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Review

Venoms of Iranian Scorpions (Arachnida, Scorpiones) and Their Potential for Drug Discovery

Seyed Mahdi Kazemi ^{1,*} and Jean-Marc Sabatier ² 

¹ Zagros Herpetological Institute, No 12, Somayyeh 14 Avenue, 3715688415 Qom, Iran

² Institute of NeuroPhysiopathology, UMR 7051, Faculté de Médecine Secteur Nord, 51, Boulevard Pierre Dramard-CS80011, 13344-Marseille Cedex 15, France

* Correspondence: kazemi_m1979@yahoo.com

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Abstract: Scorpions, a characteristic group of arthropods, are among the earliest diverging arachnids, dating back almost 440 million years. One of the many interesting aspects of scorpions is that they have venom arsenals for capturing prey and defending against predators, which may play a critical role in their evolutionary success. Unfortunately, however, scorpion envenomation represents a serious health problem in several countries, including Iran. Iran is acknowledged as an area with a high richness of scorpion species and families. The diversity of the scorpion fauna in Iran is the subject of this review, in which we report a total of 78 species and subspecies in 19 genera and four families. We also list some of the toxins or genes studied from five species, including *Androctonus crassicauda*, *Hottentotta zagrosensis*, *Mesobuthus phillipsi*, *Odontobuthus doriae*, and *Hemiscorpius lepturus*, in the Buthidae and Hemiscorpiidae families. Lastly, we review the diverse functions of typical toxins from the Iranian scorpion species, including their medical applications.

Keywords: scorpion; fauna; venom; toxin; Iran

1. Introduction

Scorpions, a characteristic group of arthropods, diverged from other arachnids relatively early, at about 440 million years ago [1,2]. Their morphology has stayed constant since they adapted to a terrestrial habitat. Their morphological stasis has not been, however, an impediment to successfully colonizing different ecological ecosystems such as caves, high peaks, and deserts [3,4].

Morphological phylogenetic analyses suggest that scorpions are sister taxa to either the rest of the arachnids or to the Opiliones [5]. However, recent phylogenomic analysis suggests that scorpions are closely related to spiders and allies, forming the clade Arachnospulmonata [6,7].

Among the 18 scorpion families with more than 2200 species described in the world, about thirty species have been identified as potentially deadly toxic to humans [8,9].

Our studies on scorpions are based on two remarkable aspects of this group: Their evolutionary origin and systematic classification, and the diversity and origin of their venom components, with emphasis on the use of these components as potential sources of molecules with therapeutic applications [10].

Scorpions have fascinated scientists and laypersons for their venom, which is a complex mixture of bioactive components secreted in specialized organs [11]. These animals inject venom to subdue prey or to defend against attackers. Their venoms consist of a variety of toxins, which may vary according to species, habitat, or fluctuations in climate [12]. Within scorpion venom components, the peptidic fraction has been considered a great source of lead compounds for drugs to treat various cancers and infectious diseases [13]. Hence, studies on scorpion venom components are important, especially in terms of medical treatments for human diseases.

Here, we review the diversity of scorpions in Iran. We also highlight the importance of the venom studies of Iranian scorpions. Establishing what is known about scorpions and scorpion venom in Iran will allow the identification of important gaps to be addressed in the future.

2. Scorpion Species from Iran

Iran is a vast land with diverse climates. There are two main mountain ranges in Iran: (1) Alborz; and (2) Zagros and neighboring mountains. Diverse climates in Iran are the direct result of the presence of the Persian Gulf, the Oman Sea bordering Southeastern Iran, and the Caspian Sea in Northern Iran. According to Safaei-Mahroo et al. [14] 16 terrestrial ecoregions have been reported from Iran including: Arabian Desert and East Saharo-Arabian xeric shrublands (0.1%), Azerbaijan shrub desert and steppe (0.4%), Badkhez-Karabil semi-desert (0.1%), Caspian lowland desert (0.3%), Central Persian desert basins (34.7%), Kopet Dagh semi-desert (0.4%), Registan-North Pakistan sandy desert (3%), South Iran Nubo-Sindian desert and semi-desert (17.3%), Mesopotamian shrub desert (0.1%), Tigris-Euphrates alluvial salt marsh (0.4%), Kopet Dagh woodlands and forest steppe (1.6%), Kuh Rud and Eastern Iran Montane woodlands (7.5%), Caspian Hyrcanian mixed forests (3.4%), Zagros Mountains forest steppe (21.8%), Alborz Range forest steppe (4.3%), and Eastern Anatolian montane steppe (4.6%).

Iran is located in a strategic position in the Palearctic region and is a bridge between the Oriental and African zoogeographical regions, suggesting the possibility of endemic arthropod species in this region. Among these arthropods, scorpions stand out as there are diverse species in desert and semi-desert regions of Iran (for more details see appendix: Table S1).

Historically, the fauna of Iran has been studied by many researchers. The earliest descriptions of the first species were made by Olivier (*Androctonus crassicauda* (Olivier, 1807)) [15]. Later, Alexei Andreevich Byalynitskii-Birulya [16–19] published a series of scorpion studies from Iran that included well known species and several rare taxa [20–26]. In addition, pioneering zoologists such as Pocock [27] and Werner [28] described a few more species in the region. In the middle of the 20th century, Max Vachon carried out preliminary studies on the scorpions of Iran, with a later report of two families, nine genera, and 15 species [29]. Later, Habibi [30] reported 24 species belonging to 11 genera and two families. Farzanpay [31,32] reported fewer species (23 species), but increased the number of genera (17), as well as two families. More recently, Kovařík [23] reported a list of three families, 17 genera, and 32 species of scorpions. A more extensive study of Iranian scorpions continued with publications by Navidpour et al. [33–37], who recorded the dispersal of scorpions in all of Iran. Lastly, Mirshamsi et al. [38] reported 51 species belonging to 18 genera in four families. According to Vachon [29] and Mirshamsi et al. [38], there are *Androctonus baluchicus*, *Androctonus crassicauda*, and *Androctonus finitimus* in Iran. However, Yağmur et al. [39] believed that *Androctonus crassicauda* and *Androctonus robustus* are present in Iran while rejecting the occurrence of *Androctonus baluchicus* and *Androctonus finitimus* in Iran. *Compsobuthus kaffai* and *Compsobuthus sobotniki* were synonymized with *Sassanidotus gracilis* [37,40]. Farzanpay [32] believed that *Hottentotta alticola alticola* are present in Iran but Mirshamsi et al. [38] believed that records show *Hottentotta alticola alticola* are in doubt. Mirshamsi [41] believed that *Mesobuthus phillipsi* includes the *Mesobuthus phillipsi pachysoma* and *Mesobuthus phillipsi mesopotamicus* subspecies. Although Vachon [29], Farzanpay [32], Mirshamsi et al. [38], and Nejati et al. [42], reported *Odontobuthus odonturus* in Iran, Lowe [43] rejected *Odontobuthus odonturus* in Iran. Based on field work, study collections, literature reviews, and personal communications, the total number of species confirmed within the Iranian border is 78 species and subspecies belonging to 19 genera and four families. The family Buthidae is the most diverse with 68 species and subspecies (87.17%), followed by Hemiscorpiidae with seven species (8.97%), Scorpionidae with two subspecies (2.56%), and Diplocentridae with one species (1.28%) [23–26,29,32–42,44–49] (Table S2). Forty-five out of 78 species and subspecies of the Iranian scorpions are endemic to Iran (57.69%, for more details see appendix: Tables S1 and S2).

3. Previous Studies on Drug Discovery of Scorpion Venoms

Animal venoms are a mixture of different compounds for defense and prey capture. Many peptide toxins from deadly animal venoms have been influenced by ion channel (including sodium, potassium, and calcium channels) functions. The ion channels play important roles in the regulation of the heart beat and neuronal excitability [50,51].

Scorpion venoms are certainly important natural drug resources for medical applications. In scorpions, family Buthidae has always been interesting from the public health perspective in terms of their dangerous venoms. Many studies have concentrated on non-Buthidae families and reported several new venom peptides and proteins which have shown unique primary structures and biological activities [52–55]. However, the first disulfide-bridged peptide toxin extracted from a non-buthid scorpion was St20 from *Scorpiops tibetanus*. This peptide has immunosuppressive and anti-inflammatory effects that suggest its potential use as a new peptide medicine for human diseases [56].

Scorpion toxins have been used in variety of fields, including biotechnology (examining the effects on ion channels), identifying cancer mass [57], treating cancer [58], and to treat neuronal [59], autoimmune [60], and cardiovascular diseases [61].

The venoms of *Pandinus imperator* and *Scorpio maurus palmatus* have peptides named imperatoxin A (IpTxa) and maurocalcin (Mca), respectively, and these venoms are of interest in many cardiovascular diseases [62,63].

Classification of polypeptide toxins is important for understanding the structure–function relationship of each individual group. The major criteria used for classification are based on receptor/ion channel specificity (e.g., K^+ , Na^+ , Ca^{2+} and Cl^-), peptide length (e.g., short- and long-chain), structural scaffold α , $\alpha\beta$ and $\beta\alpha\beta\beta$), disulfide bonds (three or four and pairing pattern), the mechanism of action/binding sites (α - or β -like toxins), their cellular target, and others. [64–66]. Ion channels play critical roles in the secretion of hormones, cell proliferation and motility, muscle activity, sense perception, and brain activities of which the functions are applicable for drug development [67,68].

4. Venomic Studies in Iranian Scorpions and Their Potential in Therapeutic

Biologically, venoms of scorpions are diverse and have activity due to their predatory and defensive use in nature [69,70]. In addition, venom of scorpions contains phospholipases A_2 , serine proteases, metalloproteases, lipolysis activating peptides (LVPs) and hyaluronidases, proteins, and peptides (antimicrobial and toxic peptides performing on ion channels) [71–73].

Several peptide toxins in venomous animals are being considered for pharmacological applications, including treating pain, diabetes, multiple sclerosis, and cardiovascular illnesses [12,51,74].

Worldwide, peptides are progressively emerging as a novel class of therapeutics. In total, 438 peptides are represented in the pharmaceutical trade, including 72 in Phase III clinical trials and 48 that have been approved. Four are famous and sold in the pharmaceutical market: Copaxane, Lupron, Byetta, and Forteo [75]. The majority of these peptides act through G protein-coupled receptors or ion channels [74].

