluh G, Macek P, Marcet R, Torres D, Sarracent J. Antiparasite activity of sea-anemone cytolysins on *Giardia duodenalis* and specific targeting with anti-Giardia antibodies. Int J Parasitol. 1999;29(3):489-98. doi: 10.1016/s0020-7519(98)00220-3, PMID 10333333.
8. Sintsova O, Gladkikh I, Kalinovskii A, Zelepuga E, Monastyrnaya M, Kim N. Magnificamide, a βdefensin-like peptide from the mucus of the sea anemone *heteractis magnifica*, is a strong inhibitor of mammalian α-amylases. Mar Drugs. 2019;17(10):542. doi: 10.3390/md17100542.
9. Ceolin Mariano DO, de Oliveira UC, Zaharenko AJ, Pimenta DC, Radis Baptista G, Prieto-da-Silva ARB. Bottom-up proteomic analysis of polypeptide venom components of the giant ant *dinoponera quadriceps*. Toxins (Basel). 2019;11(8):448. doi: 10.3390/toxins11080448, PMID 31362422.
10. Osmakov DI, Kozlov SA, Andreev YA, Koshelev SG, Sanamyan NP, Sanamyan KE. Sea anemone peptide with uncommon β-hairpin structure inhibits acid-sensing ion channel 3 (ASIC3) and reveals analgesic activity. J Biol Chem. 2013;288(32):23116-27. doi: 10.1074/jbc.M113.485516, PMID 23801332.
11. Andreev YA, Osmakov DI, Koshelev SG, Maleeva EE, Logashina YA, Palikov VA. Analgesic activity of acid-sensing. Ion channels 3 (ASIC3) inhibitors: Sea anemones peptides Ugr9-1 and APETx2 versus low molecular weight compounds. Mar Drugs. 2012;16:500.
12. Babenko VV, Mikov AN, Manuvera VA, Anikanov NA, Kovalchuk SI, Andreev YA. Identification of unusual peptides with new Cys frameworks in the venom of the cold-water sea anemone *cnidopus japonicus*. Sci Rep. 2017;7(1):14534. doi: 10.1038/s41598-017-14961-1, PMID 29109403.
13. Gladkikh I, Monastyrnaya M, Zelepuga E, Sintsova O, Tabakmakher V, Gnedenko O. New kunitz-type HCRG polypeptides from the sea anemone *heteractis crispa*. Mar Drugs. 2015;13(10):6038-63. doi: 10.3390/md13106038, PMID 26404319.

14. Gladkikh I, Peigneur S, Sintsova O, Lopes Pinheiro Junior E, Klimovich A, Menshov A. Kunitz-type peptides from the sea anemone *Heteractis crispa* demonstrate potassium channel blocking and anti-inflammatory activities. Biomedicines. 2020;8(11):473. doi: 10.3390/biomedicines8110473, PMID 33158163.
15. Sintsova O, Gladkikh I, Monastyrnaya M, Tabakmakher V, Yurchenko E, Menchinskaya E. Sea anemone kunitz-type peptides demonstrate neuroprotective activity in the 6-hydroxydopamine induced neurotoxicity model. Biomedicines. 2021;9(3):283. doi: 10.3390/biomedicines9030283, PMID 33802055.
16. D'Ambra I, Lauritano C. A review of toxins from Cnidaria. Mar Drugs. 2020;18(10):507. doi: 10.3390/md18100507, PMID 33036158.
17. Kalina RS, Peigneur S, Zelepuga EA, Dmitrenok PS, Kvetkina AN, Kim NY. New insights into the type II toxins from the sea anemone *Heteractis crispa*. Toxins. 2020;12(1):44. doi: 10.3390/toxins12010044, PMID 31936885.
18. Monastyrnaya M, Peigneur S, Zelepuga E, Sintsova O, Gladkikh I, Leychenko E. Kunitz-type peptide HCRG21 from the sea anemone *Heteractis crispa* is a full antagonist of the TRPV1 receptor. Mar Drugs. 2016;14(12):229. doi: 10.3390/md14120229, PMID 27983679.
19. Gladkikh I, Monastyrnaya M, Leychenko E, Zelepuga E, Chausova V, Isaeva M. Atypical reactive center kunitz-type inhibitor from the sea anemone *Heteractis crispa*. Mar Drugs. 2012;10(7):1545-65. doi: 10.3390/md10071545, PMID 22851925.
20. Tauil CB, VON Glehn F, Nonato Rodrigues R, Gomes JRAA, Brandao CO, Santos LMBD. From charcot's descriptions to the current understanding of neuropsychiatric symptoms in multiple sclerosis. Arq Neuropsiquiatr. 2019;77(7):521-4. doi: 10.1590/0004-282X20190049, PMID 31365644.
21. Andreev YA, Kozlov SA, Koshelev SG, Ivanova EA, Monastyrnaya MM, Kozlovskaya EP. Analgesic compound from sea anemone *Heteractis crispa* is the first polypeptide inhibitor of vanilloid receptor 1 (TRPV1). J Biol Chem. 2008;283(35):23914-21. doi: 10.1074/jbc.M800776200, PMID 18579526.
