Chapter 2

Toxins from Venomous Animals: Gene Cloning, Protein Expression and Biotechnological Applications

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Additional information is available at the end of the chapter

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1. Introduction

Venoms are the secretion of venomous animals, which are synthesized and stored in specific areas of their body i.e., venom glands. The animals use venoms for defense and/or to immobilize their prey. Most of the venoms are complex mixture of biologically active compounds of different chemical nature such as multidomain proteins, peptides, enzymes, nucleotides, lipids, biogenic amines and other unknown substances. Venomous animals as snakes, spiders, scorpions, caterpillars, bees, insects, wasps, centipedes, ants, toads and frogs have largely shown biotechnological or pharmacological applications. During long-term evolution, venom composition underwent continuous improvement and adjustment for efficient functioning in the killing or paralyzing of prey and/or as a defense against aggressors or predators. Different venom components act synergistically, thus providing efficiency of action of the components. Venom composition is highly species-specific and depends on many factors including age, sex, nutrition and different geographic regions. Toxins, occurring in venoms and poisons of venomous animals, are chemically pure toxic molecules with more or less specific actions on biological systems [1-3]. A large number of toxins have been isolated and characterized from snake venoms and snake venoms repertoire typically contain from 30 to over 100 protein toxins. Some of these molecules present enzymatic activities, whereas several others are non-enzymatic proteins and polypeptides. The most frequent enzymes in snake venoms are phospholipases A_2, serine proteinases, metalloproteinases, acetylcholinesterases, L-amino acid oxidases, nucleotidases and hyaluronidases. Higher catalytic efficiency, heat stability and resistance to proteolysis as well as abundance of snake venom enzymes provide them attractive models for biotechnologists, pharmacologists and biochemists [3-4]. Scorpion toxins are classified according to their structure, mode of action,

and binding site on different channels or channel subtypes. The venom is constituted by mucopolysaccharides, hyaluronidases, phospholipases, serotonins, histamines, enzyme inhibitors, antimicrobials and proteins namely neurotoxic peptides. Scorpion peptides presents specificity and high affinity and have been used as pharmacological tools to characterize various receptor proteins involved in normal ion channel functionating, as abnormal channel functionating in cases of diseases. The venoms can be characterized by identification of peptide toxins analysis of the structure of the toxins and also have proven to be among the most and selective antagonists available for voltage-gated channels permeable to K^+, Na^+, and Ca^{2+}. The neurotoxic peptides and small proteins lead to dysfunction and provoke pathophysiological actions, such as membrane destabilization, blocking of the central, and peripheral nervous systems or alteration of smooth or skeletal muscle activity [5-8]. Spider venoms are complex mixtures of biologically active compounds of different chemical nature, from salts to peptides and proteins. Specificity of action of some spider toxins is unique along with high toxicity for insects, they can be absolutely harmless for members of other taxons, and this could be essential for investigation of insecticides. Several spider toxins have been identified and characterized biochemically. These include mainly ribonucleotide phosphohydrolase, hyaluronidases, serine proteases, metalloproteases, insecticidal peptides and phospholipases D [9-10]. Venoms from toads and frogs have been extensively isolated and characterized showing molecules endowed with antimicrobial and/or cytotoxic activities [11]. Studies involving the molecular repertoire of the venom of bees and wasps have revealed the partial isolation, characterization and biological activity assays of histamines, dopamines, kinins, phospholipases and hyaluronidases. The venom of caterpillars has been partially characterized and contains mainly ester hydrolases, phospholipases and proteases [12]. The purpose of this chapter is to present the main toxins isolated and characterized from the venom of venomous animals, focusing on their biotechnological and pharmacological applications.

2. Biotechnological and pharmacological applications of snake venom toxins

While the initial interest in snake venom research was to understand how to combat effects of snakebites in humans and to elucidate toxins mechanisms, snake venoms have become a fertile area for the discovery of novel products with biotechnological and/or pharmacological applications [13-14]. Since then, many different products have been developed based on purified toxins from snake venoms, as well recent studies have been showing new potential molecules for a variety of applications [15].

2.1. Toxins acting on cardiovascular system

Increase in blood pressure is often a transient physiological response to stressful stimuli, which allows the body to react to dangers or to promptly increase activity. However, when the blood pressure is maintained at high levels for an extended period, its long term effects

are highly undesirable. Persistently high blood pressure could cause or accelerate multiple pathological conditions such as organ (heart and kidney) failure and thrombosis events (heart attack and stroke) [14]. So, it is important to lower the blood pressure of high-rick patients through use of specific anti-hypertensive agents, and in this scenario, snake venom toxins has been shown to be promising sources [14-15]. This is because it has long been noted that some snake venoms drastically lower the blood pressure in human victims and experimental animals [15]. The first successful example of developing a drug from an isolated toxin was the anti-hypertensive agent Capoten® (captopril), an angiotensin-converting enzyme (ACE) inhibitor modeled from a venom peptide isolated from *Bothrops jararaca* venom [16]. These bradykinin-potentiating peptides (BPPs) are venom components which inhibits the breakdown of the endogenous vasodilator bradykinin while also inhibiting the synthesis of the endogenous vasoconstrictor angiotensin II, leading to a reduction in blood pressure [15]. BPPs have also been identified in *Crotalus durissus terrificus* venom [17]. Snake venom represents one of the major sources of exogenous natriuretic peptides (NPs) [18]. The first venom NP was identified from *Dendroaspis angusticeps* snake venom and was named *Dendroaspis* natriuretic peptide (DNP) [19]. Other venom NPs were also reported in various snake species, such as *Micrurus corallinus* [20], *B. jararaca* [4], *Trimeresurus flavoviridis*, *Trimeresurus gramineus*, *Agkistrodon halys blomhoffii* [21], *Pseudocerastes persicus* [22], *Crotalus durissus cascavella* [23], *Bungarus flaviceps* [24], among others. L-type Ca^{2+}-channels blockers identified in snake venoms include calciseptine [25] and FS2 toxins [26] from *Dendroaspis polylepis polylepis*, C10S2C2 from *D. angusticeps* [27], S4C8 from *Dendroaspis jamesoni kaimosae* [28] and stejnihagin, a metalloproteinase from *Trimeresurus stejnegeri* [29].

2.2. Toxins acting on hemostasis

Desintegrins are a family of cysteine-rich low molecular weight proteins that inhibits various integrins and that usually contain the integrin-binding RGD motif, that binds the GPIIa/IIIb receptor in platelets, thus prevents the binding of fibrinogen to the receptor and consequently platelet aggregation [13]. Two drugs, tirofiban (Aggrastat®) and eptifibatide (Integrillin®) were designed based on snake venom disintegrins and are avaliable in the market as antiplatelet agents, approved for preventing and treating thrombotic complications in patients undergoing percutaneous coronay intervention and in patients with acute cornonary sydrome [30-31]. Tirofiban has a non-peptide structure mimicking the RDG motif of the disintegrin echistatin from *Echis carinatus* [30]. Eptifibatide is a cyclic peptide based on the KGD motif of barbourin from *Sisturus miliaris barbouri* snake [31]. Recently, leucurogin, a new recombinant disintegrin was cloned from *Bothrops leucurus*, being a potent agent upon platelet aggregation [32]. Thrombin-like enzymes (TLEs) are proteases reported from many different crotalid, viperid and colubrid snakes that share some functional similarity with thrombin [13]. TLEs are not inactivated by heparin-antithrombin III complex (the physiological inhibitor of thrombin), and, differently to thrombin, they are not able to activate FXIII (the enzyme that covalently cross-links fibrin monomer to form insoluble clots). These are interesting properties, because although being procoagulants *in vitro*, TLEs have the clinical results of being anti-coagulants, by the depletion of plasma level of fibrinogen, and the clots formed are easily soluble and removed from the body. At same time, thrombolysis is enhanced by

stimulation of endogenous plasminogen activators binding to the noncrosslinked fibrin [13]. Batroxobin (Defibrase®) was isolated and purified from *Bothrops atrox* venom [33] and ancrod (Viprinex®) from *Agkistrodon rhodostoma* [34]. Haemocoagulase® is a mixture of two proteinases isolated from *B. atrox* venom, acting on blood coagulation by two mechanisms: the first having a thrombin-like activity and the second having a thromboplastin-like activity, activating FX which in turn converts prothrombin into thrombin. It is indicated for the prevention and treatment of hemorrhages of a variety of origins [13]. Other toxins acting on hemostasis with potential biotechnological/pharmacological applications has been purified and characterized from several snake venoms, such as bhalternin from *Bothrops alternatus* [35], bleucMP from *B. leucurus* [36], VLH2 from *Vipera lebetina* [37], trimarin from *Trimeresurus malabaricus* [38], BE-I-PLA$_2$ from *Bothrops erythromelas* [39], among others.