5. Scorpion Venom and Cancer Therapy

Several studies have reported that scorpion peptides have antineoplastic activity [76,77]. Some researchers showed that scorpion venoms have potential as a source of drug-like molecules to treat diverse cancers such as human neuroblastoma, leukemia, glioma, brain tumor, breast cancer, melanoma, prostate cancer, and human lung adenocarcinomas [78].

Anti-proliferative, cytotoxic, and apoptogenic properties of scorpion venom peptides on different types of cancers have also been discovered. Scorpion venom peptides with fluorescent labeling have been used to visualize the boundaries of cancerous tissues in cancer patients [78].

For example, the venom of *Androctonus crassicauda* (100 µg/mL) blocked propagation of MCF-7 cells by suppressing S-phase of the cell cycle [79–81]. High doses produce necrosis, killing the cells, while apoptosis diminishes cell growth at lower doses, producing inhibition of growth of breast cancer cells [79].

The venom of *Odontobuthus doriae* causes apoptosis in breast cancer by depolarizing mitochondria membranes and controlling S-phase proliferation in human breast cancer cells. MCF-7, on the other hand, reduced catalase activity, glutathione production, DNA fragmentation, and apoptosis [80].

6. Scorpion Toxin and Ion Channels

Ion channels include voltage-gated sodium, calcium, and potassium channels which create electrical signals required for action potential generation and conduction, and are the molecular targets for a broad range of potent neurotoxins [82].

6.1. Nav or Gated Sodium Channel Specific Toxins

Voltage-gated sodium channels (Na_vs) are composed of transmembrane proteins that conduct sodium ion (Na⁺) into the cytosol upon activation. An Na_v contains a main α-subunit (220–260 kDa) and one or two auxiliary β-subunits (30–40 kDa) [83,84]. The Nav α-subunit is composed of four homologous domains (DI–DIV), each containing six transmembrane α-helices (S1–S6). The α-subunit includes multiple domains, which are involved in pore-forming, voltage-sensing, and Na⁺ selectivity [85]. Na_vs play an important role for action potential (AP) generation and proliferation in excitable cells, including cardiac myocytes, skeletal muscle cells, and neurons [86,87]. Na_vs are also marginally expressed in non-excitabile cells involved in noncanonical roles in controlling some pathophysiological activities [87,88].

Many studies have focused on roles of Na_v subtypes (Na_v1.3, 1.7, 1.8, and 1.9) in nociceptive transduction. These Na_vs probably show attractive targets for analgesic drug discovery. However, their channels also introduce valuable probes to demonstrate the structures, gating properties, and cellular functions of ion channels (for more details see Wu et al. [89]).

Three categories of Na_v toxins can be defined: (1) Pore-blocking toxins that inhibit Na⁺ conductance by interacting with neurotoxin site 1, including tetrodotoxin (TTX), µ-conotoxins, and saxitoxin (STX); (2) toxins that negatively shift the activation voltage and produce a persistent activation by connecting to membrane-embedded neurotoxin site 2 (such as veratridine, grayanotoxin, and batrachotoxin), or 5 (such as ciguatoxin and brevetoxin), and that prefer to interact with the open state of channel; and (3) toxins that delay inactivation by binding to extracellular neurotoxin site 3, such as sea-anemone toxins and α-scorpion toxins. According to recent investigations, β-scorpion toxins shift activation voltage to either a depolarized or hyperpolarized direction through main effects of neurotoxin site 4. Delta-conotoxin prolongs channel inactivation, similarly to that caused by α-scorpion toxins, by binding to neurotoxin site 6. Although the neurotoxin binding sites are topologically distinct, allosteric coupling has been elucidated between sites 3 and 6 and between sites 2 and 5 [90,91]. In addition, four β-subunits (β1–β4; encoded by *SCN1B-4B* genes) have been reported in mammals. The β-subunits are type I transmembrane proteins, including an extracellular signal peptide in the N-terminus, a transmembrane segment, and an immunoglobulin domain [92,93]. Both excitable and non-excitabile cells have considerable amounts of β-subunit expression that plays critical roles in modulating the localization, kinetics, and gating of Na_v α-subunits [87,91,93,94].

There are several studies that provide evidence of these mechanisms. As described above, there are several kinds of toxins in scorpion venoms that modulate the activity of ion channels, and these are usually responsible for several signs of envenoming. From the human perspective, the most medically important toxins are those that modulate mammalian Na_v channels [64,69].

The first neurotoxin targeting voltage-gated sodium channels extracted from an Iranian scorpion venom (*Odontobuthus doriae*) was OD₁, which blocks the fast inactivation of mammalian channels Na_v1.7, Na_v1.4, and Na_v1.6 [95,96]. Additionally, OD₁ inhibits fast inactivation of the para/tipE insect

channel (EC_{50} 80 nM), but it scarcely influences mammalian $Na_v1.3$ or $Na_v1.5$ ($EC_{50} > 1 \mu M$) and has no effect on $Na_v1.2$ and $Na_v1.8$. OD_1 rapidly induces pain when injected into animals in association with, or without, veratridine, and has been used to test the analgesic effects of $Na_v1.7$ blockers in vivo [96,97]. In fact, dose-dependent increases in the amplitude of Na^+ currents resulting in incomplete inactivation in steady-state conditions has been demonstrated by OD_1 [98,99]. It is probable that continuous inward Na^+ current causes sustained depolarization of the cell membrane, and the remaining $Na_v1.7$ channels that were not affected by OD_1 are trapped in the inactivated state, resulting in the loss of electrical excitability of nociceptor neurons [97,98].

Buthotus schach venom is an important source of active peptides, some of which affect voltage-gated sodium channels involved in local pain, inflammation, convulsion, necrosis, respiratory depression, and cardiac arrest in humans [100,101].

6.2. K^+ Channel Specific Scorpion Toxins

Potassium channels are the most abundant ion channels and are found in all living organisms [102]. The channels are involved in the resting potential, and shape the action potential, in nerves and muscles [67]. Most potassium channels are composed of tetramers of principal α -subunits (heteromeric assemblies are more common) [103], with auxiliary β -subunits as complementary parts [104]. There are 78 genes encoding α -subunits of potassium channels in the human genome divided into five classes: K_{ir} , K_{2P} , K_V , and two groups of K_{Ca} [105–108].

Based on many studies, potassium channel ligands are probably classified into two large groups. These are pore blockers that physically obstruct the channel pore, and gating modifiers that influence channel traits [82]. The potassium channel ligands can be metal ions, low-molecular-mass substances, and polypeptides [109].

Scorpion venom has K^+ channel specific toxins (KTx). Thus far, 293 KTxs have been described in UniProt and 174 KTxs have been described in the Kalium database at <http://kaliumdb.org/> [110,111]. The toxins interact with different subtypes of channels, such as the K_{v1} , K_{v3} , K_{v4} , K_{v7} , K_{v11} , and K_{Ca} channels [112].

Venom of scorpions are an important source of K^+ channel specific toxins (KTx), and are important tools for the structural and functional characterization of various K^+ [113,114]. K_V channel inhibitors have medical applications in the treatment of various specific human diseases, especially autoimmune disorders, inflammatory neuropathies, and cancer [111].

Autoimmune diseases are usually accompanied by tissue injury caused by autoantigen-specific T-cells. $K_V1.3$ channels contribute to the control of calcium signaling to induce T-cell proliferation, immune activation, and cytokine production. In many autoimmune diseases, effector memory T (TEM) cells, which play major roles, are controlled by blocking $K_V1.3$ channels on the membrane. Animal toxins are capable of suppressing the activation and proliferation of TEM cells and may improve TEM cell-mediated autoimmune diseases, for example in multiple sclerosis and type I diabetes mellitus [115].

The first K^+ channel toxin isolated from the venom of the Iranian scorpion *Odontobuthus doriae* (OdK_1) was categorized as α -KTx 8.5. The pharmacological effects of OdK_1 were investigated on *Xenopus laevis* oocytes heterologously expressing $K_V1.2$ channels. OdK_1 selectively blocked the currents through $K_V1.2$ channels, with no effect on the other channels tested [116].

There is a $K_V1.3$ channel-selective toxin, OdK_2 , in venom of *Odonthobuthus doriae*, one of the endemic scorpion species of Iran. OdK_2 is composed of 38 amino acid residues, including six conserved half-cystine residues and a C-terminal lysine residue. The toxin was named KTX3.11. Pharmacologically, OdK_2 selectively suppresses the currents via $K_V1.3$ channels. [117].

Hemitoxin (HTx), a K^+ channel blocker, was isolated from the venom of *Hemiscorpius lepturus*, which is classified in subfamily six of the α -KTx family of potassium channel scorpion toxins and has the highest amino acid sequence similarity with maurotoxin (MTX), extracted from the Tunisian scorpion *Scorpio maurus palmatus*. Additionally, MTX is also a K^+ channel inhibitor with 34 (instead of 35) amino acid residues.

HTX reversibly inhibits type $K_v1.1$, $K_v1.2$, and $K_v1.3$ channels. HTX has subtype-selective effects on K^+ channels. It is 20 times less potent on $K_v1.2$ channels, and 90 times more potent on $K_v1.3$ channels, compared to the α -KTx6 family member MTX [118].

6.3. Ca^{2+} Release-Channel Specific Peptides (Calcins)

Voltage-gated calcium channels (Ca_v) play a critical role in electrical signaling, converting depolarization of the cell membrane to an influx of calcium ions that initiates contraction, secretion, neurotransmission, and other intracellular regulatory events [92]. Voltage-gated calcium channels (Ca_v) facilitate cellular calcium influx in response to membrane depolarization. They control hormone secretion, neurotransmitter release, propagation of cardiac action potential, muscle contraction, and gene expression in different cell types [119]. Similarly to the Na_v channels, the $\alpha 1$ subunit of Ca_v channels is organized in four homologous domains (I–IV), each containing six TM segments (S1–S6). The S1–S4 segments are involved in the voltage sensor, whereas S5–S6 constitutes the pore. Auxiliary subunits usually associate with $\alpha 1$, regulating channel expression and function. Ca_v channels are classified in the following groups in terms of electrophysiological and pharmacological properties and tissue distribution—L-type (Ca_v1 subfamily: $Ca_v1.1$ – $Ca_v1.4$); P/Q-, N-, and R-types ($Ca_v2.1$, $Ca_v2.2$ and $Ca_v2.3$, respectively); and T-type (Ca_v3 subfamily: $Ca_v3.1$ – $Ca_v3.3$) [120].