22. Dominguez Perez D, Campos A, Alexei Rodriguez A, Turkina MV, Ribeiro T, Osorio H. Proteomic analyses of the unexplored sea anemone *Bunodactis verrucosa*. Mar Drugs. 2018;16(2):42. doi: 10.3390/md16020042, PMID 29364843.
23. Chi V, Pennington MW, Norton RS, Tarcha EJ, Londono LM, Sims Fahey B. Development of a sea anemone toxin as an immunomodulator for therapy of autoimmune diseases. Toxicon. 2012;59(4):529-46. doi: 10.1016/j.toxicon.2011.07.016, PMID 21867724.
24. Li R, Yu H, Li T, Li P. Comprehensive proteome reveals the key lethal toxins in the venom of jellyfish *Nemopile manomurai*. J Proteome Res. 2020;19(6):2491-500. doi: 10.1021/acs.jproteome.0c00277, PMID 32374608.
25. Ovchinnikova TV, Balandin SV, Aleshina GM, Tagaev AA, Leonova YF, Krasnodembsky ED. Aurelin, a novel antimicrobial peptide from jellyfish *Aurelia aurita* with structural features of defensins and channel-blocking toxins. Biochem Biophys Res Commun. 2006;348(2):514-23. doi: 10.1016/j.bbrc.2006.07.078, PMID 16890198.
26. Li R, Yu H, Xue W, Yue Y, Liu S, Xing R. Jellyfish venomics and venom gland transcriptomics analysis of *Stomolo phusmeleagristo* reveal the toxins associated with sting. J Proteomics. 2014;106:17-29. doi: 10.1016/j.jprot.2014.04.011, PMID 24747124.
27. Li A, Yu H, Li R, Liu S, Xing R, Li P. Inhibitory effect of metalloproteinase inhibitors on skin cell inflammation induced by jellyfish *nemopile manomurai* nematocyst venom. Toxins (Basel). 2019;11(3):156. doi: 10.3390/toxins11030156, PMID 30857352.
28. Huang C, Morlighem JR, Zhou H, Lima EP, Gomes PB, Cai J. The transcriptome of the zoanthid *protopalythoa variabilis* (Cnidaria, Anthozoa) predicts a basal repertoire of toxin-like and venom-auxiliary polypeptides. Genome Biol Evol. 2016;8(9):3045-64. doi: 10.1093/gbe/evw204, PMID 27566758.
29. Dominguez Perez D, Campos A, Alexei Rodriguez A, Turkina MV, Ribeiro T, Osorio H. Proteomic analyses of the unexplored sea anemone *Bunodactis verrucosa*. Mar Drugs. 2018;16(2):42. doi: 10.3390/md16020042, PMID 29364843.
30. Ramirez Carreto S, Vera Estrella R, Portillo Bobadilla T, Licea Navarro A, Bernaldez Sarabia J, Rudino Pinera E. Transcriptomic and proteomic analysis of the tentacles and mucus of *Anthopleuradowii verrill*, 1869. Mar Drugs. 2019;17(8):436. doi: 10.3390/md17080436, PMID 31349621.
31. Orts B DJ, Peigneur S, Silva Gonçalves LC, Arcisio Miranda M, P W Bicudo JE. AbeTx1 Is a novel sea anemone toxin with a dual mechanism of action on shaker-type K^+ channels activation. Mar Drugs. 2018;16:360.
32. Wanke E, Zaharenko AJ, Redaelli E, Schiavon E. Actions of sea anemone type 1 neurotoxins on voltage-gated sodium channel isoforms. Toxicon. 2009;54(8):1102-11. doi: 10.1016/j.toxicon.2009.04.018, PMID 19393679.
33. Honma T, Minagawa S, Nagai H, Ishida M, Nagashima Y, Shiomi K. Novel peptide toxins from acrorhagi, aggressive organs of the sea anemone *Actinia equina*. Toxicon. 2005;46(7):768-74. doi: 10.1016/j.toxicon.2005.08.003, PMID 16183092.
34. Kalina RS, Koshelev SG, Zelepuga EA, Kim NY, Kozlov SA, Kozlovskaya EP. APETx-like peptides from the sea anemone *Heteractis crispa*, diverse in their effect on ASIC1a and ASIC3 ion channels. Toxins (Basel). 2020;12(4):266. doi: 10.3390/toxins12040266, PMID 32326130.
35. Kim CH, Lee YJ, Go HJ, Oh HY, Lee TK, Park JB. Defensin-neurotoxin dyad in a basally branching metazoan sea anemone. FEBS Journal. 2017;284(19):3320-38. doi: 10.1111/febs.14194, PMID 28796463.