2.3. Toxins with antibiotic activity

Antibiotics are a heterogeneous group of molecules produced by several organisms, including bacteria and fungi, presenting an antimicrobial profile, inducing the death of the agent or inhibiting microbial growth [40]. L-amino acid oxidases (LAAOs) are enantioselective flavoenzymes catalyzing the stereospecific oxidative deamination of a wide range of L-amino acids to form α-keto acids, ammonia and hydrogen peroxide (H_2O_2). Antimicrobial activities are reported to various LAAOs, such as TJ-LAO from *Trimeresurus jerdonii* [41], Balt-LAAO-I from *Bothrops alternatus* [42], TM-LAO *Trimeresurus mucrosquamatus* [43], BpirLAAO-I from *Bothrops pirajai* [44], casca LAO from *Crotalus durissus cascavella* [45], a LAAO from *Naja naja oxiana* [46], BmarLAAO from *Bothrops marajoensis* [47], among others. Recently, studies revealed that *B. jararaca* venom induced programmed cell death in epimastigotes of *Trypanossoma cruzi*, being this anti-*T. cruzi* activity associated with fractions of venoms with LAAO activity [48]. Secreted phospholipases A_2 (sPLA$_2$s) constitute a diverse group of enzymes that are widespread in nature, being particularly abundant in snake venoms. In addition to their catalytic activity, hydrolyzing the sn-2 ester bond of glycerophospholipids, sPLA$_2$s display a range of biological actions, which may be either dependent or independent of catalytic action [49]. Eight sPLA$_2$ myotoxins purified from crotalid snake venoms, including both Lys49 and Asp49-type isoforms, were all found to express bactericidal activity [50]. EcTx-I from *Echis carinatus* [51], PnPLA$_2$ from *Porthidium nasutum* [52] and BFPA [53] from *Bungarus fasciatus* also presented antimicrobial activity. Vgf-1, a small peptide from *Naja atra* venom had *in vitro* activity against clinically isolated multidrug-resistant strains of *Mycobacterium tuberculosis* [54]. Neuwiedase, a metalloproteinase from *Bothrops neuwiedi* snake venom, showed considerable effects of *Toxoplasma gondii* infection inhibition *in vitro* [55]. Recently, a study revealed that whole venom, crotoxin and sPLA$_2$s (PLA$_2$-CB and PLA$_2$-IC) isolated from *Crotalus durissus terrificus* venom showed antiviral activity against dengue and yellow fever viruses, which are two of the most important arboviruses in public health [56].

2.4. Toxins acting on inflammatory and nociceptive responses

Various snake venoms are rich in secretory phospholipases A_2 (sPLA$_2$), which are potent pro-inflammatory enzymes producing different families of inflammatory lipid mediators

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such as arachidonic acid derived eicosanoids, various lysophospholipids and platelet activating factors through cyclooxygenase and lipoxygenase pathways [57]. In a recent study, was described the first complete nucleotide sequence of a βPLI from venom glands of *Lachesis muta* by a transcriptomic analysis [58]. Recently, was purified from the venom of *Crotalus durissus terrificus* a hyaluronidase (named Hyal) that was able to provide a highly antiedematogenic acitivity [59]. Crotapotin, a subunit of crotoxin, from *C. d. terrificus*, has been reported to possess immunossupressive activity, associated to an increase in the production of prostaglandin E_2 by macrophages, consequently reducing the proliferative response of lymphocytes [60]. Various elapid and viperid venoms have been reported to induce antinociception through their neurotoxins and myotoxins [61]. *C. d. terrificus* venom induces neurological symptoms in their victims, but, contrary to most venoms from other species, it does not induce pain or severe tissue destruction at the site of inoculation, being usual the sensation of paresthesia in the affected area [62]. Based on this, several studies have been carried out with this venom, being reported in the literature several molecules with antinociceptive activity from *C. d. terrificus* venom, such as crotamine [63] and crotoxin [64]. Has been demonstrated that the anti-nociceptive effect of crotamine involve both central and peripheral mechanisms, being 30-fold higher than the produced by morphine [63]. Studies suggest that crotoxin has antinociceptive effect mediated by an action on the central nervous system, without involvement of muscarinic and opioid receptors [64]. Other antinociceptive peptides isolated from snake venoms are cobrotoxin, a neurotoxin isolated from *Naja atra* [65] and hannalgesin, a neurotoxin isolated from *Ophiophagus hannah* [66].

2.5. Toxins acting on immunological system

Venom-derived peptides are being evaluated as immunosuppressants for the treatment of autoimmune diseases and the prevention of graft rejection [67]. Studies have shown that anti-crotalic serum possesses an antibody content usually inferior to the antibody content of other anti-venom serum suggesting that the crotalic venom is a poor immunogen or that it has components with immunosuppressor activity [68]. Indeed, the immunosuppressive effect of venom and crotoxin (a toxin isolated from *Crotalus durissus terrificus*) was reported [68]. Crotapotin, an acidic and non-toxic subunit of crotoxin, administrated by intraperitoneal route, significantly reduces the severity of experimental autoimmune neuritis, an experimental model for Guillain-Barré syndrome, which indicate a novel path for neuronal protection in this autoimmune disease and other inflammatory demyelinating neuropathies [69]. Inappropriate activation of complement system occurs in a large number of inflammatory, ischaemic and other diseases. Cobra venom factor (CVF) is an unusual venom component which exists in the venoms of different snake species, such as *Naja* sp., *Ophiophagus* sp. and *Hemachatus* sp. that activate complement system [70]. Due its similarity with C3 complement system component, after binding to mammalian fB in plasma and cleavage of fB by fD, produces a C3 convertase, that is more stable than the other C3 convertases, and resistant to the fluid phase regulators. The CVF-Bb convertase consumes all plasma C3 obliterating the functionality of complement system [70]. Recently, a CVF named OVF was purified from the crude venom of *Ophiophagus hannah* and cloned by cDNA transcriptomic analysis of the snake venom glands [71].

2.6. Toxins with anticancer and cytotoxic activities

Anticancer therapy is an important area for the application of proteins and peptides from venomous animals. Integrins play multiple important roles in cancer pathology including tumor cell proliferation, angiogenesis, invasion and metastasis [72]. Inhibition of angiogenesis is one of the heavily explored treatment options for cancer, and in this scenario snake venom disintegrins represent a library of molecules with different structure, potency and specificity [1]. RGD-containing disintegrins was identified in several snake venoms, inhibiting tumor angiogenesis and metastasis, such as accutin (from *Agkistrodon acutus*) [73], salmosin (from *Agkistrodon halys brevicaudus*) [74], contortrostatin (from *Agkistrodon contortrix*) [75], jerdonin (from *Trimeresurus jerdonii*) [76], crotatroxin (from *Crotalus atrox*) [77], rhodostomin (from *Calloselasma rhodostoma*) [78] and a novel desintegrin from *Naja naja* [79]. The cytostatic effect of L-amino acid oxidases (LAAOs) have been demonstrated using various models of human and animal tumors. Studies show that LAAOs induces apoptosis in vascular endothelial cells and inhibits angiogenesis [80]. Examples of LAAOs isolated from snake venoms with anticancer potential are a LAAO isolated from *Ophiophagus hannah* [81], ACTX-6 from *A. acutus* [82], OHAP-1 from *Trimeresurus flavoviridis* [83] and Bl-LAAO from *Bothrops leucurus* [84]. Secretory phospholipases A_2 ($sPLA_2$) also figures the snake toxins with anticancer potential [1]. $sPLA_2$ with cytotoxic activity to tumor cells was described in *Bothrops neuwiedii* [85], *Bothrops brazili* [86], *Naja naja naja* [87], among others. Crotoxin, the main polypeptide isolated from *C. d. terrificus* has shown potent antitumor activity as well the whole venom, highlighting thereby the potential of venom as a source of pharmaceutical templates for cancer therapy [88]. BJcuL, a lectin purified from *Bothrops jararacussu* venom [89] and a metalloproteinase [90] and a lectin from *B. leucurus* [91] are other examples of toxins from snake venoms with anticancer potential.

3. Biotechnological and pharmacological applications of scorpion venom toxins

Scorpions are venomous arthropods, members of Arachnida class and order Scorpiones. These animals are found in all continents except Antarctica, and are known to cause problems in tropical and subtropical regions. Actually these animals are represented by 16 families and approximately 1500 different species and subspecies which conserved their morphology almost unaltered [92-93]. The scorpion species that present medically importance belonging to the family Buthidae are represented by the genera *Androctonus, Buthus, Mesobuthus, Buthotus, Parabuthus*, and *Leirus* located in North Africa, Asia, the Middle East, and India. *Centruroides* spp. are located in Southwest of United States, Mexico, and Central America, while *Tityus* spp. are found in Central and South America and Caribbean. In these different regions of the world the scorpionism is considered a public health problem, with frequent statements that scorpion stings are dangerous [8]. It is generally known that scorpion venom is a complex mixture composed of a wide array of substances. It contains mucopolysaccharides, hyaluronidase, phopholipase, low relative molecular mass molecules like

serotonin and histamine, protease inhibitors, histamine releasers and polypeptidyl compounds. Scorpion venoms are a particularly rich source of small, mainly neurotoxic proteins or peptides interacting specifically with various ionic channels in excitable membranes [94].

3.1. Toxins acting on cardiovascular system

The first peptide from scorpion endowed effects of bradykinin and on arterial blood pressure was isolated from the Brazilian scorpion *Tityus serrulatus* [95]. These peptides named *Tityus serrulatus* Hypotensins have molecular masses ranging approximately from 1190 to 2700 Da [96]. Other scorpion bradykinin-potentiating peptides (BPPs) were reported to be found in the venom of the scorpions *Buthus martensii* Karsch [97] and *Leiurus quinquestriatus* [98]. These molecules can display potential as new drugs and could be of interest for biotechnological purposes.