The various subfamilies have been presented for classification of calcium channels as follows: Voltage-gated channels, voltage independent channels, and ligand-activated channels. Ligand-activated channels include the ryanodine receptors (RyRs), which are high-permeability Ca^{2+} channels of the sarcoplasmic reticulum in muscle and of the endoplasmic reticulum in other cells. In striated muscle fibers, contraction has been carried out via RyRs that releases Ca^{2+} rapidly. There are various isoforms of ryanodine-sensitive calcium channels including RyR_1 , RyR_2 , and RyR_3 . In mammals, RyR_1 is expressed mainly in skeletal muscle and RyR_2 is expressed mainly in cardiac muscle. RyR_3 seems to be confined to the brain, smooth muscle, and epithelial cells. RyR_1 and RyR_2 are expressed in some of these tissues as well. The activity of surface-membrane Ca^{2+} channels, the dihydropyridine receptors (DHPRs), stimulates the activation of RyRs during the early part of the excitation–contraction linking cascade [121,122].

There is selective activity on ryanodine receptors (RyRs) by the venom of *Hadrurus gertschi* [123].

In *Odontobuthus doriae*, one calcium channel toxin was recognized and is referred to as ODCaTx₁ (ID: KU365856) [124]. It shares 91% of its identity with the ryanodine receptor toxin isoform 2 isolated from *Hottentotta judaicus* [125]. Analysis and characterization of this peptide could produce remarkable biological and therapeutic research [124].

Hemicalcin is a new toxin that was extracted from the venom of *Hemiscorpius lepturus*, it represents 0.6% of the total protein content [126].

6.4. Cl^- Channels (CLCs)

CLC chloride channels contain one pore per subunit (a ‘double-barreled’ channel), and also provide clues about gating and permeation [127]. Cl^- channels are classified into three groups: Ligand-gated Cl^- channels, the cystic fibrosis transmembrane conductance regulator (CFTR) channel, and the CLC channels [128]. The mammalian CLC family contains nine members, divided into three subgroups. It includes plasma membrane channels and Cl^-/H^+ antiporters that are thought to contribute to plasma membrane transport, lysosomal acidification, and the maintenance of the cell membrane potential [128–130].

Short scorpion toxin chloride channel inhibitors are short-chain neurotoxins (SCNs) that block small-conductance chloride channels. They are 30–40-residue long and contain four intramolecular disulfide bridges, which have been labeled as C1–C4, C2–C6, C3–C7, and C5–C8 [131–133].

According to Naderi Soorki et al. [124], one chloride channel-acting toxin, ODCITx₁, was identified in *Odontobuthus doriae* venom (ID: KU-365857); it is composed of four intramolecular disulfide bridges and a putative conserved domain belonging to the toxin-5 superfamily. There are a variety of secreted

short scorpion toxins in the superfamily. Such toxins are not associated with the toxin-2 superfamily (pfam00451) that affects potassium channels [124].

7. Antimicrobial Peptides

These days, antimicrobial components represent one of the important resources for modern medical care [134]. Natural antimicrobial peptides (AMPs) have been extracted from scorpion venom, are broadly expressed, and exert different effects on bacteria, viruses, fungi, and parasites [135]. Recently, 871 peptides/proteins have been discovered from 72 scorpion species [71]. Of these molecules, 638 peptides (73%) are from 47 scorpion species of the Buthidae family [71]. These consist both of disulfide-bridged peptides (DBPs), and of non-disulfide-bridged peptides (NDBPs) [55,136,137]. According to Almaaytah and Albalas [52], DBPs cause neurotoxic effects, and NDBPs reveal diverse structures and activities. There is generally more antimicrobial activity in NDBPs, which contain 13–56 amino acid residues; their amino acid sequences show structural diversity and multifunctional activity. So far, more than 40 peptides have been recognized and functionally categorized from scorpion venoms. Therapeutic and biological applications of NDBPs are related to their antibacterial, antifungal, antiviral, insecticidal, antimalarial, anticancer, cytolytic, anti-inflammatory, immune-modulatory, and bradykinin potentiating activities [52].

Globally, approximately 36.7 million people suffer HIV, but still there is no definite cure to eradicate HIV transmission [138]. The five antimicrobial peptides (AMPs) of scorpion venoms have been separated to evaluate potential anti-HIV effects. Three of them (mocoporin-M1, BmKn₂, and Kn₂₋₇) showed powerful anti-HIV activity [78].

Moreover, some distinctive characteristics of scorpion physiology are related to the mixture, and to individual effects. These properties are mostly found in the Buthidae family, whose venom is pharmacologically the most important and prominent compared to non-buthids. Hemocyanin is a protein for transporting oxygen in all scorpions and has the ability to bind with molecular oxygen in reverse. The protein has three parts with an enzymatic role: Pseudo-catalase, peroxidase, and superoxide-dismutase [139–141]. Additionally, the hemocyanins probably have an antimicrobial function from multiple oxidative enzymatic activities [142].

Hemiscorpius lepturus scorpion venom contains several components with significant anti-HIV activity, suggesting it as a potential source of novel therapeutic agents against HIV infection [143].

An antimicrobial toxin extracted from *Mesobuthus eupeus* venom glands was isolated that was encoded by a 213 bp cDNA fragment. The full-length sequence of the coding region was 210 bp and included an open reading frame of 70 amino acid residues with a predicted molecular mass of 7970.48 Da and theoretical pI of 9.10. The precursor (70 amino acid residues) includes a signal peptide of 23 amino acid residues and a mature peptide of 34 amino acid residues with no disulfide bridge. The resulted peptide of *Mesobuthus eupeus* has been named MeVAMP-2 (98%), MeVAMP-9 (60%). The other AMPs have been reported from *Mesobuthus martensii* (94%) and *Buthus occitanus israelis* (82%) [144].

There are six AMPs in venom of *Odontobuthus doriae*, called ODAMP1-6. Four of them (ID: KU212813, KU212814, KU212815, KU212816) have signal peptides with peptides containing 55, 51, 52, and 51 amino acid residues, respectively. There are no signal peptides in ODAMPs (ODAMP1, 6). ODAMP1 (ID: KU212812) has 78 amino acid residues and resembles the antimicrobial peptide androcin 18-1 from *Androctonus bicolor* scorpion (78% identity). ODAMP6 (ID: KU365855) is a short chain peptide with only 47 amino acid residues, which is similar to Tx65 with antimicrobial activity from *Buthus occitanus israelis* (100% identity), and which could be beneficial and applicable in drug and food industries [124].

8. Metalloproteinases

Matrix metalloproteinases (MMPs) affect cellular activities like growth and cell differentiation directly or indirectly [145–147]. In addition, MMP plays a role in cellular connection to the matrix

using proteolysis of the adhesion places [148]. The enzymes can effect an increase and survival of tumor cells [149]. Metalloproteases of venom component play important role in hemorrhage [150]. Metalloproteinase sequences that have been identified in the transcriptome of *Odontobuthus doriae* include ODVP4; KU365871 [124] and those in *Hemiscorpius lepturus* include HLMP1; KX924496, HLMP2; KX924497, HLMP3; KX924498 [151–153].

9. Phospholipase A2 (PLA2)

Phospholipases (PLA) (types A₁, A₂, C, and D) are a type of enzyme with a high disulfide bridge content and a conserved histidine/aspartic catalytic dyad. They that act on phospholipids to produce different products, including lysophospholipids, diacylglycerols (DGs), free fatty acids (FFAs), choline phosphate, and phosphatidates [154,155]. The four main groups of superfamily Phospholipase A₂ (PLA₂) include secreted (sPLA₂), cytosolic (cPLA₂), calcium independent (iPLA₂), and platelet activating factor acetyl hydrolase (PAF-AH) or lipoprotein PLA₂ (LpPLA₂). In vertebrates and invertebrates, the most common type of PLA is sPLA₂, which is grouped into 15 types [156–159].

Secretory phospholipase A2 (sPLA₂) is the most common type of phospholipase observed in animals including vertebrates and invertebrates. According to primary sequences alignments, disulfide bond pattern, and their biochemical properties, it is divided into 15 groups [157,159]. The low molecular weight of sPLA₂ is 13–15 kDa, with approximately six to eight disulfide bonds [154].

sPLA₂ of scorpion venom are considered as group III and contained a long enzymatic chain and a short covalently fixed C-terminal chain generated after the release of five residues (penta-peptide) during the maturation processes [160]. HfPLA₂ has been extracted from a scorpion named *Heterometrus fulvipes* [161], MtPLA₂ from *Mesobuthus tamulus* [162], Imperatoxin (IpTx) [163] and Phospholipin from *Pandinus imperator* [164], Phaiodactylipin from *Anuroctonus phaiodactylus* [165], Heteromtoxin (HmTx) from *Heterometrus laoticus* [166], Hemilipin from *Hemiscorpius lepturus* [167], and Sm-PLVG from *Scorpio maurus* [168]. *Hemiscorpius lepturus* has potent phospholipase D activities that have been related to the highly toxic (even lethal) necrosis activity of the venom [169].

In addition, a novel sPLA₂ named hemilipin was recently isolated from dangerous scorpion of Iran, *Hemiscorpius lepturus* [167]. Edman degradation revealed its primary structure, and titration of fatty acids elucidated its enzymatic PLA₂ activity on egg yolk phospholipids. Hemilipin widely affects angiogenesis in vitro and in vivo, whereas it doesn't have any effect on apoptosis. Additionally, the study demonstrated that this new non-toxic sPLA₂ could be used as an innovative tool to disrupt human angiogenesis at various points [167]. In a subsequent study, Jridi et al. [170] proposed a second sPLA₂: Hemilipin₂. This component has a robust calcium-dependent PLA₂ activity and influences angiogenesis without any cytotoxic or apoptotic effects both in vitro and in vivo. However, there is a prominent capability in hemilipin₂ to prevent blood vessel formation both in vitro and in vivo. The results suggest a beginning point to produce novel molecules that act as specific suppressors of human angiogenesis.

