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9. Therapeutic use of scorpion venom

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Summary. Scorpion venoms contain a mixture of peptides, free amines, nucleotides, lipids and many other bioactive compounds, that when injected into humans cause a severe systemic inflammation. In some species of scorpions the presence of toxic peptides capable of affecting the normal function of excitable and non excitable cells can lead to a high degree of morbility and mortality, especially among children. The pathophysiology of envenomation involves a highly integrated response that includes the activation of a number of cell types and inflammatory mediators. Excessive immune response induced multiple organ dysfunctions in envenomed patients and/or experimental animals to large extent and contributes to strong inflammatory response. Scorpion venoms contain peptides that block or modify ion-channel function and could present some possible applications to control cell excitability, but also contain proteins that can impair development of parasites or have a potential application as antibiotics. The venom itself is used for production of antibodies in experimental animals (horse and sheep) and is normally used for neutralization of the venom deleterious effects to humans. Specific literature is revised here, concerning the effects of scorpion venom components on T-cell differentiation, autoimmunity, as well as on cardiac, hematological, neoplasic and infectious diseases.

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Introduction

Envenomation of humans by scorpion stings constitutes a serious health problem in certain regions of the word (1). The most important components, responsible for severe intoxication are short- and long-chain peptides that affect ion-channel (Na^+, K^+, Ca^{+2}, Cl^-) function, either by blocking the channels or modifying their gating mechanisms (2). The best known are those specific for Na^+ and K^+ channels (3,4). They cause abnormal depolarization of the cells and if not treated on time can lead to death. However many components might be present: enzymes such as phospholipase A2, proteases, hyaluronidase and other peptides with bradykinin-potentiating, antimicrobial, hemolytic and immune-modulating activities (5). Anti-venoms have been prepared by hyper-immunization of horses, and their immunoglobulins have been purified and are currently used for control of envenomation (see review by Espino-Solis et al., 2009 (6).

However, due to rich variety of components present in these venoms there are some that have shown potential applications as therapeutic agents. The advancements in biotechnology have made it possible to synthesize new natural products such as components of venom purified with therapeutic properties. The therapeutic effects of these agents are usually achieved by mechanisms that are different from that of conventional therapeutic agents. Scorpion and its organs have been used to cure epilepsy, rheumatism and male impotency since medieval times. This review is focus at certain scorpion venom components and their potential applications for the treatment of various diseases including autoimmune, cardiovascular, infectious, inflammatory, hematological and malignant.

1. Scorpions venoms

Scorpion body is divided into three parts: the head (cephalothorax), the abdomen (mesosoma) and the tail (metasoma). 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. The scorpion species that present medically importance belonging to the family *Buthidae* are represented by the genera *Androctonus, Buthus, Mesobuthus, Buthotus, Parabuthus* and *Leiurus* 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 heath problem, with frequent statements that scorpion stings are dangerous. The signs of the

scorpion envenomation are determined by the: a) scorpion species; b) venom composition and c) the victim´s physiological reaction to the venom. The symptoms start immediately with a few minutes after the sting and usually progress to a maximum severity within 5 hours. At this period the massive release of neurotransmitters results in sweating, nausea and vomiting (7,8). The victims may exhibit signs and symptoms involving the central nervous system, stimulation of the autonomic nervous system, and occasionally, respiratory and heart failure, and even death. The victims of scorpion envenoming that presented multi-system-organ failure characterized by changes in hormonal environment with a massive release of counter-regulatory hormones, such as catecholamine, glucagon, cortisol, angiotensin-II, and with decreased levels of insulin and an increase blood glucose level. The grading of these scorpions envenomation depend local signs and whether or not neurological signs predominate. The local signs observed in victims can present effects that can separate in a neurotoxic and cytotoxic local. Central nervous system signs are: sympathetic, parasympathetic, somatic, cranial and peripheral nervous system. The signs are also classified as non-neurological (cardiovascular, respiratory, gastrointestinal, genitourinary, hematological, and metabolic signs), and neurological signs (release of catecholamine from the adrenal glands or the release of acetylcholine from postganglionic parasympathetic neurons) (9).