3.2. Toxins with antibiotic activity

In order to defend themselves against the hostile environment, scorpions have developed potent defensive mechanisms that are part of innate and adaptive immunity [99]. Cysteine-free antimicrobial peptides have been identified and characterized from the venom of six scorpion species [100]. Antimicrobial peptides isolated from scorpion venom are important in the discovery of novel antibiotic molecules [101]. The first antimicrobial peptide isolated from scorpions were of the defensin type from *Leiurus quinquestriatus hebraeus* [102]. Later cytolitic and/or antibacterial peptides were isolated from scorpions belonging to the Buthidae, Scorpionidae, Ischnuridae, and Iuridae superfamilies hemo-lymph and venom [103-108]. The discovery of these peptides in venoms from Eurasian scorpions, Africa and the Americas, confirmed their widespread occurrence and significant biological function. Scorpine, a peptide from *Pandinus imperator* with 75 amino acids, three disulfide bridges, and molecular mass of 8350 Da has anti-bacterial and anti-malaria effects [104]. A cationic amphipatic peptide consisting of 45 amino acids has been purified from the venom of the southern African scorpion, *Parabuthus schlechteri*. At higher concentrations it forms non-selective pores into membranes causing depolarization of the cells [109]. Opistoporin1 and 2 (OP 1 and 2) was isolated from the venom of *Opistophthalmus carinatus*. These are amphipathic, cationic peptides which differ only in one amino acid residue. OP1 and PP were active against Gram-negative bacteria and both had hemolytic activity and antifungal activity. These effects are related to membrane permeabilization [106]. A new antimicrobial peptide, hadrurin, was isolated from *Hadrurus aztecus*. It is a basic peptide composed of 41 amino-acid residues with a molecular mass of 4436 Da, and contains no cysteines. It is a unique peptide among all known antimicrobial peptides described, only partially similar to the N-terminal segment of gaegurin 4 and brevinin 2e, isolated from frog skin. It would certainly be a model molecule for studying new antibiotic activities and peptide-lipid interactions [110]. Pandinin 1 and 2 are antimicrobial peptides have been identified and characterized from venom of the African scorpion *Pandinus imperator* [101]. Recently six novel peptides, named bactridines, were isolated from *Tityus discrepans* scorpion venom by mass spectrometry. The antimicrobial effects on membrane Na^+ permeability induced by bactridines were

observed on *Yersinia enterocolitica* [111]. The profile of gene in the venom glands of *Tityus stigmurus* scorpions was studied by transcriptome. Data revealed that 41 % of ESTs belong to recognized toxin-coding sequences, with transcripts encoding antimicrobial toxins (AMP-like) being the most abundant, followed by alfa KTx-like, beta KTx-like, beta NaTx-like and alfa NaTx-like. Parallel, 34% of the transcripts encode "other possible venom molecules", which correspond to anionic peptides, hypothetical secreted peptides, metalloproteinases, cystein-rich peptides and lectins [7].

3.3. Toxins acting on acting on inflammatory and nociceptive response

The use of toxins as novel molecular probes to study the structure-function relationship of ion-channels and receptors as well as potential therapeutics in the treatment of wide variety of diseases is well documented. The high specificity and selectivity of these toxins have attracted a great deal of interest as candidates for drug development [8]. At least five peptides have been identified from *Buthus martensii* (Chinese scorpion) venom that have anti-inflammatory and antinociceptive properties [61]. One peptide, J123, blocks potassium channels that activate memory T-cells [112]. The venom also contains a 61-amino acid peptide that has demonstrated antiseizure properties in an animal model [113] as well as other constituents that act as analgesics in mice, rats, and rabbits [114]. The polypeptide BmK IT2 from scorpion *Buthus martensi* Karsh stops rats from reacting to experimentally-induced pain [115]. A protein from the Indian black scorpion, *Heterometrus bengalensis*, bengalin caused human leukemic cells to undergo apoptosis *in vitro* [116]. The peptide chlorotoxin, found in the venom of the scorpion *Leiurus quinquestriatus*, retarded the activity of human glioma cells *in vitro* [117]. An investigation about the role of kinins, prostaglandins and nitric oxide in mechanical hypernociception, spontaneous nociception and paw oedema after intraplantar have been done with *Tityus serrulatus* venom in male wistar rats, proving the potential of use of the venom to alleviate pain and oedema formation [118].

3.4. Toxins acting on acting on immunological system

OSK1 (alpha-KTx3.7) is a 38-residue toxin cross-linked by three disulphide bridges initially purified from the venom of the central Asian scorpion *Orthochirus scrobiculosus* [119]. OSK1 and several structural analogues were produced by solid-phase chemical synthesis, and were tested for lethality in mice and for their efficacy in blocking a series of 14 voltage-gated and Ca^{2+} activated K^+ channels *in vitro*. The literature report that OSK1 could serve as leads for the design and production of new immunosuppressive drugs [119]. Margatoxin, a peptidyl inhibitor of K^+ channels has been purified to homogeneity from venom of the new world scorpion *Centruroides margaritatus* showed that could be used as immunosuppressive agent [120]. Kaliotoxin, a peptidyl inhibitor of the high conductance Ca^{2+}-activated K^+ channels (KCa) has been purified to homogeneity from the venom of the scorpion *Androctonus mauretanicus mauretanicus*. This peptide appears to be a useful tool for elucidating the molecular pharmacology of the high conductance Ca^{2+}-activated K^+ channel [121]. Agitoxin 1, 2, and 3, from the venom of the scorpion *Leiurus quinquestriatus* var. hebraeus have been identified on the basis of their ability to block the shaker K^+ channel [122]. Hongotoxin, a pep-

tide inhibitor of shaker-type (K(v)1) K^+ channels have been purified to homogeneity from venom of the scorpion *Centruroides limbatus* [123]. Noxiustoxin, component II-11 from the venom of scorpion *Centruroides noxius* Hoffmann, was obtained in pure form after fractionation by Sephadex G-50 chromatography followed by ion exchange separation on carboxymethylcellulose columns. This peptide is the first short toxin directed against mammals and the first K^+ channel blocking polypeptide-toxin found in scorpion venoms [124]. Pi1 is a peptide purified and characterized from the venom of the scorpion *Pandinus imperato,* showing ability to block the shaker K^+ channel [125]. All of these peptides obtained from scorpions venoms are potential toxins acting on immunological system as immunosuppressant for autoimmune diseases.

3.5. Toxins with anticancer and cytotoxic activities

One of the most notable active principles found in scorpion venom is chlorotoxin (Cltx), a peptide isolated from the species *Leiurus quinquestriatus*. Cltx has 36 amino acids with four disulfide bonds, and inhibits chloride influx in the membrane of glioma cells [126]. This peptide binds only to glioma cells, displaying little or no activity at all in normal cells. The toxin appears to bind matrix metalloproteinase II [117]. A synthetic version of this peptide (TM601) is being produced by the pharmaceutical industry coupled to iodine 131 (131I-TM601), to carry radiation to tumor cells [127]. A recent study shows that TM601 inhibited angiogenesis stimulated by pro-angiogenic factors in cancer cells, and when TM601 was co-administered with bevacizumab, the combination was significantly more potent than a ten-fold increase in bevacizumab dose [128]. A chlorotoxin-like peptide has also been isolated, cloned and sequenced from the venom of another scorpion species, *Buthus martensii* Karsch [129]. In reference [130] was expressed the recombinant chlorotoxin like peptide from *Leiurus quinquestriatus* and named rBmK CTa. Two novel peptides named neopladine 1 and neopladine 2 were purified from *Tityus discrepans* scorpion venom and found to be active on human breast carcinoma SKBR3 cells. Inmunohistochemistry assays revealed that neopladines bind to SKBR3 cell surface inducing FasL and BcL-2 expression [131]. Results indicate the venom from this scorpion represents a great candidate for the development of new clinical treatments against tumors.

3.6. Toxins with insecticides applications

Evidence for the potential application of scorpions toxins as insecticides has emerged in recent years. The precise action mechanism of several of these molecules remains unknown; many have their effects via interactions with specific ion channels and receptors of neuromuscular systems of insects and mammals. These highly potent and specific interactions make venom constituents attractive candidates for the development of novel therapeutics, pesticides and as molecular probes of target molecules [132].

Toxin Lqhα IT from the scorpion *Leiurus quinquestriatus hebraeus* venom is the best representative of anti-insect alpha toxins [133-134]. A similar effect was observed after applying the insect-selective toxin Bot IT1 from *Buthus occitanus tunetanus* venom [135]. Selective inhibition of the inactivation process of the insect para/tipNav expressed in *Xenopus oocyteswas*

was observed in the presence of Bjα IT [136] and OD1 [137], which are toxins from *Buthotus judaicus* and *Odonthobuthus doriae* scorpion venom, respectively. A second group of scorpion toxins slowing insect sodium channel inactivation was called alpha-like toxins. The first precisely described toxins from this group were the Lqh III/Lqh3 (from *L. q. hebraeus*), Bom III/ Bom 3 and Bom IV/ Bom 4 (from *B. o. mardochei*). They were all tested on cockroach axonal preparation [138-139]. BmKM1 toxin from *B. martensi* Karsch was the first alpha-like toxin available in recombinant form that was tested also on cockroach axonal preparation [140]. Toxins Lqh6 and Lqh7 from *L. q. hebraeus* scorpion venom show high structural similarity with Lqh3 toxin. Their toxicity to cockroach is in the range found for other alpha-like toxins [141]. Alpha-like toxins from scorpion venoms show lower efficiency when applied to insects, as compared to α anti-insect toxins. Therefore they seem to be less interesting from the point of view of future insecticide development [132]. Scorpion contractive and depressant toxins are highly selective for insect sodium channels. Several of these toxins were tested on cockroach axonal preparations; toxin AaH IT1 from the *A. australis* scorpion venom was the first one [142-143]. All other contractive toxins tested on cockroach axon produced very similar effects, as for example Lqq IT1 from *L. q. quinquestriatus* [133]; Bj IT1 from *B. judaicus* [143], Bm 32-1 and Bm 33-1 from *B. martensi* [144].

4. Biotechnological and pharmacological applications of spider venom toxins

Spider venoms contain a complex mixture of proteins, polypeptides, neurotoxins, nucleic acids, free amino acids, inorganic salts and monoamines that cause diverse effects in vertebrates and invertebrates [145]. Regarding the pharmacology and biochemistry of spider venoms, they present a variety of ion channel toxins, novel non-neurotoxins, enzymes and low molecular weight compounds [146].