10. Protease and Serine Protease Inhibitors

Proteases are a kind of enzymes which are necessary to preserve homeostasis in cell. So far, 12 protease therapies have been proposed by the U.S. FDA (Food and Drug Administration) [171]. Based on Cao et al. [172], proteases control cellular events by growth factors, cytokines, chemokines, and cellular receptors, both through activation and inactivation leading to downstream intracellular signaling and gene regulation. Upregulation of proteolysis is related to different types of cancer and tumor metastasis, invasion, and growth [173].

Protease peptide inhibitors that occur in scorpion venoms have broad applications in medicine. Accordingly, proteases and protease inhibitors have important affects in pharmacology [171].

Protease inhibitors (PIs) are kinds of proteins or peptides which can be used to inhibit the catalytic activity of proteolytic enzymes [174]. SPIs have been found in scorpions and are classified in two groups—(1) Kunitz-type inhibitors, and (2) Ascaris-type inhibitors [174].

10.1. Kunitz-Type Inhibitors

Kunitz-type inhibitors are a group of serine protease inhibitors that are specified by a conserved spacing between their cysteine residues. There are one or more Kunitz domains in the inhibitor and these possess a typical disulfide bonding pattern [175,176]. Kunitz-type inhibitors are frequently found in arthropod venoms. In the scorpion and spider venoms, these peptides have dual functions [177].

10.2. Primary Sequence of Kunitz-Type Inhibitors

All the Kunitz-type protease inhibitors of scorpions have been recognized by the primary amino acid sequences of some inhibitor peptides that have been found in the NCBI protein data bank [174].

10.3. Ascaris-Type Inhibitors

Ascaris-type peptides usually possess a conserved structure with four short β -strands organized in two approximately vertical β -sheets and stabilized by five disulfide bridges: C1–C7, C2–C6, C3–C5, C4–C10, and C8–C9 [178].

10.4. Primary Sequence of Ascaris-Type Inhibitors

The sequences of all the Ascaris-type protease inhibitors of scorpions which have been found in NCBI protein data bank [174].

10.5. Functional Diversity of Protease Inhibitors

Some of Kunitz-type protease inhibitors of scorpions have been found to inhibit potassium channel $K_v1.3$ [179]. Seven Kunitz-type protease inhibitors (LmKTT-1a, LmKTT-1b, LmKTT-1c, BmKTT-1, BmKTT-2, BmKTT-3, and Hg1) were tested on voltage-gated potassium channel subtype 1.3 ($K_v1.3$ channel) and it was found that six of seven scorpion toxins, excepting rBmKTT-3, which had weak activity, inhibited ~50–80% of $K_v1.3$ channel currents at a concentration of 1 μ M [174].

The serine proteinase inhibitor (serpin) superfamily participates in various necessary biological processes such as blood coagulation, complement activation, fibrinolysis, angiogenesis, inflammation, and tumor suppression. The members of this superfamily are expressed in a cell-specific manner [180]. Because of the abundance of Kunitz-type protease inhibitors in several organisms, they are the best-characterized family of serine protease inhibitors [181]. Two full-length coding sequences of *Hemiscorpius lepturus* transcriptome were coded as serine proteinase (KX932440 and KX932441 [152].

However, four putative serine protease inhibitors were discovered from the venom of three scorpion species including SjAPI (*Scorpiops jendeki* Ascaris-type protease inhibitor), SjAPI-2 (*Scorpiops jendeki* Ascaris-type protease inhibitor 2), CtAPI (*Chaerilus tricostatus* Ascaris-type protease inhibitor), and BmAPI (*Buthus martensii* Ascaris-type protease inhibitor) [182].

11. Scorpionism in Iran, a Major Public Health Problem

The risk of scorpion stings in rural areas is higher than in urban regions, and also more common in summer [183]. Much attention has been paid to the mortality rate of scorpion stings, whereas the incidence of scorpion stings is generally underestimated [8].

Scorpions are the most dangerous venomous animals for humans after snakes (venomous snakes) [184].

Climatic conditions, dryness, and heat are factors that increase the threat of scorpion stings [185]. Khuzestan is a province that is located in Southwestern Iran, along with the Persian Gulf region, with a hot and tropical climate. Scorpion stings are a main public health issue in the region especially for children and young adolescents [186]. In the Old World, Iran is acknowledged as one of the world's hotspots for scorpionism [187].

Annually, more than 42,500 scorpion stings from 2001 to 2009 have been reported with about a 19.5% fatality rate. *Hemiscorpius lepturus*, *Androctonus crassicauda*, *Mesobuthus eupeus*,

Odontobuthus doriae, *Hottentotta saulcyi*, *Hottentotta schach*, *Compsobuthus matthiesseni*, *Olivierus caucasicus*, *Orthochirus scrobiculosus*, and *Apistobuthus pterygocercus* are significant species in terms of medical and pharmacological relevance. Among Iranian scorpions, *Androctonus crassicauda* and *Hemiscorpius lepturus* have the highest risk of envenoming humans [188,189]. Distribution of *Androctonus crassicauda* (Figure 1) and *Hemiscorpius lepturus* (Figure 2) in Iran.

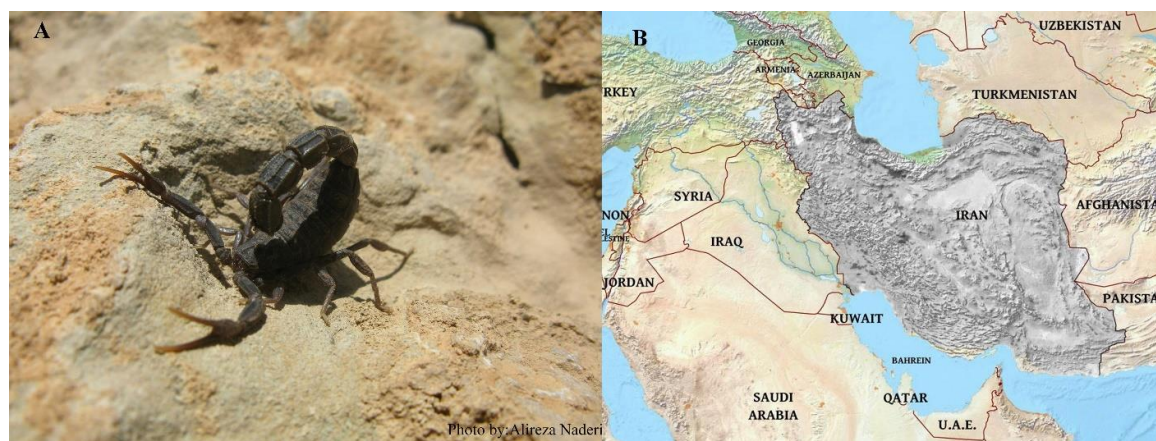


Figure 1. *Androctonus crassicauda* in its natural habitat (A) and its distribution map in gray (B).



Figure 2. Image of *Hemiscorpius lepturus* in its natural habitat (A) and its distribution map in green (B).

According to Shahbazzadeh et al. [190], 12,150 scorpion stings were reported from medical centers in six cities in the Khuzestan province in 2003. The prevalence of human scorpion stings is 3.1/1000 residents. By region, the highest prevalence is in Masjed-Soleiman (27.1%), followed by Ramhormoz (26.6%), Izeh (15.3%), Shush (12%), Baghmalek (11.7%), and Behbahan (7.3%). The most scorpion stings are inflicted by *Mesobuthus eupeus*, *Hottentotta saulcyi*, *Odontobuthus doriae*, and *Hemiscorpius lepturus*, responsible for 53.3%, whereas 17.4% were related to *Androctonus crassicauda* and *Hottentotta schach*, and 29.3% to other species. The maximum and minimum frequencies occur in June and February, respectively.

According to Mirshamsi et al. [48], specimens of *Mesobuthus eupeus* from Southwestern Iran belong to *Mesobuthus phillipsi*. Thus, all specimens of *Mesobuthus eupeus* in previous studies [144,191] should be considered *Mesobuthus phillipsi*. Based on Kovařík [23], all specimens of *Buthotus schach* or *Hottentotta schach* in prior research [100,101,188–190] should be considered *Hottentotta jayakari*, *Hottentotta khoozestanus*, and *Hottentotta zagrosensis*. Based on Lourenço [192], Mirshamsi et al. [38], and Navidpour and Lowe [193], there is no *Apistobuthus pterygocercus* in Iran and all specimens of *Apistobuthus pterygocercus* belong to *Apistobuthus susanae*, so all specimens of *Apistobuthus pterygocercus* in prior research [188,189] should be considered *Apistobuthus susanae*. The Razi Vaccine and Serum

Research Institute, Hesarak, Karaj produces antivenoms of scorpions including six of the most dangerous scorpion species, including *Androctonus crassicauda*, *Hottentotta saulcyi*, *Hottentotta schach*, *Mesobuthus eupeus*, *Odontobuthus doriae*, and *Hemiscorpius lepturus* in Iran.

The Razi Vaccine and Serum Research Institute (Department of Venomous Animals and Antivenin Production) extracts venoms of *Hottentotta jayakari*, *Hottentotta khoozestanus*, *Hottentotta lorestanus*, and *Hottentotta zagrosensis*. These have previously been considered as *Hottentotta schach*, but occur in the southern provinces of Iran. Venoms of *Mesobuthus brutus*, *Mesobuthus caucasicus*, and *Mesobuthus phillipsi* have been considered as *Mesobuthus eupeus*. According to Mirshamsi et al. [38,48] and Fet et al. [45], specimens of *Mesobuthus eupeus* should be named *Mesobuthus brutus*, *Mesobuthus caucasicus*, and *Mesobuthus phillipsi* based on geographical distribution. Also, According to Kovařík [23] and Navidpour et al. [33,35], specimens of *Hottentotta schach* should be named *Hottentotta jayakari jayakari*, *Hottentotta khoozestanus*, *Hottentotta lorestanus*, and *Hottentotta zagrosensis*. The Department of Venomous Animals and Antivenin Production, Razi Vaccine and Serum Research Institute should recognize the specimens carefully and then produce high quality scorpion antivenoms.