Scorpions use their venoms for killing or paralyzing their prey. The venom helps the capture and digestion of preys, but also can serve to defend them against predators. The venom is constituted by mucopolysaccharides, hyaluronidase, phospholipase, serotonin, histamine, enzyme inhibitors and proteins usually named neurotoxins (10,11). This reflects millions of years of evolution of specialized venom producing glands. Scorpions are among the oldest (400 million years) living groups of animals. They are represented by 1,500 distinct species and sub-species and their venoms are a mixture of components containing about 50 – 100 distinct polypeptides (12-17).

Scorpion toxins are classified according to their structural properties, mode of action and binding site on different channels or channel subtypes (2,3,18). Several studies have shown the effect and the biochemistry of these toxins (2,18-28). The long-chain toxins affecting sodium channels have been subdivided primarily into two major sub-types, α- and β-toxins (19,20). While the α-toxins bind to receptor site 3 of the voltage-gated Na^+ channels of vertebrates in a membrane-dependent manner and induce a prolongation of the action potential of muscles and nerves (21), the β-toxins present in American scorpions bind to receptor site 4 of vertebrate Na^+ channels producing a shift to a more negative membrane potential (29-38). The β-scorpion toxin is believed to bind, to only one of the four voltage sensors of the sodium channel

(30,32,38-40). In accordance to the classical models of sodium channel gating, the voltage sensors of the sodium channel activate independently, and at least three of them have to be in an activated position for the channel to open (41-44). However, if one of them is activated by the β-toxin, the threshold of activation is unlikely to shift significantly since other voltage sensors remain unaffected.

Sodium channels toxins (NaTx) are critical for generation and propagation of action potentials initiation and propagation in excitable cells (21,29,45). The sodium channel specific toxins are composed of 60-76 amino acid residues and are usually stabilized by four disulfide bridges. They are targeted to various receptors of different organisms, affecting in different manners distinct sub-types of sodium channels through recognition of several receptor sites on the pore-forming α-subunit (30,31,45). Some toxins were shown to be species specific, recognizing only certain types of tissues, such as those from mammals, insects, crustaceans and others (29-31,46,47). Although sodium-channel activators are typically toxic, the sub-type selective inhibitors might have considerable therapeutic potential.

Potassium channels toxins (KTx) play an important role in a large variety of biological processes and their therapeutic value are involved in an increasing number of human pathologies specially autoimmune disorders, inflammatory neuropathies and cancer (14,48). The scorpion toxin that target K^+ channels (KTx) are composed by circa 31-39 amino acid residues. The potassium channels specific toxins are authentic blockers of the channels; they bind to the extracellular face of the channel and impede the flow of ions through the biological membrane. The α-KTx family is constitutes by more than 50 different α-KTx. They have been reported and listed in more than 18 families (3,49-52). Various studies describe the three-dimensional structure of these KTx toxins. In case of *T. serrulatus* venom the neurotoxin α-KTx 12.1 initially named as TsTX-IV is constituted by four disulfide-bridged (3,50,53-56). The voltage gated potassium channel has been shown to play a role in decreasing of T cell activation and delayed type hypersensitivity (57). In venoms of three Brazilian scorpions *T. serrulatus*, *T. bahiensis* and *T. stigmurus*, the butantoxin has shown to block reversibly the potassium channels and inhibit the proliferation of T cells and IL-2 production (54).

More recently two inmunomodulatory peptides (Vm23 and Vm24) were purified from the venom of the Mexican scorpion Vaejovis mexicanus smithi, and described to block with high affinity (picomolar concentration) and high specificity the Kv1.3 channels of human lymphocytes (58). These peptides are supposed to be potential therapeuthic agents for the control of inmunological diseases (59).

Calcium and chloride channel toxins play important roles in regulating a variety of cellular functions such as second messenger-coupling-receptor to active many cellular processes that including cellular excitability, neurotransmitter release, intracellular metabolism and gene expression (14,21). Chlorotoxin specific for Cl^- channels, has only 36 amino acid residues and stabilized by four disulfide bridges.

As earlier mentioned scorpion venom consists of numerous peptides that may interfere with the activity of ion channels and modulate their functional properties. Various studies have been shown that scorpion toxins have different physiological and pharmacological activities with potential therapeutic uses.

Cysteine-free peptides with and without antimicrobial activity
Scorpion venoms have been reported to contain peptides such as:

a) *Cysteine-free antimicrobial peptides (AMP)* capable of self-integrating into mammalian and bacterial membranes to form transmembrane pores, that make the membranes leaky (60,61).
b) *Cysteine-free non-antimicrobial peptides (NAMPs)* which might show the ability of potentiating bradykinin activity (62-64).