36. Honma T, Minagawa S, Nagai H, Ishida M, Nagashima Y, Shiomi K. Novel peptide toxins from acrorhagi, aggressive organs of the sea anemone *Actinia equina*. Toxicon. 2005;46(7):768-74. doi: 10.1016/j.toxicon.2005.08.003, PMID 16183092.
37. Dominguez Perez D, Campos A, Alexei Rodriguez A, Turkina MV, Ribeiro T, Osorio H. Proteomic analyses of the unexplored sea anemone *Bunodactis verrucosa*. Mar Drugs. 2018;16(2):42. doi: 10.3390/md16020042, PMID 29364843.
38. Prentis PJ, Pavasovic A, Norton RS. Sea anemones: quiet achievers in the field of peptide toxins. Toxins (Basel). 2018;10(1):36. doi: 10.3390/toxins10010036, PMID 29316700.
39. James FK Jr, Pence HL, Driggers DP, Jacobs RL, Horton DE. Imported fire ant hypersensitivity. Studies of human reactions to fire ant venom. J Allergy Clin Immunol. 1976;58:110-20. doi: 10.1016/0091-6749(76)90112-3, PMID 947974.
40. Kim SC, Hong CS. A case of anaphylaxis by ant (Ectomomyrmex spp.) venom and measurements of specific IgE and IgG subclasses. Yonsei Med J. 1992;33(3):281-7. doi: 10.3349/ymj.1992.33.3.281, PMID 1292253.
41. Stafford CT. Hypersensitivity to fire ant venom. Ann Allergy Asthma Immunol. 1996;77(2):9587-96. doi: 10.1016/S1081-1206(10)63493-X, PMID 8760773.
42. Sousa PL, Quinet YP, Cavalcante Brizeno LA, Sampaio TL, Torres AF, Martins AM, Assreuy AM. The acute inflammatory response induced in mice by the venom of the giant ant *Dinoponera quadriceps* involves macrophage and interleukin-1β. Toxicon. 2016;117:22-9. doi: 10.1016/j.toxicon.2016.03.009, PMID 27018043.
43. Song Y, Kumar V, Wei HX, Qiu J, Stanley P. Lunatic, manic, and radical fringe each promote T and B cell development. J Immunol. 2016;196(1):232-43. doi: 10.4049/jimmunol.1402421, PMID 26608918.
44. Tani N, Kazuma K, Ohtsuka Y, Shigeri Y, Masuko K, Konno K, Inagaki H. Mass spectrometry analysis and biological characterization of the predatory ant *odontomachus monticola* venom and venom sac components. Toxins (Basel). 2019;11(1):50. doi: 10.3390/toxins11010050, PMID 30658410.
45. Touchard A, Aili SR, Fox EG, Escoubas P, Orivel J, Nicholson GM, Dejean A. The biochemical toxin arsenal from ant venoms. Toxins (Basel). 2016;8(1):30. doi: 10.3390/toxins8010030, PMID 26805882.
46. Krayem N, Abdelkefi Koubaa Z, Marrakchi N, Luis J, Gargouri Y. Anti-angiogenic effect of phospholipases A_2 from scorpio

maurus venom glands on Human umbilical vein Endothelial cells. Toxicon. 2018;145:6-14. doi: 10.1016/j.toxicon.2018.02.042, PMID 29486161.
47. Kvetkina A, Leychenko E, Chausova V, Zelepuga E, Chernysheva N, Guzev K. A newmultigene HCIQ subfamily from the sea anemone *heterotactic crispa* encodes kunitz-peptides exhibiting neuroprotective activity against 6-hydroxydopamine. Sci Rep. 2020;10(1):4205. doi: 10.1038/s41598-020-61034-x, PMID 32144281.
48. Lee H, Bae SK, Kim M, Pyo MJ, Kim M, Yang S. Anticancer effect of *nemopile manomurai* jellyfish venom on Hep G2 cells and a tumor xenograft animal model. Evid Based Complement Alternat Med. 2017:2752716. doi: 10.1155/2017/2752716, PMID 28785288.
49. Babenko VV, Mikov AN, Manuvera VA, Anikanov NA, Kovalchuk SI, Andreev YA. Identification of unusual peptides with new Cys frameworks in the venom of the cold-water sea anemone *Cnidopus japonicus*. Sci Rep. 2017;7(1):14534. doi: 10.1038/s41598-017-14961-1, PMID 29109403.
50. Mariottini GL, Pane L. Cytotoxic and cytolytic cnidarian venoms. A review on health implications and possible therapeutic applications. Toxins (Basel). 2013;6(1):108-51. doi: 10.3390/toxins6010108, PMID 24379089.
51. Mariottini GL, Pane L. Mediterranean jellyfish venoms: a review on scyphomedusae. Mar Drugs. 2010;8(4):1122-52. doi: 10.3390/md8041122, PMID 20479971.