In conclusion, studying toxins of scorpion species from Iran is a way to present patterns and connection between species of scorpion and their venoms, which could be useful for understanding the molecular and functional diversities of scorpion venom sources, their evolutions, and probably the connection between scorpion species and their toxins.

Supplementary Materials: The following are available online, Table S1: List of Scorpion species of Iran. Asterisk indicates endemic species, Table S2: Number and percentage of scorpions in Iran.

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References

1. Dunlop, J.A.; Selden, P.A. Scorpion fragments from the Silurian of Powys, Wales. *Arachnology* **2013**, *16*, 27–32. [[CrossRef](#)]
2. Waddington, J.; Rudkin, D.M.; Dunlop, J.A. A new mid-Silurian aquatic scorpion—One step closer to land? *Biol. Lett.* **2015**, *11*, 20140815. [[CrossRef](#)] [[PubMed](#)]
3. Polis, G.A. Ecology. In *The Biology of Scorpions*; Polis, G.A., Ed.; Stanford University Press: Palo Alto, CA, USA, 1990; p. 587.
4. Santibáñez-López, C.E.; Francke, O.F.; Ureta, C.; Possani, L.D. Scorpions from Mexico: From species diversity to venom complexity. *Toxins* **2016**, *8*, 2. [[CrossRef](#)] [[PubMed](#)]
5. Shultz, J.W. A phylogenetic analysis of the arachnid orders based on morphological characters. *Zool. J. Linn. Soc.* **2007**, *150*, 221–265. [[CrossRef](#)]
6. Sharma, P.P.; Kaluziak, S.T.; Pérez-Porro, A.R.; González, V.L.; Hormiga, G.; Wheeler, W.C.; Giribet, G. Phylogenomic interrogation of Arachnida reveals systemic conflicts in phylogenetic signal. *Mol. Biol. Evol.* **2014**, *31*, 2963–2984. [[CrossRef](#)] [[PubMed](#)]
7. Sharma, P.P.; Fernández, R.; Esposito, L.; González-Santillán, E.; Monod, L. Phylogenomic resolution of scorpions reveals multilevel discordance with morphological phylogenetic signal. *Proc. R. Soc. B* **2015**, *282*, 20142953. [[CrossRef](#)] [[PubMed](#)]
8. Chippaux, J.P.; Goyffon, M. Epidemiology of scorpionism: A global appraisal. *Acta Trop.* **2008**, *107*, 71–79. [[CrossRef](#)] [[PubMed](#)]

9. Lourenço, W.R. Scorpion diversity and distribution; past and present patterns. In *Scorpion Venoms, Toxinology*; Gopalakrishnakone, P., Possani, L.D., Schwartz, E.F., Rodríguez de la Vega, R.C., Eds.; Springer + Business Media: Dordrecht, The Netherlands, 2015; pp. 3–23.
10. Smith, J.J.; Vetter, I.; Lewis, R.J.; Peigneur, S.; Tytgat, J.; Lam, A.; Gallant, E.M.; Beard, N.A.; Alewood, P.F.; Dulhunty, A.F. Multiple actions of phi-LITX-Lw1a on ryanodine receptors reveal a functional link between scorpion DDH and ICK toxins. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 8906–8911. [[CrossRef](#)]
11. King, G.F. Venoms to Drugs: Translating Venom Peptides into Therapeutics. *Aust. Biochem.* **2013**, *44*, 13–15.
12. Rodríguez de la Vega, R.C.; Schwartz, E.F.; Possani, L.D. Mining on scorpion venom biodiversity. *Toxicon* **2010**, *56*, 1155–1161. [[CrossRef](#)]
13. Ortiz, E.; Gurrola, G.B.; Schwartz, E.F.; Possani, L.D. Scorpion venom components as potential candidates for drug development. *Toxicon* **2015**, *93*, 125–135. [[CrossRef](#)] [[PubMed](#)]
14. Safaei-Mahroo, B.; Ghaffari, H.; Fahimi, H.; Broomand, S.; Yazdani, M.; Najafi-Majd, E.; Hosseini, Y.; Yousefkhani, S.S.; Rezazadeh, E.; Hosseinzadeh, M.S.; Nasrabadi, R.; et al. The herpetofauna of Iran: Checklist of taxonomy, distribution and conservation status. *Asian Herpetol. Res.* **2015**, *6*, 257–290.
15. Olivier, G.A. *Voyage dans l'Empire Ottoman, l'Égypte et la Perse, fait par Ordre du Gouvernement, Pendant les Six Premières Années de la République*; Agasse, C.H., Ed.; Imprimeur-Libraire: Paris, France, 1807; Volume 3, pp. 96–98.
16. Birula, A.A. Beiträge zur Kenntniss der Skorpionenfauna Ost-Persiens (1. Beitrag). *Bull. Acad. Imp. Sci. St.-Petersbg. Sér.* **1900**, *12*, 355–375.
17. Birula, A.A. Beiträge zur Kenntniss der Skorpionenfauna Ost-Persiens (2. Beitrag). *Bull. Acad. Imp. Sci. St.-Petersbg. Sér.* **1903**, *19*, 67–80.
18. Birula, A.A. Beiträge zur Kenntniss der Skorpionenfauna Persien (3. Beiträge). *Bull. Imp. Acad. Sci. St.-Petersbg. Sér.* **1905**, *23*, 119–148.
19. Birula, A.A. Fauna of Russia and Adjacent Countries. Arachnoidea, Scorpions. *Fauna Rossii St. Petersburg. Acad. Sci. Mus. Zool.* **1917**, *1*, 1–224; English translation by Israel Program for Scientific Translations, Jerusalem 1965, 154p.
20. Fet, V. New for the USSR genus and species of scorpions from Badkhyz, *Kraepelinia palpator* (Birula, 1903) (Scorpiones, Buthidea). *Proc. Acad. Sci. Turkm.* **1984**, *4*, 37–43. (In Russian)
21. Fet, V. *Neohemibuthus zarudnyi* (Birula, 1903) from Iran, a senior synonym of *N. kinzelbachi* Lourenço, 1996 (Scorpiones, Buthidae). *Rev. Arachnol.* **1997**, *12*, 65–68.
22. Fet, V.; Capes, E.M.; Sissom, W.D. A new genus and species of psammophilic scorpion from eastern Iran (Scorpiones: Buthidae). In *Scorpions 2001*; Gary, M., Polis, A., Fet, V., Selden, P.A., Eds.; British Arachnological Society: Bucks, UK, 2001; pp. 183–189.
23. Kovařík, F. Results of the Czech Biological Expedition to Iran. Part 2. Arachnida: Scorpiones, with descriptions of *Iranobuthus krali* gen. n. et sp. n. and *Hottentotta zagrosensis* sp. n. (Buthidae). *Acta Soc. Zool. Bohem.* **1997**, *61*, 39–52.
24. Kovařík, F.; Navidpour, S.; Soleglad, M.E. *Hemiscorpius shahii* sp. n. from Iran (Scorpiones: Hemiscorpiidae). *Euscorpius* **2017**, *249*, 1–9. [[CrossRef](#)]
25. Kovařík, F.; Yağmur, E.A.; Fet, V.; Hussien, F.S. A review of *Orthochirus* from Turkey, Iraq, and Iran (Khozestan, Ilam, and Lorestan Provinces), with descriptions of three new species (Scorpiones: Buthidae). *Euscorpius* **2019**, *278*, 1–31. [[CrossRef](#)]
26. Kovařík, F.; Yağmur, E.A.; Moradi, M. Two new *Hottentotta* species from Iran, with a review of *Hottentotta saulcyi* (Scorpiones: Buthidae). *Euscorpius* **2018**, *265*, 1–14. [[CrossRef](#)]
27. Pocock, R.I. Arachnida. In *Fauna of British India Including Ceylon and Burma*; Blanford, W.T., Ed.; Taylor and Francis: London, UK, 1900; p. 279.
28. Werner, F. Reptilien und Gliedertiere aus Persien. *Festsch Embrik Strand Riga* **1936**, *2*, 193–204.
29. Vachon, M. Liste des scorpions connus en Égypte, Arabie, Israël, Liban, Syrie, Jordanie, Turquie, Irak, Iran. *Toxicon* **1966**, *4*, 209–218. [[CrossRef](#)]
30. Habibi, T. Liste de scorpions de l'Iran. *Bull. Fac. Sci. Teheran Univ.* **1971**, *2*, 42–47, (In French and Farsi).
31. Farzanpay, R. *Knowing Scorpions*; Central University Publications: Tehran, Iran, No. 312, Biology, 4, in Farsi, with Latin Index; 1987; p. 231.
32. Farzanpay, R. A catalogue of the scorpions occurring in Iran, up to January 1986. *Rev. Arachnol.* **1988**, *8*, 33–44.