Venoms and toxins have found a niche in the pharmaceutical market. Several isolated toxins with known mode of action have practical applications as pharmaceutical agents, diagnostic reagents or preparative tools.

2. Effect of scorpion venom on T-cell differentiation

T lymphocyte response to antigenic challenges is called the immune response. T lymphocytes can be categorized and functionally divided into CD4+ (T helper lymphocytes) cells and CD8+ (cytotoxic T lymphocytes) by the type of antigen receptors and small number of accessory markers on their cell surface. Naive T cells can differentiate into at least two different types of T helpers Th1 and Th2 cells (65).

The presence of IL-12 T-cells undergoing an immune response show varying patterns of cytokine production. The patterns are represented in both T helper and T cytolytic populations, and have been named type 1 and type 2 (65). The original patterns were identified by analysis of murine CD4+ T helper cell clones. Th1/Th2 concept rests largely on a dichotomy of cytokine; however, as with other immune cells, the array of cytokines produced by the Th1 and Th2 cells varies greatly and is influenced by a larger number of experimental variables. Both the Th1 and Th2 cells are produced from a

non-committed population of precursor T cells. The differentiation proceeds within a few days of direct contact with naive cells by APC (65,66). This process is called polarization. The naive T cells may pass through a transient, pre-activation state (T0) on their way to becoming Th1 or Th2 cells. Both subsets contain effector cells that do the immediate work, and memory cells that retain the experience for future action as necessary. The polarization already begins with those cells having the primary contact with antigens, including the DC, monocytes and macrophages, and other APCs. These APC likely polarize into type 1 and type 2 in response to the type of antigen, then subsequently bias the polarization of the T-helper population functionally. The polarization process is driven mainly by cytokines. The Th1 cells differentiation is promoting by IL-12; IFN-α and IL-18; while IL-4 and to extent IL-13 are the cytokines that determine Th2 differentiation.

3. Therapeutic use of scorpion venom

Autoimmune diseases

Immunoregulatory abnormalities have been shown to exist in a wide variety of autoimmune and chronic inflammatory diseases including systemic lupus erythematosis, chronic rheumatoid arthritis, diabetes mellitus types I and II, inflammatory bowel disease, cirrhosis biliar, uveitis, multiple sclerosis and other disorders such as Crohn´s disease, ulcerative colitis, psoriasis, ichthyosis and Graves ophthalmopathy. Although the underlying pathogenesis of each of these conditions may be quite different they have in common the appearance of a variety of autoantibodies and self-reactive lymphocytes. Such self-reactivity may be due, in part to a loss of the homeostatic controls under which the normal immune system operates. The end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Anti-inflammatory agents act principally by blocking the effect or secretion of these mediators without modifying the immunologic basis of the disease. The process of inhibition of potassium channels has been described by immunosuppressive response. Potassium channels can modulate a number of cellular events such as muscle contraction, neuro-endocrine secretion, frequency and duration of action potentials, electrolyte homeostasis, and resting membrane potential. The process of inhibition of potassium channels has been described by immunosuppressive response. Scorpion venoms have been recognized as a source of peptidyl inhibitors of various types of potassium-channels. Some of these peptides are capable of depolarizing human T cells, and preventing inflammatory and proliferative responses, and thus might play a potent treatment of autoimmune diseases, in the prevention of rejection of foreign organ transplants and/or related

afflictions diseases and illness. The recently described Vm23 and Vm24 are capable of decreasing significantly the delay type of hypersensitive (DTH) in rats, applied at very low amounts (10 micrograms per rat), (see 59). In Table 1 are described the peptides with potential for the treatment to autoimmune diseases.

Table 1. Autoimmune diseases.