52. Lazcano Perez F, Zavala Moreno A, Rufino Gonzalez Y, Ponce Macotela M, Garcia Arredondo A, Cuevas Cruz M. Hemolytic, anticancer and antigiardial activity of *palythoa caribaeorum* venom. J Venom Anim Toxins Incl Trop Dis. 2018;24:12. doi: 10.1186/s40409-018-0149-8, PMID 29692802.
53. Alvarez C, Ros U, Valle A, Pedrera L, Soto C, Hervis YP. Biophysical and biochemical strategies to understand membrane binding and pore formation by sticholysins, pore-forming proteins from a sea anemone. Biophys Rev. 2017;9(5):529-44. doi: 10.1007/s12551-017-0316-0, PMID 28853034.
54. Merrifield RB, Juvvadi P, Andreu D, Ubach J, Boman A, Boman HG. Retro and retroenantio analogs of cecropin-melittin hybrids. Proc Natl Acad Sci USA. 1995;92(8):3449-53. doi: 10.1073/pnas.92.8.3449, PMID 7724582.
55. Anju G, Reetu G, Sudarshan K. Hanbook of research on diverse applications of nanotechnology in biomedicine, chemistry, and engineering. Soni Hershey, PA: Shivani; Hershey PA USA; 2015.
56. Stockwell VO, Duffy B. Use of antibiotics in plant agriculture. Rev Sci Tech. 2012;31(1):199-210. doi: 10.20506/rst.31.1.2104, PMID 22849276.
57. Badosa E, Ferre R, Planas M, Feliu L, Besaluu E, Cabrefiga J. A library of linear undecapeptides with bactericidal activity against phyto-pathogenic bacteria. Peptides. 2007;28(12):2276-85. doi: 10.1016/j.peptides.2007.09.010, PMID 17980935.
58. Rubner MF, Yang SY, Qiu Y, Lynn C, Lally JM. Method for making medical devices having antimicrobial coatings thereon. US20140112994. Toxins 2014;7:1126-50.
59. Baghian A, Jaynes J, Enright F, Kousoulas KG. An amphipathic alpha-helical synthetic peptide analogue of melittin inhibits herpes simplex virus-1 (HSV-1)-induced cell fusion and virus spread. Peptides. 1997;18(2):177-83. doi: 10.1016/s0196-9781(96)00290-2, PMID 9149288.
60. Wachinger M, Saermark T, Erfle V. Influence of amphipathic peptides on the HIV-1 production in persistently infected T lymphoma cells. FEBS Lett. 1992;309(3):235-41. doi: 10.1016/0014-5793(92)80780-k, PMID 1516693.
61. Ayed Y, Sghaier RM, Laouini D, Bacha H. Evaluation of anti-proliferative and anti-inflammatory activities of *Pelagia noctiluca* venom in lipopolysaccharide/interferon-γ stimulated RAW264.7 macrophages. Biomed Pharmacother. 2016;84:1986-91. doi: 10.1016/j.biopha.2016.11.010, PMID 27876211.
62. Loret EP, Luis J, Nuccio C, Villard C, Mansuelle P, Lebrun R. A low molecular weight protein from the sea anemone *anemonia viridis* with anti-angiogenic activity. Mar Drugs. 2018;16(4):134. doi: 10.3390/md16040134.
63. Kvetkina A, Leychenko E, Chausova V, Zelepuga E, Chernysheva N, Guzev K. A new multigene HCIQ subfamily from the sea anemone *heteractis crispa* encodes Kunitz-peptides exhibiting neuroprotective activity against 6-hydroxydopamine. Sci Rep. 2020;10(1):4205. doi: 10.1038/s41598-020-61034-x, PMID 32144281.
64. Daly JW, Noimai N, Kongkathip B, Kongkathip N, Wilham JM, Garraffo HM. Biologically active substances from amphibians: preliminary studies on anurans from twenty-one genera of Thailand. Toxicon. 2004;44(8):805-15. doi: 10.1016/j.toxicon.2004.08.016, PMID 15530960.
65. Kauskot A, Cominetti MR, Ramos OH, Bechyne I, Renard JM, Hoylaerts MF. Hemostatic effects of recombinant DisBa-01, a disintegrin from Bothrops alternatus. Front Biosci. 2008;13:6604-16. doi: 10.2741/3176, PMID 18508682.
66. Morjen M, Othman H, Abdelkafi-Koubaa Z, Messadi E, Jebali J, El Ayeb M. Targeting α1 inserted domain (I) of α1β1 integrin by Lebetin 2 from M. lebetina transmediterranea venom decreased tumorigenesis and angiogenesis. Int J Biol Macromol. 2018;117:790-9. doi: 10.1016/j.ijbiomac.2018.05.230, PMID 29870815.
67. Chalier F, Mugnier L, Tarbe M, Aboudou S, Villard C, Kovacic H, Gigmes D, Mansuelle P, de Pomyers H, Luis J, Mabrouk K. Isolation of an anti-tumour disintegrin: dabmaurin-1, a peptide lebein-1-Like, from *daboia mauritanica* venom. Toxins (Basel). 2020;12(2):102. doi: 10.3390/toxins12020102, PMID 32033352.