4.1. Toxins acting on cardiovascular system

Venom from the South American tarantula *Grammostola spatulata* presents GsMtx-4, a small peptide belonging to the "cysteine-knot" family that blocks cardiac stretch-activated ion channels and suppresses atrial fibrillation in rabbits [147]. Studies are being conducted to develop therapeutics for atrial fibrillation based on GsMtx-4.

4.2. Toxins acting on hemostasis

ARACHnase (Hemostasis Diagnostics International Co., Denver, CO) is a normal plasma that contains a venom extract from the brown recluse spider, *Loxosceles reclusa*, which mimics the presence of a lupus anticoagulant (LA). ARACHnase is a biotechnological product usefulness like a positive control for lupus anticoagulant testing [148]. Native dermonecrotic toxins (phospholipase-D) from *Loxosceles* sp. are agents that stimulate platelet aggregation [149].

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4.3. Toxins with antibiotic activity

Two peptide toxins with antimicrobial activity, lycotoxins I and II, were identified from venom of the wolf spider *Lycosa carolinensis* (Araneae: Lycosidae). The lycotoxins may play a dual role in spider-prey interaction, functioning both in the prey capture strategy as well as to protect the spider from potentially infectious organisms arising from prey ingestion. Spider venoms may represent a potentially new source of novel antimicrobial agents with important medical implications [150].

4.4. Toxins acting on inflammatory and nociceptive response

Psalmotoxin 1, a peptide extracted from the South American tarantula *Psalmopoeus cambridgei*, has very potent analgesic properties against thermal, mechanical, chemical, inflammatory and neuropathic pain in rodents. It exerts its action by blocking acid-sensing ion channel 1a, and this blockade results in an activation of the endogenous enkephalin pathway [151]. Phospholipases from both *Loxosceles laeta* and *Loxosceles reclusa* cleaved LPC (lysophosphatidylcholine) to LPA (lysophosphatidic acid) and choline. LPA receptors are potential targets for *Loxosceles* sp. envenomation treatment [152]. The possibilities for biotechnological applications in this area are enormous. Recombinant dermonecrotic toxins could be used as reagents to establish a new model to study the inflammatory response, as positive inducers of the inflammatory response and edema [9, 153-154]. The phospholipase-D from *Loxosceles* venom could be used in phospholipid studies, specially studies on cell membrane constituents with emphasis upon sphingophospholipids, lysophospholipids, lysophosphatidic acid and ceramide-1-phosphate, as models for elucidating lipid product receptors, signaling pathways and biological activities; this new wide field of *Loxosceles* research could also reveal new targets for the treatment of envenomation [10].

4.5. Toxins acting on immunological system

The antiserum most commonly used for treatment of loxoscelism in Brazil is anti-arachnidic serum. This serum is produced by the Instituto Butantan (São Paulo, Brazil) by hyperimmunization of horses with venoms of the spiders *Loxosceles gaucho* and *Phoneutria nigriventer* and the scorpion *Tityus serrulatus*. Several studies have indicated that sphingomyelinase D (SMase D) in venom of *Loxosceles* sp. spiders is the main component responsible for local and systemic effects observed in loxoscelism [153, 155]. Neutralization tests showed that anti-SMase D serum has a higher activity against toxic effects of *L. intermedia* and *L. laeta* venoms and similar or slightly weaker activity against toxic biological effects of *L. gaucho* than that of Arachnidic serum. These results demonstrate that recombinant SMase D can replace venom for anti-venom production and therapy [155].

4.6. Toxins with anticancer and cytotoxic activities

Psalmotoxin 1 was evaluated on inhibited Na^+ currents in high-grade human astrocytoma cells (glioblastoma multiforme, or GBM). These observations suggest this toxin may prove useful in determining whether GBM cells express a specific ASIC-containing ion channel

type that can serve as a target for both diagnostic and therapeutic treatments of aggressive malignant gliomas [156]. The antitumor activity of a potent antimicrobial peptide isolated from hemocytes of the spider *Acanthoscurria gomesiana*, named gomesin, was tested *in vitro* and *in vivo*. Gomesin showed cytotoxic and antitumor activities in cell lines, such as melanoma, breast cancer and colon carcinoma [157].

4.7. Toxins with insecticides applications

Several spider toxins have been studied as potential insecticidal bioactive with great biotechnological possible applications [10]. A component of the venom of the Australian funnel web spider *Hadronyche versuta* that is a calcium channel antagonist retains its biological activity when expressed in a heterologous system. Transgenic expression of this toxin in tobacco effectively protected the plants from *Helicoverpa armigera* and *Spodoptera littoralis* larvae, with 100% mortality within 48h [158]. LiTxx1, LiTxx2 and LiTxx3 from *Loxosceles intermedia* venom were identified containing peptides that were active against *Spodoptera frugiperda*. These venom-derived products open a source of insecticide toxins that could be used as substitutes for chemical defensives and lead to a decrease in environmental problems [159]. An insecticidal peptide referred to as Tx4(6-1) was purified from the venom of the spider *Phoneutria nigriventer* by a combination of gel filtration, reverse-phase fast liquid chromatography on Pep-RPC, reverse-phase high performance liquid chromatography (HPLC) on Vydac C18 and ion-exchange HPLC. The protein contains 48 amino acids including 10 Cys and 6 Lys. The results showed that Tx4(6-1) has no toxicity for mice, and suggest that it is a specific anti-insect toxin [160]. SMase D and homologs in the SicTox gene family are the most abundantly expressed toxic protein in venoms of *Loxosceles* and *Sicarius* spiders (Sicariidae). A recombinant SMase D from *Loxosceles arizonica* was obtained and compared its enzymatic and insecticidal activity to that of crude venom. SMase D and crude venom have comparable and high potency in immobilization assays on crickets. These data indicate that SMase D is a potent insecticidal toxin, the role for which it presumably evolved [161]. δ-PaluIT1 and δ-paluIT2 are toxins purified from the venom of the spider *Paracoelotes luctuosus*. Similar in sequence to μ-agatoxins from *Agelenopsis aperta*, their pharmacological target is the voltage-gated insect sodium channel, of which they alter the inactivation properties in a way similar to α-scorpion toxins. Electrophysiological experiments on the cloned insect voltage-gated sodium channel heterologously co-expressed with the tipE subunit in *Xenopus laevis* oocytes, that δ-paluIT1 and δ-paluIT2 procure an increase of Na^+ current [162]. Recently, several toxins have been isolated from spiders with potential biotechnological application as insecticide.

5. Biotechnological and pharmacological applications of toad and frog toxins

Amphibians (toads, frogs, salamanders etc.) during their evolution have developed skin glands covering most parts of their body surface. From these glands small amounts of a mu-

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cous slime are secreted permanently, containing substances with different pharmacologic activities such as cardiotoxins, neurotoxins, hypotensive as well as hypertensive agents, hemolysins, and many others. Chemically they belong to a wide variety of substance classes such as steroids, alkaloids, indolalkylamines, catecholamines and low molecular peptides [11, 163]. Several studies have been showing new potential molecules for a variety of pharmacological applications from toads and frogs venoms.

5.1. Toxins acting on cardiovascular system

Neurotensin-like peptides has been identified from frog skin, such as margaratensin, isolated from *Rana margaratae* [164], a potential antihypertensive drug. Similar to the cardiac glycosides, bufadienolides from *Bufo bufo gargarizans* toad skin are able of inhibiting Na^+/K^+-ATPase, having an important role on treatment of congestive heart failure and arterial hypertension [165]. Examples of these bufadienolides are arenobufagin [166], cinobufagin, bufalin, resibufogenin, among others [165]. In the skin of *Rana temporaria* and *Rana igromaculata* frogs, bradykinin, a hypotensive and smooth muscle exciting substance, has been found [11]. Atelopidtoxin, a water-soluble toxin from skin of *Atelopus zeteki* frog, when injected into mammals, produces hypotension and ventricular fibrillation [167]. Semi-purified skin extracts from *Pseudophryne coriacea* frog displayed effects on systemic blood pressure, reducing it by a probably cholinergic mechanism [168].

5.2. Toxins acting on hemostasis

Annexins are a well-known multigene family of Ca^{2+}-regulated membrane-binding and phospholipid-binding proteins. A novel annexin A2 (Bm-ANXA2) was isolated and purified from *Bombina maxima* skin homogenate, being the first annexin A2 protein reported to possess platelet aggregation-inhibiting activity [169].

5.3. Toxins with antibiotic activity

Toxins with antibiotic activity are the most well studied toxins in toads and frogs. Two antimicrobial bufadienolides, telocinobufagin and marinobufagin, were isolated from skin secretions of the Brazilian toad *Bufo rubescens* [170]. Antimicrobial peptides, named syphaxins (SPXs), were isolated from skin secretions of *Leptodactylus syphax* frog [171]. The alkaloids apinaceamine, 6-methyl-spinaceamine isolated from the skin gland secretions of *Leptodactylus pentadactylus* showed in screening tests bactericidal activity [172]. The cinobufacini and its active components bufalin and cinobufagin, from *Bufo bufo gargarizans* Cantor skin, presented anti-hepatitis B virus (HBV) activity [173]. Telocinobufagin from *Rhinella jimi* toad were demonstrated to be active against *Leishmania chagasi* promastigotes and *Trypanosoma cruzi* trypomastigotes, while hellebrigenin, from same source, was active against only *T. cruzi* trypomastigotes [174].