Scorpion	***Peptide***	***Activity***
Buthus occitanus tunetanus *Buthus tamulus*	Kaliotoxin KTX Limbatustoxin LbTX Iberiotoxin IbTX	To possess greater selectivity for the activated potassium channel (67)
Centruroides margaritatus	Margatoxin MgTX	To depolarize human T-cells immunosuppressive with inhibitor of IL-2 (68-73)
Leiurus quinquestriatus	Charybdotoxin ChTX	To inhibit a number of different medium- and small-condutance Ca^{2+} (74)
Mesobuthus eupeus	MeuKTX	To inhibit T-cell proliferation (75)
Vaejovis mexicanus smithi	Vm23, Vm24	Block Kv1.3 channel of human lymphocytes (58,59)

Antivenom production

Scorpion antivenom treatment, initially introduced in 1909, is still the only method used for the therapy against scorpion stings (76,77). The first application of the venom of scorpions is the preparation of heterologous antibodies capable of been used as anti-venoms. Normally, homogenates of telsons are used to prepare a raw extract that is injected in small dosis to horses and/or sheeps with increasing amounts during several months (78). After a long period of immunization, the blood of the hiper-immunized animal is obtained and the immunoglobulins are purified for use as anti-venoms. Some special antivenoms are also available, which are the same horse antibodies treated with enzymes to produce F(ab)'2 fragments that are used for immunotherapy (Table 2) (6). Recently smaller recombinant fragments, such as classic monovalent antibody fragments (FAB, scFv and engineered variants: diabodies, triabodies, minibodies and single-domain antibodies) are now engineering as credible alternatives. These fragments retain the targeting specificity of whole antibody and can be used for therapeutic applications (79). Single-chain Fvs are a popular format in which the VH and VL domains are joined with a flexible polypeptide linker preventing dissociation. Antibody Fab and scFv fragments, comprising both VH and VL domains, usually retain the

Tabla 2. Antivenoms.

Antivenom	***Scorpion***	***Neutralization***
Alacramyn	*C. limpidus, C. noxius, C. suffusus*	*C. limpidus, C. noxius, C. suffusus*
Antiscorpion	*Tityus serrulatus*	*Tityus spp.*
Polyvalent scorpion antinvenoms	*Leiurus quinquetriatus Androctonus crassicauda*	*A. amoreuxi, A. crassicauda, A. australis: B. arenicola, B. mimax, B. occitanus, L.quinquestriatus hebreus, Scorpiomarus palmatus*

specific, monovalent, antigen binding affinity of the parent IgG, while showing improved pharmacokinetics for tissue penetration (79). In this context, recently single chain antibodies of human origin were developed and shown to be effective for neutralization of scorpion toxin envenomation (80,81,82)

Cardiac diseases

Cardiac diseases are constituted by coronary heart and cerebro-vascular diseases. Peptides from animal venoms are active as bradykinin-potentiating factors are of particular interest because of their strong effect as hypotensive agent. These factors have been found in *Leiurus quinquestriatus*, *Tityus serrulatus*, *Buthus martensii* and *B. occitanus* scorpions. Pharmacologically, these peptides obtained from scorpions venoms act as bradykinin-potentiating peptides and can be used as hypotensive agents in the treatment of hypertension. Moraes et al., 2011 (83) described that sodium channel gating from *Tityus bahiensis* scorpion venom modified present different effects on sodium channel isoforms.

Hematological diseases

The scorpion venom exerts its lethal action by interference with blood coagulation, either by accelerating the process or inhibits the coagulation processes. A peptide with anti-thrombotic action was described to be present in the venom from the scorpion *Buthus martensii* Karsch (84). This same peptide is related to the resistance against platelet aggregation and causes increment of the concentration of prostanglandin I2 in plasma (84). *Tityus discrepans* scorpion venom modifies clotting times in humans. Brazon et al., 2008 (85) described the effect of *T. discrepans* venom on a partial thromboplastin time prothrombin time and its direct clotting activity. This venom contains anticoagulant components which prolong prothrombin time and partial thromboplastic time.

Infectious diseases

Cationic host defense peptides are produced by many organisms as part of their host defense system (86-88). These peptides are considered as antimicrobial agents against microorganisms such as: bacteria, fungi, parasites and virus (36,89). Various studies are shown that the targets of cationic host defense peptides varied from the outer membrane to the signaling pathway (90,91). These peptides are usually constituted of 10-50 amino acids (86). The diversity of scorpion venom is well known to contain about 400 such polypeptides with or without disulfide bonds. In the literature various studies described the presence of cationic host defense peptides in hemolymph and venoms from different species of scorpions.