33. Navidpour, S.; Kovařík, F.; Soleglad, M.E.; Fet, V. Scorpions of Iran (Arachnida, Scorpiones). Part I. Khuzestan Province. *Euscorpius* **2008**, *65*, 1–41.
34. Navidpour, S.; Kovařík, F.; Soleglad, M.E.; Fet, V. Scorpions of Iran (Arachnida, Scorpiones). Part X. Alborz, Markazi and Tehran Provinces with a description of *Orthochirus carinatus* sp. n. (Buthidae). *Euscorpius* **2019**, *276*, 1–20. [[CrossRef](#)]
35. Navidpour, S.; Nayebzadeh, H.H.; Soleglad, M.E.; Fet, V.; Kovařík, F.; Kayedi, M.H. Scorpions of Iran (Arachnida, Scorpiones). Part VI. Lorestan Province. *Euscorpius* **2010**, *99*, 1–23. [[CrossRef](#)]
36. Navidpour, S.; Soleglad, M.E.; Fet, V.; Kovařík, F. Scorpions of Iran (Arachnida, Scorpiones). Part II. Bushehr Province. *Euscorpius* **2008**, *67*, 1–33. [[CrossRef](#)]
37. Navidpour, S.; Soleglad, M.E.; Fet, V.; Kovařík, F. Scorpions of Iran (Arachnida, Scorpiones). Part IX. Hormozgan Province, with a description of *Odontobuthus tavighiae* sp. n. (Buthidae). *Euscorpius* **2013**, *170*, 1–29. [[CrossRef](#)]
38. Mirshamsi, O.; Sari, A.; Hosseini, S. History of study and checklist of the scorpion fauna (Arachnida: Scorpiones) of Iran. *Prog. Biol. Sci.* **2011**, *1*, 16–28.
39. Yağmur, E.A.; Moradi, M.; Larti, M.; Lashkari, S. First record of *Androctonus robustus* Kovařík & Ahmed, 2013 (Scorpiones: Buthidae) for Iran. *Zool. Middle East.* **2016**, *62*, 370–372.
40. Kovařík, F.; Ojanguren Affilastro, A.A. *Illustrated catalog of scorpions Part II. Bothriuridae; Chaerilidae; Buthidae I., genera Compsobuthus, Hottentotta, Isometrus, Lychas, and Sassanidotus*; Clairon Production: Prague, Czech Republic, 2013; 400p.
41. Mirshamsi, O. A Biosystematic Approach to *Mesobuthus eupeus* in Iran. Ph.D. Thesis, University of Tehran, Tehran, Iran, 2010; 200p.
42. Nejati, J.; Mozafari, E.; Saghafipour, A.; Kiyani, M. Scorpion fauna and epidemiological aspects of scorpionism in southeastern Iran. *Asian Pac. J. Trop. Biomed.* **2014**, *4*, S217–S221. [[CrossRef](#)] [[PubMed](#)]
43. Lowe, G. A New Species of *Odontobuthus* (Scorpiones: Buthidae) from Northern Oman. *Euscorpius* **2010**, *96*, 1–22. [[CrossRef](#)]
44. Kovařík, F.; Yağmur, E.A.; Fet, V. Review of *Hottentotta* described by A. A. Birula, with descriptions of two new species and comments on Birula's collection (Scorpiones: Buthidae). *Euscorpius* **2019**, *282*, 1–30.
45. Fet, V.; Kovařík, F.; Gantenbein, B.; Kaiser, R.C.; Stewart, A.K.; Graham, M.R. Revision of the *Mesobuthus caucasicus* complex from Central Asia, with descriptions of six new species (Scorpiones: Buthidae). *Euscorpius* **2018**, *255*, 1–77. [[CrossRef](#)]
46. Karataş, A.; Mouradi-Gharkheloo, M. A new *Hemiscorpius* Peters, 1861 (Scorpiones: Hemiscorpiidae) from southwestern Iran. *Turk. J. Zool.* **2013**, *37*, 15–23.
47. Mirshamsi, O.; Azghadi, S.; Navidpour, S.; Aliabadian, M.; Kovařík, F. *Odontobuthus tirgari* sp. nov. (Scorpiones, Buthidae) from the eastern region of the Iranian Plateau. *Zootaxa* **2013**, *3731*, 153–170. [[CrossRef](#)]
48. Mirshamsi, O.; Sari, A.; Elahi, E.; Hosseini, S. *Mesobuthus eupeus* (Scorpiones: Buthidae) from Iran: A polytypic species complex. *Zootaxa* **2011**, *2929*, 1–21.
49. Teruel, R.; Kovařík, F.; Navidpour, S.; Fet, V. The first record of the genus *Anomalobuthus* Kraepelin, 1900 from Iran, with description of a new species (Scorpiones: Buthidae). *Euscorpius* **2014**, *192*, 1–10. [[CrossRef](#)]
50. Catterall, W.A. Structure and function of voltage-gated ion channels. *Annu. Rev. Biochem.* **1995**, *64*, 493–531. [[CrossRef](#)]
51. Lewis, R.J.; Garcia, M.L. Therapeutic potential of venom peptides. *Nat. Rev. Drug Discov.* **2003**, *2*, 790–802. [[CrossRef](#)]
52. Almaaytah, A.; Albalas, Q. Scorpion venom peptides with no disulfide bridges: A review. *Peptides* **2014**, *51*, 35–45. [[CrossRef](#)]
53. Bhavya, J.; Francois, N.N.; More, V.S.; More, S.S. Scorpion toxin polypeptides as therapeutic agents: An overview. *Protein Pept. Lett.* **2016**, *23*, 848–859. [[CrossRef](#)]
54. He, Y.W.; Zhao, R.M.; di, Z.Y.; Li, Z.J.; Xu, X.B.; Hong, W.; Wu, Y.L.; Zhao, H.B.; Li, W.X.; Cao, Z.J. Molecular diversity of Chaerilidae venom peptides reveals the dynamic evolution of scorpion venom components from Buthidae to non-Buthidae. *J. Proteom.* **2013**, *89*, 1–14. [[CrossRef](#)]
55. Schwartz, E.F.; Diego-Garcia, E.; Rodríguez de la Vega, R.C.; Possani, L.D. Transcriptome analysis of the venom gland of the Mexican scorpion *Hadrurus gertschi* (Arachnida: Scorpiones). *BMC Genom.* **2007**, *8*, 119. [[CrossRef](#)]

56. Xiao, M.; Ding, L.; Yang, W.; Chai, L.; Sun, Y.; Yang, X.; Li, D.; Zhang, H.; Li, W.; Cao, Z.; et al. St20, a new venomous animal derived natural peptide with immunosuppressive and anti-inflammatory activities. *Toxicon* **2017**, *127*, 37–43. [[CrossRef](#)]
57. Veiseh, M.; Gabikian, P.; Bahrami, S.B.; Veiseh, O.; Zhang, M.; Hackman, R.C.; Ravanpay, A.C.; Stroud, M.R.; Kusuma, Y.; Hansen, S.J.; et al. Tumor paint: A chlorotoxin: cy5.5 bioconjugate for intraoperative visualization of cancer foci. *Cancer Res.* **2007**, *67*, 6882–6888. [[CrossRef](#)]
58. Sarfo-Poku, C.; Eshun, O.; Lee, K.H. Medical application of scorpion venom to breast cancer: A mini-review. *Toxicon* **2016**, *122*, 109–112. [[CrossRef](#)]
59. De Souza, J.M.; Goncalves, B.D.C.; Gomez, M.V.; Vieira, L.B.; Ribeiro, F.M. Animal toxins as therapeutic tools to treat neurodegenerative diseases. *Front. Pharmacol.* **2018**, *9*, 145. [[CrossRef](#)]
60. Shen, B.; Cao, Z.; Li, W.; Sabatier, J.M.; Wu, Y. Treating autoimmune disorders with venom-derived peptides. *Expert Opin. Biol. Ther.* **2017**, *17*, 1065–1075. [[CrossRef](#)]
61. Chan, Y.S.; Cheung, R.C.; Xia, L.; Wong, J.H.; Ng, T.B.; Chan, W.Y. Snake venom toxins: Toxicity and medicinal applications. *Appl. Microbiol. Biotechnol.* **2016**, *100*, 6165–6181. [[CrossRef](#)]
62. Estève, E.; Smida-Rezgui, S.; Sarkozi, S.; Szegedi, C.; Regaya, I.; Chen, L.; Altafaj, X.; Rochat, H.; Allen, P.; Pessah, I.N.; et al. Critical amino acid residues determine the binding affinity and the Ca²⁺ release efficacy of maurocalcine in skeletal muscle cells. *J. Biol. Chem.* **2003**, *278*, 37822–37831. [[CrossRef](#)]
63. Gurrola, G.B.; Capes, E.M.; Zamudio, F.Z.; Possani, L.D.; Valdivia, H.H. Imperatoxin A, a Cell-Penetrating Peptide from Scorpion Venom, as a Probe of Ca²⁺Release Channels/Ryanodine Receptors. *Pharmaceuticals* **2010**, *3*, 1093–1107. [[CrossRef](#)]
64. Possani, L.D.; Becerril, B.; Delepierre, M.; Tytgat, J. Scorpion toxins specific for Na⁺channels. *Eur. J. Biochem.* **1999**, *264*, 287–300. [[CrossRef](#)]
65. Goudet, C.; Chi, C.W.; Tytgat, J. An overview of toxins and genes from the venom of the Asian scorpion *Buthus martensi* Karsch. *Toxicon* **2002**, *40*, 1239–1258. [[CrossRef](#)]
66. Possani, L.D.; Merino, E.; Corona, M.; Bolivar, F.; Becerril, B. Peptides and genes coding for scorpion toxins that affect ion-channels. *Biochimie* **2000**, *82*, 861–868. [[CrossRef](#)]
67. Hille, B. *Ion Channels of Excitable Membranes*, 3rd ed.; Sinauer Associates, Inc.: Sunderland, MA, USA, 2001.
68. Wickenden, A.; Priest, B.; Erdemli, G. Ion channel drug discovery: Challenges and future directions. *Future Med. Chem.* **2012**, *4*, 661–679. [[CrossRef](#)]
69. Rodríguez de la Vega, R.C.; Possani, L.D. Overview of scorpion toxins specific for Na⁺ channels and related peptides: Biodiversity, structure function relationships and evolution. *Toxicon* **2005**, *46*, 831–844. [[CrossRef](#)]
70. Martin-Eauclaire, M.F.; Couraud, F. Scorpion neurotoxins: Effects and mechanisms. In *Handbook of Neurotoxicity*; Chang, L.W., Dyer, R.S., Eds.; Marcel Dekker: New York, NY, USA, 1995; pp. 683–716.
71. Abdel-Rahman, M.A.; Quintero-Hernández, V.; Possani, L.D. Scorpion venom gland transcriptomics and proteomics: An overview. In *Venom Genomics Proteomics*; Springer Science+Business Media Dordrecht: Berlin/Heidelberg, Germany, 2016; pp. 105–124.
72. Morey, S.S.; Kiran, K.M.; Gadag, J.R. Purification and properties of hyaluronidase from *Palamneus gravimanus* (Indian black scorpion) venom. *Toxicon* **2006**, *47*, 188–195. [[CrossRef](#)]
73. Pessini, A.C.; Takao, T.T.; Cavalheiro, E.C.; Vichnewski, W.; Sampaio, S.V.; Giglio, J.R.; Arantes, E.C. A hyaluronidase from *Tityus serrulatus* scorpion venom: Isolation, characterization and inhibition by flavonoids. *Toxicon* **2001**, *39*, 1495–1504. [[CrossRef](#)]
74. Dardevet, L.; Rani, D.; Aziz, T.A.; Bazin, I.; Sabatier, J.M.; Fadl, M.; Brambilla, E.; De Waard, M. Chlorotoxin: A helpful natural scorpion peptide to diagnose glioma and fight tumor invasion. *Toxins* **2015**, *7*, 1079–1101. [[CrossRef](#)]
75. Kastin, A. *Handbook of Biologically Active Peptides*, 2nd ed.; Academic Press: San Diego, CA, USA, 2013; p. 408.
76. Fu, Y.J.; Yin, L.T.; Liang, A.H.; Zhang, C.F.; Wang, W.; Chai, B.F.; Fan, X.J. Therapeutic potential of chlorotoxin-like neurotoxin from the Chinese scorpion for human gliomas. *Neurosci. Lett.* **2007**, *412*, 62–67. [[CrossRef](#)]
77. Mamelak, A.N.; Jacoby, D.B. Targeted Delivery of Antitumoral Therapy to Glioma and Other Malignancies with Synthetic Chlorotoxin (TM 601). *Expert Opin. Drug Deliv.* **2007**, *4*, 175–186. [[CrossRef](#)]
78. Mishal, R.; Tahir, H.M.; Zafar, K.; Arshad, M. Anti-cancerous applications of scorpion venom. *Int. J. Biol. Pharm. Res.* **2013**, *4*, 356–360.