5.4. Toxins acting on inflammatory and nociceptive responses

Epibatidine, an azabicycloheptane alkaloid isolated from the skin of frog *Epipedobates tricolor*, was found to be a potent antinociceptive compound. Although its toxicity, this toxin could be a lead compound in the development of therapeutic agents for pain relief as well for treatment of disorders whose pathogenesis involves nicotinic receptors [175]. A variety of toxins acting on opioid receptors have been isolated from amphibians. Dermorphin (Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2) and related heptapeptide [Hyp^6]-dermorphin isolated from the frog skin of *Phyllomedusa* sp., show higher affinity for μ-opioid receptors. Several peptides belonging to the dermorphin family have been isolated from frog skin [61]. Deltorphins (also referred as dermenkephalin) and related peptides isolated from the frog skin have been found to exhibit high selectivity for δ-opiate receptors [176].

5.5. Toxins with anticancer and cytotoxic activities

Venenum Bufonis is a traditional Chinese medicine obtained from the dried white secretion of auricular and skin glands of Chinese toads (*Bufo melanostictus* Schneider or *Bufo bufo gargarzinas* Cantor). Cinobufagin (CBG), isolated from *Venenum Bufonis*, had potential immune system regulatory effects and is suggested that this compound could be developed as a novel immunotherapeutic agent to treat immune-mediated diseases such as cancer [177]. Bufadienolides from toxic glands of toads are used as anticancer agents, mainly on leukemia cells. Bufalin and cinobufagin from *Bufo bufo gargarizans* Cantor were tested and studies shown that these toxins suppress cell proliferation and cause apoptosis in prostate cancer cells via a sequence of apoptotic modulators [178]. Bufotalin, one of the bufadienolides isolated from Formosan Ch'an Su, which is made of the skin and parotid glands of toads, induce apoptosis in human hepatocellular carcinoma, probably involving caspases and apopotosis-inducing factor [179]. Cutaneous venom of *Bombina variegata pachypus* toad presented a cytolitic effect on the growth of the human HL 60 cell line [180]. Brevinin-2R, a non-hemolytic defensin has been isolated from the skin of the frog *Rana ridibunda*, showing pronounced cytotoxicity towards malignant cells [181].

5.6. Toxins with insulin releasing activity

Diabetes mellitus is a disease in which the body is unable to sufficiently produce or properly use insulin. Newer therapeutic modalities for this disease are extremely needed. Peptides with insulin-releasing activity have been isolated from the skin secretions of the frog *Agalychnis litodryas* and may serve as templates for a novel class of insulin secretagogues [182].

6. Biotechnological and pharmacological applications of bee and wasp toxins

Stinging accidents caused by wasps and bees generally produce severe pain, local damage and even death in various vertebrates including man, caused by action of their venoms. Bee

venom contains a variety of compounds peptides including melittin, apamin, adolapin, and mast cell degranulating (MCD) peptide, in addition of hyaluronidase and phospholipase A enzymes, that plays a variety of biological activities. The chemical constituents of venoms from wasps species include acetylcholine, serotonin, norepinephrine, hyaluronidase, histidine decarboxylase, phospholipase A_2 and several polycationic peptides and proteins [12].

6.1. Toxins acting on cardiovascular system

Honey bee venom and its main constituents have a marked effect on the cardiovascular system, most notably a fall in arterial blood pressure [183]. From the hemodynamic point of view, the venom, in higher doses, is extremely toxic to the circulatory system and in smaller doses, however, produce a stimulatory effect upon the heart [184]. Melittin, a strongly basic 26 amino-acid polypeptide which constitutes 40–60% of the whole dry honeybee venom, induces contractures and depolarization in skeletal muscle [12]. Melittin is cardiotoxic *in vitro*, causing arrest of the rat heart, but only induces a slight hypertension *in vivo* [183]. Apamin, without direct effect on contraction or relaxation, could attenuate the relaxation evoked by melittin at lower concentrations, and thus contribute to the conversion of melittin's relaxing activity into the contractile activity of the venom. Another peptide found in bee venom that outlines effects on the cardiovascular system is the Cardiopep. Cardiopep is a relatively nonlethal component, compared to phospholipase A, melittin, or whole bee venom itself. It is a potent nontoxic beta-adrenergio-like stimulant that possesses definite anti-arrhythmic properties [185]. Studies on the cardiovascular effects of mastoparan B, isolated from the venom of the hornet *Vespa basalis,* has shown that the peptide caused a dose-dependent inhibition of blood pressure and cardiac function in the rat. Research has shown that the cardiovascular effects of mastoparan B are mainly due to the actions of serotonin, and by a lesser extent to other autacoids, released from mast cells as well from other biocompartments [186].

6.2. Toxins acting on hemostasis

The mechanism by which bee venom affects the hemostatic system remains poorly understood [187]. Among the serine proteases isolated from bees, which acts as a fibrin(ogen)olytic enzyme, activator prothrombin and directly degrades fibrinogen into fibrin degradation products, are the Bi-VSP (*Bombus ignitus*) [188], Bt-VSP (*Bombus terrestris*) [189] and Bs-VSP (*Bombus hypocrita sapporoensis*) [190]. According reference [188], the activation of prothrombin and fibrin(ogen)olytic activity may cooperate to effectively remove fibrinogen, and thus reduce the viscosity of blood. The injection fibrin(ogen)olytic enzyme can be used to facilitate the propagation of components of bee venom throughout the bloodstream of mammals. Bumblebee venom also affects the hemostatic system through by Bi-KTI (*B. ignitus*), a Kunitz-type inhibitor, that strongly inhibited plasmin during fibrinolysis, indicating that Bi-KTI specifically targets plasmin [187]. A toxin protein named magnvesin was purified of *Vespa magnifica*. This protein contains serine protease-like activity inhibits blood coagulation, and was found to act on factors TF, VII, VIII, IX and X [191]. Other anticoagulant protein (protease I) with proteolytic activity was purified from *Vespa orientalis* venom, involving mainly coagulation factors VIII and IX [192]. Magnifin, a phospholipase A_1 (PLA_1) purified

from wasp venoms of *V. magnifica*, is very similar to other (PLA_1), especially to other wasp allergen PLA_1. Magnifin can activate platelet aggregation and induce thrombosis *in vivo*. It was the first report of PLA_1 from wasp venoms that can induce platelet aggregation [193].

6.3. Toxins with antibiotic activity

Antimicrobial peptides have attracted much attention as a novel class of antibiotics, especially for antibiotic-resistant pathogens. They provide more opportunities for designing novel and effective antimicrobial agents [194]. Melittin has various biological, pharmacological and toxicological actions including antibacterial and antifungal activities [195]. Bombolitin (structural and biological properties similar to those of melittin), isolated from the venom of *B. ignitus* worker bees, possesses antimicrobial activity and show inhibitory effects on bacterial growth for Gram-positive, Gram-negative bacteria and fungi, suggesting that bombolitin is a potential antimicrobial agent [196]. Osmin, isolated of solitary bee *Osmia rufa*, shows some similarities with the mast cell degranulation (MCD) peptide family. Free acid and C-terminally amidated osmins were chemically synthesized and tested for antimicrobial and haemolytic activities. Antimicrobial and antifungal tests indicated that both peptides were able to inhibit bacterial and fungal growth [197]. Two families of bioactive peptides which belongs to mastoparans (12a and 12b) and chemotactic peptides (5e, 5g and 5f) were purified and characterized from the venom of *Vespa magnifica*. MP-VBs (vespa mastoparan) and VESP-VBs (vespa chemotactic peptide) were purified from the venom of the wasp *Vespa bicolor* Fabricius and demonstrated antimicrobial action [198]. The amphipathic α-helical structure and net positive charge (which permits electrostatic interaction with the negatively charged microbial cell membrane) of mastoparan appear to be critical for MCD activity and because of these structural properties, mastoparans are often highly active against the cell membranes of bacteria, fungi, and erythrocytes, as well as mast cells [199].

6.4. Toxins acting on inflammatory and nociceptive responses

Bee venom has been used in Oriental medicine and evidence from the literature indicates that bee venom plays an anti-inflammatory or anti-nociceptive role against inflammatory reactions associated with arthritis and other inflammatory diseases [200]. Bee venom demonstrated neuroprotective effect against motor neuron cell death and suppresses neuroinflammation-induced disease progression in symptomatic amyotrophic lateral sclerosis (ALS) mice model [200]. Melittin has effects on the secretion of phospholipase A_2 and inhibits its enzymatic activity, which is important because phospholipases may release arachidonic acid which is converted into prostaglandins [201]. Have also been reported that melittin decreased the high rate of lethality, attenuated hepatic inflammatory responses, alleviated hepatic pathological injury and inhibited hepatocyte apoptosis. Protective effects were probably carried out through the suppression of NF-jB activation, which inhibited TNF-α liberation. Therefore, melittin may be useful as a potential therapeutic agent for attenuating acute liver injury [202]. In addition of melittin, others agents has shown anti-inflammatory activity. Among them are adolapin and MCDP. Adolapin showed marked anti-inflammatory and anti-nociceptive properties due to inhibition of prostaglandin synthase

system [203]. MCDP, isolated of *Apis mellifera* venom, is a strong mediator of mast cell degranulation and releases histamine at low concentrations [204].