68. Roy A, Bharadvaja N. Venom derived bioactive compounds as potential anticancer agents: a review. Int J Pept Res Ther. 2021;27(1):129-47. doi: 10.1007/s10989-020-10073-z.
69. Jameel Al-Tamimi, Abdelhabib Semlali, Iftekhar Hassan, Hossam Ebaid, Ibrahim M Alhazza, Syed H Mehdi, Mohammed Al-Khalifa, Mohammad S. Alanazi cancer biotherapy and radiopharmaceuticals; 2018. p. 65-73.
70. Ebaid H, Al-Tamimi J, Hassan I, Alhazza I, Al-Khalifa M. Antioxidant bioactivity of samsum ant (*Pachycondyla sennaarensis*) venom protects against CCL_4-induced nephrotoxicity in mice. Oxid Med Cell Longev. 2014;2014:763061. doi: 10.1155/2014/763061, PMID 24803985.
71. Monincova L, Veverka V, Slaninova J, Budesinsky M, Fucik V, Bednarova L. "Structure-activity study of macropin, a novel antimicrobial peptide from the venom of solitary bee *Macropis fulvipes* (Hymenoptera: Melittidae). J Pept Sci. 2014;20(6):2014375-84375-84. doi: 10.1002/psc.2625, PMID 24616110.
72. Kim BY, Lee KS, Zou FM, Wan H, Choi YS, Yoon HJ. Antimicrobial activity of a honeybee (*Apis cerana*) venom Kazal-type serine protease inhibitor. Toxicon. 2013;76:110-7. doi: 10.1016/j.toxicon.2013.09.017, PMID 24076031.
73. Cujova S, Slaninova J, Monincova L, Fucik V, Bednarova L, Stokrova J. Panurgines, novel antimicrobial peptides from the venom of communal bee *panurgus calcaratus* (Hymenoptera: Andrenidae). Amino Acids. 2013;45(1):143-57. doi: 10.1007/s00726-013-1482-4, PMID 23483218.
74. Camara GA. A multi-omics approach unravels new toxins with possible in silico antimicrobial, antiviral, and antitumoral activities in the venom of *acanthos curriarondoniae*. Front Pharmacol 2020;11:1075.
75. Silva JC, Neto LM, Neves RC, Gonçalves JC, Trentini MM, Mucury Filho R. Evaluation of the antimicrobial activity of the mastoparan Polybia-MPII isolated from the venom of the social wasp *Pseudo polybiavespicepstestacea* (Vespidae, Hymenoptera). Int J Antimicrob Agents. 2017;49(2):167-75. doi: 10.1016/j.ijantimicag.2016.11.013, PMID 28108242.
76. Das Neves RC, Trentini MM, de Castro e Silva J, Simon KS, Bocca AL, Silva LP. Antimycobacterial activity of a new peptide polydim-I Iisolated from neotropical social wasp *polybiadimorpha.* PLoS One. 2016;11(3):e0149729. doi: 10.1371/journal.pone.0149729, PMID 26930596.
77. Ha YJ, Kim SW, Lee CW, Bae CH, Yeo JH, Kim IS. Anti-salmonella activity modulation of mastoparan V1-A wasp venom toxin-using protease inhibitors and its efficient production via an *Escherichia coli* secretion system. Toxins (Basel). 2017;9(10):321. doi: 10.3390/toxins9100321, PMID 29027924.
78. Rangel M, Castro FFDS, Mota Lima LD, Clissa PB, Martins DB, Cabrera MPDS. Polydim-I antimicrobial activity against MDR

bacteria and its model membrane interaction. PLOS ONE. 2017;12(6):e0178785. doi: 10.1371/journal.pone.0178785, PMID 28570651.
79. Dos Santos Cabrera MP, Rangel M, Ruggiero Neto J, Konno K. Chemical and biological characteristics of antimicrobial α-helical peptides found in solitary wasp venoms and their interactions with model membranes. Toxins (Basel). 2019;11(10):112019:559. doi: 10.3390/toxins11100559, PMID 31554187.
80. Kim BY, Lee KS, Zou FM, Wan H, Choi YS, Yoon HJ. Antimicrobial activity of a honeybee (*Apis cerana*) venom Kazal-type serine protease inhibitor. Toxicon. 2013;76:110-7. doi: 10.1016/j.toxicon.2013.09.017, PMID 24076031.
81. Cesa Luna C, Munoz Rojas J, Saab Rincon G, Baez A, Morales Garcia YE, Juarez Gonzalez VR. Structural characterization of scorpion peptides and their bactericidal activity against clinical isolates of multidrug-resistant bacteria. PLOS ONE. 2019;14(11):e0222438. doi: 10.1371/journal.pone.0222438, PMID 31710627.
82. Zhang S, Gao B, Wang X, Zhu S. Loop replacement enhances the ancestral antibacterial function of a bifunctional scorpion. Toxins (Basel). 2018;4201810(6):227. doi: 10.3390/toxins10060227, PMID 29867003.