79. Zargan, J.; Sajad, M.; Umar, S.; Naime, M.; Ali, S.; Khan, H.A. Scorpion (*Androctonus crassicauda*) venom limits growth of transformed cells (SH-SY5Y and MCF-7) by cytotoxicity and cell cycle arrest. *Exp. Mol. Pathol.* **2011**, *91*, 447–454. [[CrossRef](#)]
80. Zargan, J.; Sajad, M.; Umar, S.; Naime, M.; Ali, S.; Khan, H.A. Scorpion (*Odontobuthus doriae*) venom induces apoptosis and inhibits DNA synthesis in human neuroblastoma cells. *Mol. Cell. Biochem.* **2011**, *348*, 173–181. [[CrossRef](#)]
81. Zargan, J.; Umar, S.; Sajad, M.; Naime, M.; Ali, S.; Khan, H.A. Scorpion venom (*Odontobuthus doriae*) induces apoptosis by depolarization of mitochondria and reduces S-phase population in human breast cancer cells (MCF-7). *Toxicol. In Vitro* **2011**, *25*, 1748–1756. [[CrossRef](#)]
82. Catterall, W.A.; Cestèle, S.; Yarov-Yarovoy, V.; Yu, F.H.; Konoki, K.; Scheuer, T. Voltage-gated ion channels and gating modifier toxins. *Toxicon* **2007**, *49*, 124–141. [[CrossRef](#)]
83. Beneski, D.A.; Catterall, W.A. Covalent labeling of protein components of the sodium channel with a photoactivable derivative of scorpion toxin. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 639–643. [[CrossRef](#)] [[PubMed](#)]
84. Payandeh, J.; Scheuer, T.; Zheng, N.; Catterall, W.A. The crystal structure of a voltage-gated sodium channel. *Nature* **2011**, *475*, 353–358. [[CrossRef](#)] [[PubMed](#)]
85. Wang, J.T.; Yarov-Yarovoy, V.; Kahn, R.; Gordon, D.; Gurevitz, M.; Scheuer, T.; Catterall, W.A. Mapping the receptor site for α -scorpion toxins on a Na⁺ channel voltage sensor. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 15426–15431. [[CrossRef](#)] [[PubMed](#)]
86. Catterall, W.A. Voltage-gated sodium channels at 60: Structure, function and pathophysiology. *J. Physiol.* **2012**, *590*, 2577–2589. [[CrossRef](#)] [[PubMed](#)]
87. Catterall, W.A.; Goldin, A.L.; Waxman, S.G. International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol. Rev.* **2005**, *57*, 397–409. [[CrossRef](#)] [[PubMed](#)]
88. Black, J.A.; Waxman, S.G. Noncanonical roles of voltage-gated sodium channels. *Neuron* **2013**, *80*, 280–291. [[CrossRef](#)] [[PubMed](#)]
89. Wu, Y.; Ma, H.; Zhang, F.; Zhang, C.; Zou, X.; Cao, Z. Selective Voltage-Gated Sodium Channel Peptide Toxins from Animal Venom: Pharmacological Probes and Analgesic Drug Development. *ACS Chem. Neurosci.* **2018**, *9*, 187–197. [[CrossRef](#)] [[PubMed](#)]
90. Cestèle, S.; Catterall, W.A. Molecular mechanisms of neurotoxin action on voltage-gated sodium channels. *Biochimie* **2000**, *82*, 883–892. [[CrossRef](#)]
91. Zhang, F.; Xu, X.; Li, T.; Liu, Z. Shellfish toxins targeting voltage-gated sodium channels. *Mar. Drugs* **2013**, *11*, 4698–4723. [[CrossRef](#)]
92. Catterall, W.A. Structure and regulation of voltage-gated calcium channels. *Annu. Rev. Cell Dev. Biol.* **2000**, *16*, 521–555. [[CrossRef](#)] [[PubMed](#)]
93. Patino, G.A.; Isom, L.L. Electrophysiology and beyond: Multiple roles of Na⁺ channel beta subunits in development and disease. *Neurosci. Lett.* **2010**, *486*, 53–59. [[CrossRef](#)] [[PubMed](#)]
94. Savio-Galimberti, E.; Gollob, M.H.; Darbar, D. Voltage-gated sodium channels: Biophysics, pharmacology, and related channelopathies. *Front. Pharmacol.* **2012**, *3*, 124. [[CrossRef](#)] [[PubMed](#)]
95. Durek, T.; Vetter, I.; Wang, C.I.; Motin, L.; Knapp, O.; Adams, D.J.; Lewis, R.J.; Alewood, P.F. Chemical engineering and structural and pharmacological characterization of the α -scorpion toxin OD1. *ACS Chem. Biol.* **2013**, *8*, 1215–1222. [[CrossRef](#)] [[PubMed](#)]
96. Jalali, A.; Bosmans, F.; Amininasab, M.; Clynen, E.; Cuypers, E.; Zaremirakabadi, A.; Sarbolouki, M.N.; Schoofs, L.; Vatanpour, H.; Tytgat, J. OD1, the first toxin isolated from the venom of the scorpion *Odontobuthus doriae* active on voltage-gated Na⁺ channels. *FEBS Lett.* **2005**, *579*, 4181–4186. [[CrossRef](#)] [[PubMed](#)]
97. Maertens, C.; Cuypers, E.; Amininasab, M.; Jalali, A.; Vatanpour, H.; Tytgat, J. Potent modulation of the voltage-gated sodium channel Nav1.7 by OD1, a toxin from the scorpion *Odontobuthus doriae*. *Mol. Pharmacol.* **2006**, *70*, 405–414. [[CrossRef](#)] [[PubMed](#)]
98. Bosmans, F.; Maertens, C.; Verdonck, F.; Tytgat, J. The poison dart frog's batrachotoxin modulates Nav1.8. *FEBS Lett.* **2004**, *577*, 245–248. [[CrossRef](#)] [[PubMed](#)]
99. Gold, M.S.; Reichling, D.B.; Shuster, M.J.; Levine, J.D. Hyperalgesic agents increase a tetrodotoxin-resistant Na⁺ current in nociceptors. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 1108–1112. [[CrossRef](#)] [[PubMed](#)]