6.5. Toxins acting on immunological system

Characterization of the primary structure of allergens is a prerequisite for the design of new diagnostic and therapeutic tools for allergic diseases. Major allergens in bee venom (recognized by IgE in more than 50% of patients) include phospholipase A_2 (PLA_2), acid phosphatase, hyaluronidase and allergen C, as well as several proteins of high molecular weights (MWs) [205]. Besides these, Api m 6, was frequently (42%) recognized by IgE from bee venom hypersensitive patients [206]; from wasp venom were purified Vesp c 1 (phospholipase A1) and Vesp c 5 (antigen-5) from *Polistes gallicus*, and Vesp ma 2 and Vesp ma 5 from *Vespa magnifica*, [207-208]. Formulations of poly(lactic-co-glycolic acid) (PLGA) microspheres represent a strategy for replacing immunotherapy in multiple injections of venom. The results obtained with bee venom proteins encapsulated showed that the allergens may still be effective in the induction of an immune response and so may be a new formulation for VIT [209]. Recombinant proteins with immunosuppressive properties have been reported in the literature, such as rVPr1 and rVRr3, identified, cloned and expressed from isolated VPR1 and VPr2 from *Pimpla hypochondriaca* [210]. Chemotactic peptide protonectin 1-6 (ILGTIL-NH2) was detected in the venom of the social wasp *Agelaia pallipes pallipes* [211]. Polybia-MPI and Polybia-CP were isolated from the venom of the social wasp *Polybia paulista* and characterized as chemotactic peptides for PMNL cells [212]. Under the diagnosis, the microarray was reported. Protein chips can be spotted with thousands of proteins or peptides, permitting to analyses the IgE responses against a tremendous variety of allergens. First attempts to microarray with Hymenoptera venom allergens included Api m 1, Api m 2, Ves v 5, Ves g 5 and Pol a 5 in a set-up with 96 recombinant or natural allergen molecules representative of most important allergen sources. The venom allergens from different bee, wasp and ant species can be offered on a single chip, allowing to differentiate the species that has stung based on species-specific markers. The allergen microarray allows the determination and monitoring of allergic patients' IgE reactivity profiles to large numbers of disease-causing allergens by using single measurements and minute amounts of serum [213].

6.6. Toxins with anticancer and cytotoxic activities

Bee venom is the most studied among the arthropods covered in this chapter regarding its anti-cancer activities, due mainly to two substances that have been isolated and characterized: melittin and phospholipase A_2 (PLA_2). Melittin and PLA_2 are the two major components in the venom of the species *Apis mellifera* [214]. Melittin is inhibitor of calmodulin activity and is an inhibitor of cell growth and clonogenicity of human and murine leukemic cells [215]. Study indicated that key regulators in bee venom-induced apoptosis are Bcl-2 and caspase-3 in human leukemic U937 cells through down-regulation of the ERK and Akt signal pathway [216]. Furthermore recent reports indicate that BV is also able to inhibit tumor growth and exhibit anti-tumor activity *in vitro* and *in vivo* and can be used as a chemotherapeutic agent against malignancy [217]. The adjuvant treatment with PLA_2 and

phosphatidylinositol-(3,4)-bisphosphate was more effective in the blocking of tumor cell growth [218]. New peptides have been isolated from bee venom and tested in tumor cells, exhibiting promising activities in the treatment of cancer. Lasioglossins isolated from the venom of the bee *Lasioglossum laticeps* exhibited potency to kill various cancer cells *in vitro* [219]. Briefly the bee venom acts inhibiting cell proliferation and promoting cell death by different means: increasing Ca^{2+} influx; inducing cytochrome C release; binding calmodulin; decreasing or increasing the expression of proteins that control cell cycle or activating PLA_2, causing damage to cell membranes interfering in the apoptotic pathway [220]. Among potential anticancer compounds, one of the most studied is mastoparan, peptide isolated from wasp venom that has been reported to induce a potent facilitation of the mitochondrial permeability transition. It should be noted that this recognized action of mastoparan is marked at concentrations <1 μM [221]. Two novel mastoparan peptides, Polybia-MP-II e Polybia-MP-III isolated from venom of the social wasp *Polybia paulista*, exhibited hemolytic activity on erythrocytes [222]. Polybia-MPI, also was purified from the venom of the social wasp *P. paulista*, synthesized and studied its antitumor efficacy and cell selectivity. Results revealed that polybia-MPI exerts cytotoxic and antiproliferative efficacy by pore formation and have relatively lower cytotoxicity to normal cells [223].

6.7. Toxins with insulin releasing activity

Bee venom inhibits insulitis and development of diabetes in non-obese diabetic (NOD) mice. The cumulative incidence of diabetes at 25 weeks of age in control was 58% and NOD mice bee venom treated was 21% [224]. Mastoparan, component of wasp venom, is known to affect phosphoinositide breakdown, calcium influx, exocytosis of hormones and neurotransmitters and stimulate the GTPase activity of guanine nucleotide-binding regulatory proteins [225]. Thus, it is reported in the literature that mastoparan stimulates insulin secretion in human, as well as in rodent. Furthermore, glucose and alpha-ketoisocaproate (alfa-KIC) increase the mastoparan-stimulated insulin secretion [226].

7. Biotechnological and pharmacological applications of ant, centipede and caterpillar venom toxins

Ant, centipede and caterpillar venoms have not been studied so extensively as the venoms of snakes, scorpions and spiders. Ant venoms are rich in the phospholipase A_2 and B, hyaluronidase, and acid and alkaline phosphatase as well as in histamine itself [227]. Centipede venoms have been poorly characterized in the literature. Studies have reported in centipede venoms the presence of esterases, proteinases, alkaline and acid phosphatases, cardiotoxins, histamine, and neurotransmitter releasing compounds in *Scolopendra* genus venoms [228]. Among the most studied caterpillar venoms are *Lonomia obliqua* and *Lonomia achelous* venoms, which cause similar clinical effects [229]. Based on cDNA libraries, was possible to identify several proteins from *L. obliqua,* such as cysteine proteases, group III phospholipase A_2, C-type lectins, lipocalins, in addition to protease inhibitors including serpins, Kazal-type inhibitors, cystatins and trypsin inhibitor-like molecules [230].

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7.1. Toxins acting on cardiovascular system

A study showed that the *Lonomia obliqua* caterpillar bristles extract (LOCBE) directly releases kinin from low-molecular weight kininogen, being suggested that kallikrein-kinin system plays a role in the edematogenic and hypotensive effects during *L. obliqua* envenomation [231].

7.2. Toxins acting on hemostasis

There are numerous studies in literature reporting the effects on the hemostatic system of toxins from caterpillars. The effect of a crude extract of spicules from *Lonomia obliqua* caterpillar on hemostasis was found to activate both prothrombin and factor X [232]. Lopap is a prothrombin activator isolated from the bristles of *L. obliqua* caterpillar. Lopap demonstrated ability to induce activation, expression of adhesion molecules and to exert an anti-apoptotic effect on human umbilical vein endothelial cells [233]. Lonofibrase, an α-fibrinogenase from *L. obliqua* was isolated from venomous secretion [234]. Losac, a protein with procoagulant activity, which acts as a growth stimulator and an inhibitor of cellular death for endothelial cells, was purified of the bristle extract of *L. obliqua*. Losac may have biotechnological applications, including the reduction of cell death and consequently increased productivity of animal cell cultures [235]. Lonomin V, serine protease isolated from *Lonomia achelous* caterpillar, inhibited platelet aggregation, probably caused by the degradation of collagen. It is emphasized that Lonomin V shows to be a potentially useful tool for investigating cell-matrix and cell-cell interactions and for the development of antithrombotic agents in terms of their anti-adhesive activities [236]. The venom from the tropical ant, *Pseudomyrmex triplarinus*, inhibited arachidonic acid and induced platelet aggregation, suggesting that venom prevented the action of prostaglandins. The venom was fractionated and factor F (adenosine) with antiplatelet activity were detected [237].

7.3. Toxins with antibiotic activity

Venom alkaloids from *Solenopsis invicta,* fire ant, inhibit the growth of Gram-positive and Gram-negative bacteria and presumably act as a brood antibiotic. Peptides named ponericins were identified from the venom of ant *Pachycondyla goeldii*. Fifteen peptides were classified into three different families according to their primary structure similarities: ponericins G, W, and L. Ponericin G1, G3, G4 and G6 demonstrated antimicrobial activity. Ponericins G share about 60% sequence similarity with cecropins and these have a broad spectrum of activity against bacteria. Peptides family W shares about 70% sequence similarity with Gaegurin 5 (*Rana rugosa*) and melittin (discussed in previous topics). Gaegurin 5 exhibits a broad spectrum of antimicrobial action against bacteria, fungi, and protozoa and has very little hemolytic action. The ponericin L2 from the third family has only an antibacterial action, and shares important sequence similarities with dermaseptin 5, which has strong antimicrobial action against bacteria, yeast, fungi, and protozoa [238]. A cytotoxic peptide from the venom of the ant *Myrmecia pilosula*, Pilosulin 1, was identified as a potential novel antimicrobial peptide sequence. It outlined a potent and broad spectrum antimicrobial activity including standard and multi-drug resistant gram-positive and gram-negative bacteria and

Candida albicans [239]. Two antimicrobial peptides from centipede venoms, scolopin 1 and 2 were identified from venoms of *Scolopendra subspinipes mutilan* [240].

7.4. Toxins acting on inflammatory and nociceptive responses

Venom from the tropical ant *Pseudomyrex triplarinus* relieves pain and inflammation in rheumatoid arthritis [241]. Venom from the *P. triplarinus* contains peptides called myrmexins that relieve pain and inflammation in patients with rheumatoid arthritis and inhibit inflammatory carragenin-induced edema in mice [242].

7.5. Toxins acting on immunological system

The most frequent cause of insect venom allergy in the Southeastern USA is the imported fire ant and the allergens are among the most potent known. Fire ant venom is a potent allergy-inducing agent containing four major allergens, Sol i I, Sol i II, Sol i III and Sol i IV [243-244].

7.6. Toxins with anticancer and cytotoxic activities

Solenopsin A, a primary alkaloid from the fire ant *Solenopsis invicta*, exhibits antiangiogenic activity. Among the results obtained in this study, one of the most interesting was the selective inhibition of Akt by solenopsin *in vitro*, that is of great interest since few Akt inhibitors have been developed, and Akt is a key molecular target in the pharmacological treatment of cancer [245]. Glycosphingolipid 7, identified in the millipede *Parafontaria laminata armigera*, suppressed cell proliferation and this effect was associated with suppression of the activation of FAK (focal adhesion kinase), Erk (extracellular signal-regulated kinase), and Akt in melanoma B16F10 cells. Cells treated with glycosphingolipid 7 reduced the expression of the proteins responsible for the progression of cell cycle, cyclin D1 and CDK4 [246].