83. Dubovskii PV, Vassilevski AA, Kozlov SA, Feofanov AV, Grishin EV, Efremov RG. Latarcins: versatile spider venom peptides. Cell Mol Life Sci. 2015;72(23):722015:4501-224501-22. doi: 10.1007/s00018-015-2016-x, PMID 26286896.
84. Monincova L, Budesinsky M, Cujova S, Cerovsky V, Veverka V. Structural basis for antimicrobial activity of lasiocepsin. ChemBioChem. 2014;15(2):301-8. doi: 10.1002/cbic.201300509, PMID 24339323.
85. Ha YJ, Kim SW, Lee CW, Bae CH, Yeo JH, Kim IS. Anti-salmonella activity modulation of mastoparan V1-A wasp venom toxin-using protease inhibitors, and its efficient production via an *Escherichia coli* secretion system. Toxins (Basel). 2017;92017(10):321. doi: 10.3390/toxins9100321, PMID 29027924.
86. Rangel M. Polydim-I antimicrobial activity against MDR bacteria and its model membrane interaction. PLOS ONE. 2017;12(6):e0178785. doi: 10.1371/journal.pone.0178785, PMID 28570651.
87. Konno K, Kazuma K, Rangel M, Stolarz-de-Oliveira J, Fontana R, Kawano M. New mastoparan peptides in the venom of the solitary eumenine wasp *Eumenes micado*. Toxins (Basel). 2019;11(3):112019:155. doi: 10.3390/toxins11030155, PMID 30857348.
88. Lin Z, Wang RJ, Cheng Y, Du J, Volovych O, Han LB, Li JC. Insights into the venom protein components of Microplitis mediator, an endoparasitoid wasp. Insect Biochem Mol Biol. 2019;105:33-42. doi: 10.1016/j.ibmb.2018.12.013, PMID 30602123.
89. Vanha Aho LM, Anderl I, Vesala L, Hultmark D, Valanne S, Ramet M. Edin expression in the fat body is required in the defense against parasitic wasps in *Drosophila melanogaster*. PLOS Pathog. 2015;11(5):e1004895. doi: 10.1371/journal.ppat.1004895, PMID 25965263.
90. Dodou Lima HV, Sidrim de Paula Cavalcante C, Radis Baptista G. Antimicrobial activity of synthetic Dq-3162, a 28-residue ponericin G-like dinoponeratoxin from the giant ant *dinoponera quadriceps* venom, against carbapenem-resistant bacteria. Toxicon. 2020;187:19-28. doi: 10.1016/j.toxicon.2020.08.015, PMID 32861765.
91. Guzman J, Tene N, Touchard A, Castillo D, Belkhelfa H, Haddioui Hbabi L, Treilhou M, Sauvain M. Anti-helicobacter pylori properties of the ant-venom peptide bicarinalin. Toxins (Basel). 2017;10(1):21. doi: 10.3390/toxins10010021, PMID 29286296.
92. Tene N, Bonnafe E, Berger F, Rifflet A, Guilhaudis L, Segalas Milazzo I, Pipy B, Coste A, Leprince J, Treilhou M. Biochemical and biophysical combined study of bicarinalin, an ant venom antimicrobial peptide. Peptides. 2016;79:103-13. doi: 10.1016/j.peptides.2016.04.001, PMID 27058430.
93. Sabia Junior EF, Menezes LFS, de Araujo IFS, Schwartz EF. Natural occurrence in venomous arthropods of antimicrobial peptides active against protozoan parasites. Toxins (Basel). 2019;11(10):563. doi: 10.3390/toxins11100563, PMID 31557900.
94. Dominguez Perez D, Campos A, Alexei Rodriguez A, Turkina MV, Ribeiro T, Osorio H, Vasconcelos V, Antunes A. Proteomic analyses of the unexplored sea anemone *Bunodactis verrucosa*. Mar Drugs. 2018;16(2):42. doi: 10.3390/md16020042, PMID 29364843.
95. Mason B, Cooke I, Moya A, Augustin R, Lin MF, Satoh N, Bosch TCG, Bourne DG, Hayward DC, Andrade N, Foret S, Ying H, Ball EE, Miller DJ. AmAMP1 from *Acropora millepora* and damicornin define a family of coral-specific antimicrobial peptides related to the Shk toxins of sea anemones. Dev Comp Immunol. 2021;114:103866. doi: 10.1016/j.dci.2020.103866, PMID 32937163.
96. Zhao L, Huang Y, Dong Y, Han X, Wang S, Liang X. Aptamers and aptasensors for highly specific recognition and sensitive detection of marine biotoxins: recent advances and perspectives. Toxins (Basel). 2018;10(11):427. doi: 10.3390/toxins10110427, PMID 30366456.