The vaccination with SARS-CoV, influenza A (H5N1, H1N1) and measles virus have demonstrated variable efficacy. The cationic host defense peptides from scorpion venom can be modified for antiviral activity, especially against SARS-CoV, influenza A and measles virus. Another study described by Li et al., 2011 (92), identified the microporin, a cationic host defense peptide from scorpion venom, which can effectively inhibit bacteria growth. The optimized

Table 3. Infectious diseases.

Scorpion	***Peptide***	***Activity***
Androctonus australis (hemolymph)		Inseticidal fungus and mosquitoes (93)
Hadrurus aztecus	hadrurin	Antimicrobial: *S.typhi, K.pneumoniae, E.cloacae, P.aerugonosa, E.coli, S.marsences* (94)
Isometrus maculates	imcorporin	Antibacterial gram-positive bacteria (95)
Leiurus quinquestriatus	cationic peptid	Antimicrobial (96)
Lychas mucronatus	mucroporin	To inhibit gram-positive and gram-negative bacteria (97)
Opisthacanthus cayaporum	scorpine	Anti-malaria (98)
Opistopthalmus carinatus	opistoporins	Antimicrobial (99)
Pandinus imperator	Scorpine, pandinins	Antimicrobial (100) antimalarial (98)
Parabuthus schlechteri	parabutoporin	Antimicrobial (101)
Scorpion Southern Africa		Antibacterial and antifungi (60,99)
Tityus discrepans	bactridines	To inhibit gram-positive and gram-negative bacteria and anti-leishmanicidal (102-104)
Vaejovis mexicanus	vejovine	Antibacterial *P.aeruginosa, K.pneumoniae, E.cloacae, Acitenobactr baumarii* (96,105)

microporin-M1 can inhibit grow of gram-positive bacteria at low concentrations and antibiotic-resistant pathogens. Table 3 shows some cationic host defense peptide from different scorpions.

Inflammatory response

The inflammatory response is triggered by a cascade of events that includs: systems, cell elements and release of mediators (106). Scorpion venoms can stimulate the release of immunological mediator cytokines. There is now accumulating evidence to suggest a causal relationship between overproduction of certain cytokines such as IL-1 and IL-6 and morbility and mortality associated with critically ill patients. Sofer 1995, (107), was the first that reported the involvement of the inflammatory systems after scorpion envenomation in humans. In this work is documented the increment of IL-6 levels in serum of children severely envenomed by the scorpions *L. quinquestriatus* and *B. judaicus*. The elevated levels of IL-6 were observed at 1 to 3 hours after the sting. The IL-6 levels gradually returned to normal values at 12 and 24 hours measurements, but remained above control levels in all measurements. These results were quite similar to those found by others authors that described the cytokine production after sting caused by *Tityus serrulatus* scorpion in humans (108,109). With respect the experimental animal high levels of cytokines were found in serum from mice injected with *Centruroides noxius* and *T. serrulatus* venom (110,111). In all these works the authors concluded that the activation and release of cytokines may play an important role in the pathophysiology of envenomation after stings and may be responsible for some systemic inflammatory manifestations with cytokine release and organ failure (112). Cytokine have been shown that in local action of cytokines promote recruitment of inflammatory cells to inflammation sites, whereas their systemic effect to induce fever and increase symptoms. During both responses local and systemic are observed the release of pro-inflammatory cytokines, arachidonic acid metabolites proteins of the contact phase and coagulation system, complement factors; it is defined as systemic inflammatory response. Experimental models have been described that following the injection of scorpion venoms and their fractions, a variety of cytokines are released, and the outcome of an inflammatory response is dictated by a variety of factors, that including the duration of the stimulus, and the balance between the pro-inflammatory and anti-inflammatory response. The imbalance determines the degree and extent of inflammation, and thus can lead to multiple organ dysfunctions (112-121). With respect to the tissue injury most of them have been related to the acute autonomic disturbances triggered by the venom, which can provoke both the activation and delayed inactivation

of neuronal sodium channels, where they modulate the release of neurotransmitters, that leads to a variety of adverse effects which include respiratory failure, lung edema, arrythmias, tachycardia followed by bradycardia, skeletal muscle stimulation, lacrimation, convulsions, and enlarged pupils, among others (116,120-128). However, the role of other members of IL-family in envenomation is increasingly appreciated, and in the present work are summarized all currently available information from human and experimental studies. With respect the scorpion envenomation the immune response also is triggered by cascade that including the released of mediators such as nitric oxide, and complement system (112,129).