7.7. Toxins with insecticides applications

Peptides named ponericins from ant *Pachycondyla goeldii* have a marked action as insecticides. Among the peptides showed insecticidal activity are the ponericins G1, G2 and ponericins belonging to the family W [238].

In Table 1, is presented a summary of the main biotechnological/pharmacological applications of toxins from venomous animals covered in this chapter.

Source		Toxin	Application	Ref.
		Toxins acting on cardiovascular system		
Snakes	*Agkistrodon halys blomhoffii*	NP	Anti-hypertensive agent	[21]
	Bothrops jararaca	BPP	Anti-hypertensive agent (development of captopril and derivatives)	[16]

		NP	Anti-hypertensive agent	[4]
	Bungarus flaviceps	NP	Anti-hypertensive agent	[24]
	Crotalus durissus cascavella	NP	Anti-hypertensive agent	[23]
	Crotalus durissus terrificus	BPP	Anti-hypertensive agent	[17]
	Dendroaspis angusticeps	DNP	Anti-hypertensive agent: natriuretic peptide	[19]
		C10S2C2	Anti-hypertensive drug: L-type Ca^{2}+channels blocker	[27]
	Dendroaspis jamesoni kaimosae	S4C8	Anti-hypertensive agent: L-type Ca^{2}+channels blocker	[27]
	Dendroaspis polylepis polylepis	Calciseptine	Anti-hypertensive agent: L-type Ca^{2}+channels blocker	[25]
		FS2 toxins	Anti-hypertensive agent: L-type Ca^{2}+channels blocker	[26]
	Micrurus corallinus	NP	Anti-hypertensive agent	[20]
	Pseudocerastes persicus	NP	Anti-hypertensive agent	[22]
	Trimeresurus flavoviridis	NP	Anti-hypertensive agent	[21]
	Trimeresurus stejnegeri	Stejnihagin	Anti-hypertensive agent: L-type Ca^{2}+channels blocker	[29]
Scorpions	*Buthus martensii*	BPP	Anti-hypertensive agent	[97]
	Leiurus quinquestriatus	BPP	Anti-hypertensive agent	[98]
	Tityus serrulatus	BPP	Anti-hypertensive agent	[96]
Spiders	*Grammostola spatulata*	GsMtx-4	Blocks cardiac stretch-activated ion channels and suppresses atrial fibrillation in rabbits	[147]
Toads and Frogs	*Atelopus zeteki*	Atelopidtoxin	Hypotensive agent and ventricular fibrillation inductor	[167]
	Bufo bufo gargarizans	Bufalin	Na^{K}+-ATPase inhibitor	[165]
	Pseudophryne coriacea	Semi-purified skin extracts	Hypotensive agent	[168]
	Rana igromaculata	Bradykinin	Hypotensive agent and smooth muscle exciting substance	[11]
	Rana margaratae	Margaratensin	Neurotensin-like peptide	[164]
		Cinobufagin	Na^{K}+ATPase inhibitor	[165]
	Rana temporaria	Bradykinin	Hypotensive agent and smooth muscle exciting substance	[11]
Bees and Wasps	*Apis mellifera*	Cardiopep	Beta-adrenergio-like stimulant and anti-arrhythmic agent	[185]

	Vespa basalis	Mastoparan B	Anti-hypertensive agent	[186]
		Toxins acting on hemostasis		
Snakes	*Agkistrodon rhodostoma*	Ancrod	Anticoagulant and defibrinogenating agent (Viprinex®)	[34]
	Bothrops alternatus	Bhalternin	Treatment and prevention of thrombotic disorders	[35]
	Bothrops atrox	Batroxobin	Anticoagulant and defibrinogenating agent (Defibrase®)	[33]
		Mixture of a TLE with a thromboplastin-like enzyme	Treatment of hemorrhages (Haemocoagulase®)	[13]
	Bothrops erythromelas	BE-I-PLA^2	Antiplatelet agent	[39]
	Bothrops leucurus	BleucMP	Treatment and prevention of cardiovascular disorders and strokes	[36]
		Leucurogin	Antiplatelet agent	[32]
	Echis carinatus	Echistatin	Antiplatelet agent	[30]
	Sisturus miliaris barbouri	Barbourin	Antiplatelet agent	[31]
	Trimeresurus malabaricus	Trimarin	Treatment and prevention of thrombotic disorders	[38]
	Vipera lebetina	VLH2	Treatment and prevention of thrombotic disorders	[37]
Spiders	*Loxosceles.*	Phospholipase-D	Platelet aggregation inductor	[149]
Toads and Frogs	*Bombina maxima*	Bm-ANXA2	Antiplatelet agent	[169]
Bees and Wasps	*Bombus hypocrita sapporoensis*	Bs-VSP	Prothrombin activator, thrombin-like protease and a plasmin-like protease agent	[190]
	Bombus ignites	Bi-VSP	Prothrombin activator, thrombin-like protease and a plasmin-like protease agent	[188]
		Bi-KTI	Plasmin inhibitor agent	[187]
	Bombus terrestris	Bt-VSP	Prothrombin activator, thrombin-like protease and a plasmin-like protease agent	[189]
	Vespa orientalis	Protease I	Anticoagulant agent	[192]
	Vespa magnifica	Magnifin	Inductor platelet aggregation agent	[193]
		Magnvesin	Anticoagulant agent	[191]
Ants, Centipedes and Caterpillars	*Lonomia achelous*	Lonomin V	Inhibitor platelet aggregation agent	[236]
	Lonomia obliqua	Lopap	Prothrombin activator agent	[233]
		Lonofibrase	Fibrinogenolytic and fibrinolytic agent Agent	[234]
		Losac	Procoagulant agent	[235]
		Toxins with antibiotic activity		
Snakes	*Bothrops alternatus*	Balt-LAAO-I	Anti-bacterial agent	[42]

	Bothrops asper	Myotoxin II	Anti-bacterial agent	[50]
	Bothrops jararaca	LAAO	Antiparasitic agent	[48]
	Bothrops marajoensis	BmarLAAO	Anti-bacterial, antifungal and antiparasitic agent	[47]
	Bothrops neuwiedi	Neuwiedase	Antiparasitic agent	[55]
	Bothrops pirajai	BpirLAAO-I	Anti-bacterial and antiparasitic agent	[44]
	Bungarus fasciatus	BFPA	Anti-bacterial agent	[53]
	Crotalus durissus cascavella	Casca LAO	Anti-bacterial agent	[45]
	Crotalus durissus terrificus	Crotoxin	Antiviral agent	[56]
		PLA_2-CB	Antiviral agent	[56]
		PLA_2-IC	Antiviral agent	[56]]
	Echis carinatus	EcTx-I	Anti-bacterial agent	[51]
	Naja atra	Vgf-1	Anti-bacterial agent	[54]
	Naja naja oxiana	LAAO	Anti-bacterial agent	[46]
	Porthidium nasutum	$PnPLA_2$	Anti-bacterial agent	[52]
	Trimeresurus jerdonii	TJ-LAO	Anti-bacterial agent	[41]
	Trimeresurus mucrosquamatus	TM-LAO	Anti-bacterial agent	[43]
Scorpions	*Hadrurus aztecus*	Hadrurin	Anti-bacterial agent	[110]
	Leiurus quinquestriatus	Defensin	Anti-bacterial agent	[102]
	Opistophthalmus carinatus	Opistoporin I/II	Anti-bacterial and antifungal agent	[106]
	Pandinus imperator	Pandinin I/II	Antimicrobial agent	[101]
		Scorpine	Anti-bacterial and antiparasitic agent	[104]
	Parabuthus schlechteri	Cationic amphipatic peptide	Antimicrobial agent	[109]
	Tityus discrepans	Bactridines	Anti-bacterial agent	[111]
Spiders	*Lycosa carolinensis*	Lycotoxins I/II	Antimicrobial agent	[150]
Toads and Frogs	*Bufo bufo gargarizans*	6-methyl-spinaceamine	Anti-bacterial agent	[172]
		Bufalin	Antiviral agent	[173]
		Cinobufagin	Antiviral agent	[173]
	Bufo rubescens	Telocinobufagin	Anti-bacterial agent	[170]
		Marinobufagin	Anti-bacterial agent	[170]
	Leptodactylus pentadactylus	Apinaceamine	Anti-bacterial agent	[172]
	Leptodactylus syphax	SPXs	Anti-bacterial agent	[171]
	Rhinella jimi	Telocinobufagin	Antiparasitic agent	[174]