97. Dubovskii PV, Vassilevski AA, Kozlov SA, Feofanov AV, Grishin EV, Efremov RG. Latarcins: versatile spider venom peptides. Cell Mol Life Sci. 2015;72(23):4501-22. doi: 10.1007/s00018-015-2016-x, PMID 26286896.
98. Silva JC, Neto LM, Neves RC, Gonçalves JC, Trentini MM, Mucury Filho R, Smidt KS. Evaluation of the antimicrobial activity of the mastoparan Polybia-MPII isolated from venom of the social wasp *Pseudopolybia vespiceps testacea* (Vespidae, Hymenoptera). Int J Antimicrob Agents. 2017;49(2):167-75. doi: 10.1016/j.ijantimicag.2016.11.013, PMID 28108242.
99. Jouvenaz DP, Blum MS, MacCONNELL JG. Antibacterial activity of venom alkaloids from the imported fire ant, *Solenopsis invicta* Buren. Antimicrob Agents Chemother. 1972;2(4):291-3. doi: 10.1128/AAC.2.4.291, PMID 4670503.
100. Wang K, Yan J, Chen R, Dang W, Zhang B, Zhang W, Song J, Wang R. Membrane-active action mode of polybia-CP, a novel antimicrobial peptide isolated from the venom of *Polybia paulista*. Antimicrob Agents Chemother. 2012;56(6):3318-23. doi: 10.1128/AAC.05995-11, PMID 22450985.
101. Hansen PR, Munk JK. Synthesis of antimicrobial peptoids. Methods Mol Biol. 2013;1047:151-9. doi: 10.1007/978-1-62703-544-6_11, PMID 23943485.
102. Willems J, Noppe W, Moerman L, van der Walt J, Verdonck F. Cationic peptides from scorpion venom can stimulate and inhibit polymorphonuclear granulocytes. Toxicon. 2002;40(12):1679-83. doi: 10.1016/s0041-0101(02)00183-6, PMID 12457879.
103. Dodou Lima HV, de Paula Cavalcante CS, Radis Baptista G. Corrigendum to "Antimicrobial activity of synthetic Dq-3162, a 28-residue ponericin G-like dinoponeratoxin from the giant ant *dinoponera quadriceps* venom, against carbapenem-resistant bacteria" [Toxicon 187 November 2020 19-28]. Toxicon. 2021;189:105-6. doi: 10.1016/j.toxicon.2020.11.004, PMID 33246629.
104. Rocha LQ, Orzaez M, Garcia Jareno AB, Nunes JVS, Duque BR, Sampaio TL, Alves RS, Lima DB, Martins AMC. *Dinoponera quadriceps* venom as a source of active agents against staphylococcus aureus. Toxicon. 2021;189:33-8. doi: 10.1016/j.toxicon.2020.11.003, PMID 33188823.
105. Tene N, Bonnafe E, Berger F, Rifflet A, Guilhaudis L, Segalas Milazzo I, Pipy B, Coste A, Leprince J, Treilhou M. Biochemical and biophysical combined study of bicarinalin, an ant venom antimicrobial peptide. Peptides. 2016;79:103-13. doi: 10.1016/j.peptides.2016.04.001, PMID 27058430.
106. Rifflet A, Gavalda S, Tene N, Orivel J, Leprince J, Guilhaudis L, Genin E, Vetillard A, Treilhou M. Identification and characterization of a novel antimicrobial peptide from the venom of the ant *Tetramorium bicarinatum*. Peptides. 2012;38(2):363-70. doi: 10.1016/j.peptides.2012.08.018, PMID 22960382.
107. Sabia Junior EF, Menezes LFS, de Araujo IFS, Schwartz EF. Natural occurrence in venomous arthropods of antimicrobial peptides active against protozoan parasites. Toxins (Basel). 2019;11(10):563. doi: 10.3390/toxins11100563, PMID 31557900.

108. Guo Z, Gu Y, Wang C, Zhang J, Shan S, Gu X, Wang K, Han Y, Ren T. Enforced expression of miR-125b attenuates LPS-induced acute lung injury. Immunol Lett. 2014 Nov;162:18-26. doi: 10.1016/j.imlet.2014.06.008, PMID 25004393.
109. Jindrichova B, Burketova L, Novotna Z. Novel properties of antimicrobial peptide anoplin. Biochem Biophys Res Commun. 2014;444(4):520-4. doi: 10.1016/j.bbrc.2014.01.097, PMID 24472551.
110. Singulani JL, Galeane MC, Ramos MD, Gomes PC, Dos Santos CT, de Souza BM, Palma MS, Fusco Almeida AM, Mendes Giannini MJS. Antifungal activity, toxicity, and membranolytic action of a mastoparan analog peptide. Front Cell Infect Microbiol. 2019 Dec 6;9:419. doi: 10.3389/fcimb.2019.00419, PMID 31867293.
111. Marcos CM, de Oliveira HC, Assato PA, de Andrade CR, Fusco-Almeida AM, Mendes Giannini MJS. *Paracoccidioides brasiliensis* 14-3-3 protein is important for virulence in a murine model. Med Mycol. 2019;57(7):900-4. doi: 10.1093/mmy/myy112, PMID 30476159.