Multiple sclerosis is an inflammatory disease of the central nervous system characterized by localized areas with demyelination. It is an autoimmune disorder mediated by activated immune cells such as T- and B-lymphocytes and macrophages/microglia. In the venom of the Moroccan scorpion *Androctonus mauretanicus* a peptide was found and characterized, which shows many toxins cross-reaction with lethal α-toxins found in North African scorpion venoms and are considered as potent toxins for treatment of the inflammatory diseases (130).

Malignant diseases

Cancer is the major public health burden in all developed countries. The search for cancer cure from natural product such as plants and animals has been practiced for over a century and the use of purified chemicals to treat cancer still continues. With respect to chlorotoxin, it is considered a potent tool for early detection of skin, cervical, esophageal, colon and lung cancers (131). These ion-channels recognize by this toxin are among the many membrane proteins overexpressed in different types of cancers. Scorpion venoms have been used as traditional and folk therapy in various pathphysiological conditions that has been mentioned in folk and traditional medicine of India, China, Africa and Cuba (131). Various studies have suggested that the cancer preventive and therapeutic efficacy of scorpion venom in different animal tumor models and cell culture systems might be usefull. Bioactivies polypeptides and enzymes as serine proteinase and hyaluronidase extract from scorpion venoms from different species has been exhibited as potential usefull as anti-proliferative agent with anti-tumor activity (131). Table 4 shows some polypeptides and enzymes from scorpion venom with their principal action.

Bioinseticides

Natural venoms are a rich source of molecules that interact with membrane receptors and ionic channels. Due to peptide toxins derived from venoms of a

Table 4. Malignant diseases.

Scorpion	*Peptide*	*Activity*
Androctonus crassicauda		Apoptotic (132)
Buthus martensii Karsch		Anti-proliferative and apoptotic against HUVEC, suppression of tumor growth S180 sarcoma, glioma cells and H22 hepatocellular carcionoma (133-144).
	Serine proteinase-like BMK-CBP	To inhibit the growth of cancer cell line MCF-7 (136)
	Hyaluronidase BmHYA1	Hydrolysis of hyaluronic acid and is potent as cell surface markers in the breast cancer cells line MDA-MB-23 (137)
Buthus occitanus tunetanus	Nontoxic peptide	Adipocyte lypolysis (138)
Heterometrus bengalensis	Bengalin	Anticancer on U937 and K562 cells (139-141)
Leiurus quinquestriatus	Charybtoxin	Anticancer (142-144)
Odontobuthus doriae		Apoptotic and anti-proliferative neuroblastoma cells (132)

variety of invertebrates and lower vertebrates, valuable information about mechanisms of neurotransmission, properties and physiological role of voltage-dependent sodium, calcium and different potassium channels has been obtained. Scorpions deliver a powerful, paralyzing venom, some of the toxins damage only insects. Insect toxin induced a progressive slow depolarization of the membrane potential and repetitive firing of action potentials (145). Several such peptides were isolated from scorpion venoms and their properties as bioisectide described (146). The search for new insect-specific neurotoxin to be used as starting points for the development of highly selective bioinsecticides (Table 5).

Table 5. Bioinsecticides.

Scorpion	*Peptide*
Androctonus australis	AaIT5
Buthacus arenicola	BaIT2
Buthus martensii Karsch *Buthus occitanus tunetanus*	BmKIT5, BotIT4, BotIT5
Buthotus judaicus	BjIT2
Centruroides noxius	Cn10
Leiurus quinquestriatus	LqqIT2
Leiurus quinquestriatus hebraeus	LqhIT2

Conclusion

In summary, most of the evidence that has emerged from the investigation of venom and toxins from scorpions shows a clear therapeutic utility. Apart from the production of specific anti-venoms to save life of people envenomated by scorpion stings, many possible application of scorpion venom components are forseen. Future research in the next decade with venoms and toxins will definitely add information to be used as ion-channels inhibitors for control of cell excitability, immune-modulation of T-cells, antibiotics against bacteria and parasites, peptides for control of agricultural pests, and also for management of neoplasic cells. These complex chemicals derived from animal venom, could provide tools to study more in dept the biology of cancer.

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