		Hellebrigenin	Antiparasitic agent	[174]
Bees and Wasps	*Apis mellifera*	Melittin	Anti-bacterial agent	[195]
	Bombus ignites	Bi-Bombolitin	Anti-bacterial and antifungal agent	[196]
	Osmia rufa	Osmin	Anti-bacterial and antifungal agent	[197]
	Vespa bicolor	MP-VB1	Anti-bacterial and antifungal agent	[198]
		VESP-VB1	Anti-bacterial and antifungal agent	[198]
Ants, Centipedes and Caterpillars	*Myrmecia pilosula*	Pilosulin 1	Anti-bacterial and antifungal agent	[239]
	Scolopendra subspinipes mutilan	Scolopin 1	Anti-bacterial and antifungal agent	[240]
		Scolopin 2	Anti-bacterial and antifungal agent	[240]
Toxins acting on inflammatory and nociceptive responses				
Snakes	*Crotalus durissus terrificus*	Crotamine	Antinociceptive agent	[63]
		Crotoxin	Antinociceptive agent	[64]
		Hyal	Anti-edematogenic agent	[59]
	Lachesis muta	βPLI	Phospholipase inhibitor	[58]
	Naja atra	Cobrotoxin	Antinociceptive agent	[65]
	Ophiophagus hannah	Hannalgesin	Antinociceptive agent	[66]
Scorpions	*Buthus martensii*	BmKIT2	Antinociceptive agent	[115]
		J123 peptide	K^+ channel blocker	[112]
Spiders	*Loxosceles laeta*	SMase D	Pro-inflammatory agent	[152]
	Loxosceles reclusa	Phospholipase D	Pro-inflammatory agent	[152]
	Psalmopoeus cambridgei	Psalmotoxin 1	Antinociceptive and anti-inflammatory agent	[151]
Toads and Frogs	*Epipedobates tricolor*	Epibatidine	Antinociceptive agent	[175]
	Phyllomedusa sp	Deltorphins	Opioid analgesic agents	[176]
		Dermorphins	Opioid analgesic agents	[61]
Bees and Wasps	*Apis mellifera*	Melittin	Anti-inflammatory agent	[202]
		MCDP	Anti-inflammatory agent	[204]
Ants, Centipedes and Caterpillars	*Pseudomyrex triplarinus*	Myrmexins	Anti-inflammatory agent	[242]
Toxins acting on immunological system				
Snakes	*Crotalus durissus terrificus*	Crotapotin	Immunossupressive agent	[69]
		Crotoxin	Immunossupressive agent	[68]
	Ophiophagus hannah	OVF	Complement system activator agent	[71]
Scorpions	*Androctonus mauretanicus*	Kaliotoxin	Ca^{2+} activated K^+ channel	[121]
	Centruroides limbatus	Hongotoxin	K^+ channel blocker	[123]
	Centruroides margaritatus	Margatoxin	Immunosuppressive agent	[120]
	Centruroides noxius	Noxiustoxin	K^+ channel blocker	[124]

	Leiurus quinquestriatus	Agitoxin I/II/III	K^+ channel blocker	[122]
	Orthochirus scrobiculosus	OSK1	Immunosuppressive agent	[119]
	Pandinus imperator	Pi1	K^+ channel blocker	[125]
Spiders	*Loxosceles laeta*	SMase D	Antiserum	[155]
	Loxosceles reclusa	SMase D	Antiserum	[155]
Bees and Wasps	*Agelaia pallipes pallipes*	Protonectin 1-6	Chemotactic agent	[211]
	Apis mellifera	Api m 1	Allergen	[213]
		Api m 2	Allergen	[213]
		Api m 6	Allergen	[206]
	Pimpla hypochondriaca	rVPr1	Immunosuppressive agent	[210]
		rVPr3	Immunosuppressive agent	[210]
	Polistes annularis	Pol a 5	Allergen	[213]
	Polistes gallicus	Vesp c 1 (phospholipase A1)	Allergen	[207-208]
		Vesp c 5 (antigen-5)	Allergen	[207-208]
	Polybia paulista	Polybia-MPI	Chemotactic agent	[212]
		Polybia-CP	Chemotactic agent	[212]
	Vespa magnifica	Vesp ma 2	Allergen agent	[207-208]
		Vesp ma 5	Allergen	[207-208]
	Vespula germanica	Ves g 5	Allergen	[213]
	Vespula vulgaris	Ves v 5	Allergen	[213]
Ants, Centipedes and Caterpillars	*Solenopsis invicta*	Sol i I	Allergen	[244]
		Sol i II	Allergen	[243]
		Sol i III	Allergen	[243]
		Sol i IV	Allergen	[243]
Toxins with anticancer and cytotoxic activity				
Snakes	*Agkistrodon acutus*	Accutin	Anticancer agent: disintegrin	[73]
		ACTX-6	Anticancer agent: L-amino acid oxidase	[82]
	Agkistrodon contortrix	Contortrostatin	Anticancer agent: disintegrin	[75]
	Agkistrodon halys brevicaudus	Salmosin	Anticancer agent: disintegrin	[74]
	Bothrops brazili	$sPLA_2$	Anticancer agent	[86]
	Bothrops jararacussu	BJcuL	Anticancer agent	[89]
	Bothrops leucurus	Bl-LAAO	Anticancer agent	[84]

		Metalloproteinase	Anticancer agent	[90]
		Lectin	Anticancer agent	[91]
	Bothrops neuwiedii	$sPLA_2$	Anticancer agent	[85]
	Calloselasma rhodostoma	Rhodostomin	Anticancer agent: disintegrin	[78]
	Crotalus atrox	Crotatroxin	Anticancer agent: disintegrin	[77]
	Naja naja	Disintegrin	Anticancer agent	[79]
	Naja naja naja	$sPLA_2$	Anticancer agent	[87]
	Ophiophagus hannah	LAAO	Anticancer agent	[81]
	Trimeresurus flavoviridis	OHAP-1	Anticancer agent: L-amino acid oxidase	[83]
	Trimeresurus jerdonii	Jerdonin	Anticancer agent: disintegrin	[76]
Scorpions	*Heterometrus bengalensis*	Bengalin	Anticancer agent	[116]
	Leiurus quinquestriatus	Chlorotoxin	Anticancer agent	[126]
		rBmK CTa	Anticancer agent	[130]
	Tityus discrepans	Neopladine 1 and 2	Anticancer agent	[131]
Spiders	*Acanthoscurria gomesiana*	Gomesin	Cytotoxic and anticancer agent	[157]
	Psalmopoeus cambridgei	Psalmotoxin 1	Anticancer agent	[156]
Toads and Frogs	*Bombina variegata pachypus*	Cutaneous venom	Anticancer agent	[180]
	Bufo bufo gargarizans	Bufalin	Anticancer agent	[178]
		Cinobufagin	Anticancer agent	[178]
	Formosan Ch'an Su	Bufotalin	Anticancer agent	[179]
	Rana ridibunda	Brevinin-2R	Anticancer agent	[181]
	Venenum Bufonis	CBG	Anticancer and immunotherapeutic agent to treat immune-mediated diseases	[177]
Bees and Wasps	*Lasioglossum laticeps*	Lasioglossins	Anticancer agent	[219]
	Polybia paulista	Polybia-MPI	Cytotoxic and antiproliferative agent	[223]
		Polybia-MP-II	Cytotoxic agent (hemolytic activity on erythrocytes)	[222]
		Polybia-MP-III	Cytotoxic agent (hemolytic activity on erythrocytes)	[222]
Ants, Centipedes and Caterpillars	*Parafontaria laminata armigera*	Glycosphingolipid 7	Anticancer agent	[246]
	Solenopsis invicta	Solenopsin A	Anticancer agent	[245]

Toxins with insulin releasing activity

Toads and Frogs	*Agalychnis litodryas*	Peptides from skin secretion	Insulin-releasing activity	[182]
Bees and Wasps	Wasp venom	Mastoparan	Stimulator of insulin secretion agent	[226]
		Toxins with insecticides applications		
Scorpions	*Androctonus australis*	AaH IT1	Anti-insect agent	[142]
	Buthotus judaicu	Bjα IT	Anti-insect agent	[137]
	Buthus martensii	BmKM1	Anti-insect agent	[140]
	Buthus martensii	Bm 32/33	Anti-insect agent	[144]
	Buthus occitanus	Bot IT1	Anti-insect agent	[135]
	Buthus occitanus mardochei	Bom III/IV	Anti-insect agent	[139]
	Leiurus quinquestriatus	Lqhα IT	Anti-insect agent	[134]
	Leiurus quinquestriatus hebraeus	Lqh III/ VI/ VII	Anti-insect agent	[141]
	Odonthobuthus doriae	OD1	Anti-insect agent	[137]
Spiders	*Loxosceles arizonica*	SMase D	Anti-insect agent	[161]
	Loxosceles intermedia	LiTxx1/ LiTxx2/ LiTxx3	Anti-insect agent	[158]
	Paracoelotes luctuosus	δ-PaluIT1/ δ-PaluIT2	Anti-insect agent	[162]
	Phoneutria nigriventer	Tx4(6-1)	Anti-insect agent	[160]
Ants, Centipedes and Caterpillars	*Pachycondyla goeldii*	Ponericins G1	Insecticide Agent	[238]
		Ponericins G2	Insecticide Agent	[238]
		Ponericins family W	Insecticide Agent	[238]

Table 1. Summary of the main biotechnological/pharmacological applications of toxins from venomous animals.

8. Conclusion

The biodiversity of venoms and toxins made it a unique source of leads and structural templates from which new therapeutic agents may be developed. Such richness can be useful to biotechnology and/or pharmacology in many ways, with the prospection of new toxins in this field. Venoms of several animal species such as snakes, scorpions, toads, frogs and their active components have shown potential biotechnological applications. Recently, using molecular biology techniques and advanced methods of fractionation, researchers have obtained different native and/or recombinant toxins and enough material to afford deeper insight into the molecular action of these toxins. The mechanistic elucidation of toxins as well as their use as drugs will depend on insight into toxin biochemical classification, structure/conformation determination and elucidation of toxin biological activities based on their molecular organization, in addition to their mechanism of action upon different cell models as well as their cellular receptors. Furthermore, expansions in the fields of chemistry and bi-

ology have guided new drug discovery strategies to maximize the identification of biotechnological relevant toxins. In fact, with so much diversity in the terrestrial fauna to be explored in the future, is extremely important providing a further stimulus to the preservation of the precious ecosystem in order to develop the researches focusing on identify and isolate new molecules with importance in biotechnology or pharmacology.

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