112. Salas RL, Garcia JKDL, Miranda ACR, Rivera WL, Nellas RB, Sabido PMG. Effects of truncation of the peptide chain on the secondary structure and bioactivities of palmitoylated anoplin. Peptides. 2018;104:7-14. doi: 10.1016/j.peptides.2018.03.019, PMID 29614317.
113. Torres Rego M, Glaucia Silva F, Rocha Soares KS, de Souza LBFC, Damasceno IZ, Santos Silva ED, Lacerda AF, Chaves GM, Silva Junior AAD, Fernandes Pedrosa MF. Biodegradable cross-linked chitosan nanoparticles improve anti-Candida and anti-biofilm activity of TistH, a peptide identified in the venom gland of the *Tityus stigmurus* scorpion. Mater Sci Eng C Mater Biol Appl. 2019;103:109830. doi: 10.1016/j.msec.2019.109830, PMID 31349502.
114. Zeitler, Benjamin, Herrera Diaz A, Dangel A, Thellmann M, Meyer H, Sattler M. De-novo design of antimicrobial peptides for plant protection. PLOS ONE. 2013 Aug 12;8(8):e71687e71687. doi: 10.1371/journal.pone.0071687, PMID 23951222.
115. Ben-Ari H, Paz M, Sher D. The chemical armament of reef-building corals: inter- and intra-specific variation and the identification of an unusual actinoporin in *stylophora pistilata*. Sci Rep 2017;8:251.
116. Nicosia A, Maggio T, Mazzola S, Cuttitta A. Evidence of accelerated evolution and ectodermal-specific expression of presumptive BDS toxin cDNAs from *Anemonia viridis*. Mar Drugs. 2013;11(11):4213-31. doi: 10.3390/md11114213, PMID 24177670.
117. Gladkikh I, Peigneur S, Sintsova O, Lopes Pinheiro Junior E, Klimovich A, Menshov A. Kunitz type peptides from the sea anemone *heterotactic crispa* demonstrate potassium channel blocking and anti-inflammatory activities. Biomedicines. 2020;8(11):473. doi: 10.3390/biomedicines8110473, PMID 33158163.
118. Sintsova O, Gladkikh I, Monastyrnaya M, Tabakmakher V, Yurchenko E, Menchinskaya E. Sea anemone Kunitz type peptides demonstrate neuroprotective activity in the 6-hydroxydopamine induced neurotoxicity model. Biomedicines. 2021;9(3):283. doi: 10.3390/biomedicines9030283, PMID 33802055.
119. Uddin MB, Lee BH, Nikapitiya C, Kim JH, Kim TH, Lee HC, Kim CG, Lee JS, Kim CJ. Inhibitory effects of bee venom and its components against viruses *in vitro* and *in vivo*. J Microbiol. 2016;54(12):853-66. doi: 10.1007/s12275-016-6376-1, PMID 27888461.
120. Lee WR, Kim KH, An HJ, Kim JY, Chang YC, Chung H, Park YY, Lee ML, Park KK. The protective effects of melittin on *propionibacterium* acnes-induced inflammatory responses *in vitro* and *in vivo*. J Invest Dermatol. 2014;134(7):1922-30. doi: 10.1038/jid.2014.75, PMID 24496237.
121. Sarhan M, El-Bitar AMH, Hotta H. Potent virucidal activity of honeybee "*Apis mellifera*" venom against hepatitis C virus. Toxicon. 2020;188:55-64. doi: 10.1016/j.toxicon.2020.10.014, PMID 33068557.
122. Sample CJ, Hudak KE, Barefoot BE, Koci MD, Wanyonyi MS, Abraham S, Staats HF, Ramsburg EA. A mastoparan-derived peptide has broad-spectrum antiviral activity against enveloped viruses. Peptides. 2013;48:96-105. doi: 10.1016/j.peptides.2013.07.014, PMID 23891650.
123. Zhang J, Yu C, Zhang X, Chen H, Dong J, Lu W, Song Z, Zhou W. *Porphyromonas gingivalis* lipopolysaccharide induces cognitive dysfunction, mediated by neuronal inflammation via activation of the TLR4 signaling pathway in C57BL/6 mice. J Neuroinflammation. 2018;15(1):37. doi: 10.1186/s12974-017-1052-x, PMID 29426327.
124. Lu HY, Chen YH, Liu HJ. Baculovirus as a vaccine vector. Bioengineered. 2012;3(5):271-4. doi: 10.4161/bioe.20679, PMID 22705893.
125. Preet P. Peptides: a new therapeutic approach. Int J Curr Pharm Sci. 2018;10(2):29-34. doi: 10.22159/ijcpr.2018v10i2.25887.
126. Ahulwalia S, Shah N. Animal venom for treating breast cancer. International Journal of Pharmacy and Pharmaceutical Sciences. 2014;9:24-30.