100. Aboutorabi, A.; Naderi, N.; Gholami Pourbadie, H.; Zolfagharian, H.; Vatanpour, H. Voltage-gated sodium channel modulation by *Bothriocentrus schach* venom scorpion. *Iran. J. Pharm. Sci.* **2016**, *12*, 55–64.
101. Vatanpour, H.; Ahmadi, F.; Zare Mirakabadi, A.; Jalali, A. Two Biological Active Fractions Isolated from *Buthotus schach* (BS) Scorpion Venom Examined on Striated Muscle Preparation, In-vitro. *Iran. J. Pharm. Res.* **2012**, *11*, 905–911.
102. González, C.; Baez-Nieto, D.; Valencia, I.; Oyarzún, I.; Rojas, P.; Naranjo, D.; Latorre, R. K (+) channels: Function-structural overview. *Compr. Physiol.* **2012**, *2*, 2087–2149.
103. Doyle, D.A.; Morais Cabral, J.; Pfuetzner, R.A.; Gulbis, J.M.; Cohen, S.L.; Chait, B.T.; MacKinnon, R. The structure of the potassium channel: Molecular basis of K⁺ conduction and selectivity. *Science* **1998**, *280*, 69–77. [[CrossRef](#)] [[PubMed](#)]
104. Heinemann, S.H.; Rettig, J.; Graack, H.R.; Pongs, O. Functional characterization of K_v channel beta-subunits from rat brain. *J. Physiol.* **1996**, *493*, 625–633. [[CrossRef](#)] [[PubMed](#)]
105. Kubo, Y.; Adelman, J.P.; Clapham, D.E.; Jan, L.Y.; Karschin, A.; Kurachi, Y.; Lazdunski, M.; Nichols, C.G.; Seino, S.; Vandenberg, C.A. International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol. Rev.* **2005**, *57*, 509–526. [[CrossRef](#)] [[PubMed](#)]
106. Goldstein, S.A.N.; Bayliss, D.A.; Kim, D.; Lesage, F.; Plant, L.D.; Rajan, S. International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol. Rev.* **2005**, *57*, 527–540. [[CrossRef](#)] [[PubMed](#)]
107. Gutman, G.A.; Chandy, K.G.; Grissmer, S.; Lazdunski, M.; MacKinnon, L.; Pardo, L.A.; Robertson, G.A.; Rudy, B.; Sanguinetti, M.C.; Stühmer, W.; et al. International union of pharmacology. Liii. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol. Rev.* **2005**, *57*, 473–508. [[CrossRef](#)]
108. Wei, A.D.; Gutman, G.A.; Aldrich, R.; Chandy, K.G.; Grissmer, S.; Wulff, H. International Union of Pharmacology. Lii. Nomenclature and molecular relationships of calcium-activated potassium channels. *Pharmacol. Rev.* **2005**, *57*, 463–472. [[CrossRef](#)]
109. Wulff, H.; Zhorov, B.S. K⁺ channel modulators for the treatment of neurological disorders and autoimmune diseases. *Chem. Rev.* **2008**, *108*, 1744–1773. [[CrossRef](#)] [[PubMed](#)]
110. Kuzmenkov, A.I.; Krylov, N.A.; Chugunov, A.O.; Grishin, E.V.; Vassilevski, A.A. Kalium: A Database of Potassium Channel Toxins from Scorpion Venom. *Database* **2016**. [[CrossRef](#)]
111. Mouhat, S.; Andreotti, N.; Jouirou, B.; Sabatier, J.M. Animal toxins acting on voltage-gated potassium channels. *Curr. Pharm. Des.* **2008**, *14*, 2503–2518. [[CrossRef](#)]
112. Bergeron, Z.L.; Bingham, J.P. Scorpion toxins specific for potassium (K) channels: A historical overview of peptide bioengineering. *Toxins* **2012**, *4*, 1082–1119. [[CrossRef](#)]
113. Rodríguez de la Vega, R.C.; Possani, L.D. Current views on scorpion toxins specific for K⁺-channels. *Toxicon* **2004**, *43*, 865–875. [[CrossRef](#)] [[PubMed](#)]
114. Rodríguez de la Vega, R.C.; Vidal, N.; Possani, L.D. *Handbook of Biologically Active Peptides*, 2nd ed.; Kastin, A., Ed.; Academic Press: San Diego, CA, USA, 2013; p. 423.
115. Zhao, Y.; Huang, J.; Yuan, X.; Peng, B.; Liu, W.; Han, S.; He, X. Toxins Targeting the Kv1.3 Channel: Potential Immunomodulators for Autoimmune Diseases. *Toxins* **2015**, *7*, 749–764. [[CrossRef](#)] [[PubMed](#)]
116. Abdel-Mottaleb, Y.; Clynen, E.; Jalali, A.; Bosmans, F.; Vatanpour, H.; Schoofs, L.; Tytgat, J. The first potassium channel toxin from the venom of the Iranian scorpion *Odonthobuthus doriae*. *FEBS Lett.* **2006**, *580*, 6254–6258. [[CrossRef](#)] [[PubMed](#)]
117. Abdel-Mottaleb, Y.; Vandendriessche, T.; Clynen, E.; Landuyt, B.; Jalali, A.; Vatanpour, H.; Tytgat, J. OdK2, a Kv1.3 channel-selective toxin from the venom of the Iranian scorpion *Odonthobuthus doriae*. *Toxicon* **2008**, *51*, 1424–1430. [[CrossRef](#)] [[PubMed](#)]
118. Srairi-Abid, N.; Shahbazzadeh, D.; Chatti, I.; Mlayah-Bellalouna, S.; Mejdoub, H.; Borchani, L.; Benkhalifa, R.; Akbari, A.; El Ayeb, M. Hemitoxin, the first potassium channel toxin from the venom of the Iranian scorpion *Hemiscorpius lepturus*. *FEBS J.* **2008**, *275*, 4641–4650. [[CrossRef](#)] [[PubMed](#)]
119. Catterall, W.A. Voltage-gated calcium channels. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a003947. [[CrossRef](#)] [[PubMed](#)]
120. Bajaj, S.; Han, J. Venom-Derived Peptide Modulators of Cation-Selective Channels: Friend, Foe or Frenemy. *Front. Pharmacol.* **2019**, *10*, 58. [[CrossRef](#)] [[PubMed](#)]

121. Franzini-Armstrong, C.; Protasi, F. Ryanodine receptors of striated muscles: A complex channel capable of multiple interactions. *Physiol. Rev.* **1997**, *77*, 699–729. [[CrossRef](#)] [[PubMed](#)]
122. Van Petegem, F. Ryanodine receptors: Structure and function. *J. Biol. Chem.* **2012**, *287*, 31624–31632. [[CrossRef](#)] [[PubMed](#)]
123. Schwartz, E.F.; Capes, E.M.; Diego-García, E.; Zamudio, F.Z.; Fuentes, O.; Possani, L.D.; Valdivia, H.H. Characterization of hadrucalcin, a peptide from *Hadrurus gertschi* scorpion venom with pharmacological activity on ryanodine receptors. *Br. J. Pharmacol.* **2009**, *157*, 392–403. [[CrossRef](#)] [[PubMed](#)]
124. Naderi Soorki, M.; Galehdari, H.; Baradaran, M.; Jalali, A. First venom gland transcriptomic analysis of Iranian yellow scorpion “*Odonthobuthus doriae*” with some new findings. *Toxicon* **2016**, *120*, 69–77. [[CrossRef](#)] [[PubMed](#)]
125. Morgenstern, D.; Rohde, B.H.; King, G.F.; Tal, T.; Sher, D.; Zlotkin, E. The tale of a resting gland: Transcriptome of a replete venom gland from the scorpion *Hottentotta judaicus*. *Toxicon* **2011**, *57*, 695–703. [[CrossRef](#)] [[PubMed](#)]
126. Shahbazzadeh, D.; Srairi-Abid, N.; Feng, W.; Ram, N.; Borchani, L.; Ronjat, M.; Akbari, A.; Pessah, I.N.; De Waard, M.; El Ayeb, M. Hemicalcin, a new toxin from the Iranian scorpion *Hemiscorpius lepturus* which is active on ryanodine-sensitive Ca²⁺ channels. *Biochem. J.* **2007**, *404*, 89–96. [[CrossRef](#)] [[PubMed](#)]
127. Estévez, R.; Jentsch, T.J. CLC chloride channels: Correlating structure with function. *Curr. Opin. Struct. Biol.* **2002**, *12*, 531–539. [[CrossRef](#)]
128. Jentsch, T.J.; Stein, V.; Weinreich, F.; Zdebik, A.A. Molecular structure and physiological function of chloride channels. *Physiol. Rev.* **2002**, *82*, 503–568. [[CrossRef](#)] [[PubMed](#)]
129. Alexander, S.P.; Kelly, E.; Marrion, N.; Peters, J.A.; Benson, H.E.; Faccenda, E.; Pawson, A.J.; Sharman, J.L.; Southan, C.; Davies, J.A.; et al. The concise guide to pharmacology 2015/16: Other ion channels. *Br. J. Pharmacol.* **2015**, *172*, 5942–5955. [[CrossRef](#)] [[PubMed](#)]
130. Thompson, C.H.; Olivetti, P.R.; Fuller, M.D.; Freeman, C.S.; McMaster, D.; French, R.J.; Pohl, J.; Kubanek, J.; McCarty, N.A. Isolation and characterization of a high affinity peptide inhibitor of ClC-2 chloride channels. *J. Biol. Chem.* **2009**, *284*, 26051–26062. [[CrossRef](#)] [[PubMed](#)]
131. Lippens, G.; Najib, J.; Tartar, A.; Lippens, G.; Wodak, S.J. NMR sequential assignments and solution structure of chlorotoxin, a small scorpion toxin that blocks chloride channels. *Biochemistry* **1995**, *34*, 13–21. [[CrossRef](#)]
132. Adjadj, E.; Naudat, V.; Quiniou, E.; Wouters, D.; Sautière, P.; Craescu, C.T. Solution structure of Lqh-8:6, a toxin-like peptide from scorpion venom. *Eur. J. Biochem.* **1997**, *246*, 218–227. [[CrossRef](#)]
133. Ali, S.A.; Stoeva, S.; Schütz, J.; Kayed, R.; Abbasi, A.; Zaidi, Z.H.; Voelter, W. Purification and primary structure of low molecular mass peptides from scorpion (*Buthus indicus*) venom. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **1998**, *121*, 323–332. [[CrossRef](#)]
134. Harrison, P.L.; Abdel-Rahman, M.A.; Miller, K.; Strong, P.N. Antimicrobial peptides from scorpion venoms. *Toxicon* **2014**, *88*, 115–137. [[CrossRef](#)] [[PubMed](#)]
135. Boman, H.G. Innate immunity and the normal microflora. *Immunol. Rev.* **2000**, *173*, 5–16. [[CrossRef](#)] [[PubMed](#)]
136. Chen, T.; Walker, B.; Zhou, M.; Shaw, C. Molecular cloning of a novel putative potassium channel-blocking neurotoxin from the venom of the North African scorpion, *Androctonus amoreuxi*. *Peptides* **2005**, *26*, 731–736. [[CrossRef](#)] [[PubMed](#)]
137. Chen, T.; Folan, R.; Kwok, H.; O’Kane, E.J.; Bjourson, A.J.; Shaw, C. Isolation of scorpion (*Androctonus amoreuxi*) putative alpha neurotoxins and parallel cloning of their respective cDNAs from a single sample of venom. *Regul. Pept.* **2003**, *115*, 115–121. [[CrossRef](#)]
138. Anonymous. United Nations Programme on HIV/AIDS. UNAIDS. 20: UNAIDS Report on the Global AIDS Epidemic 2016. 2016. Available online: <http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016> (accessed on 31 May 2016).
139. Huyart, N.; Calvayrac, R.; Briand, J.; Goyffon, M.; Vuillaume, M. Catalatic properties of hemocyanin in helping to account for the scorpion’s radioresistance. *Comp. Biochem. Physiol.* **1983**, *76*, 153–159. [[CrossRef](#)]
140. Quéinnec, E.; Gardes-Albert, M.; Goyffon, M.; Ferradini, C.; Vuillaume, M. Antioxidant activity of hemocyanin; a pulse radiolysis study. *Biochim. Biophys. Acta* **1990**, *1041*, 153–159. [[CrossRef](#)]
141. Vuillaume, M.; Ducancel, F.; Calvayrac, R.; Rabilloud, T.; Hubert, M.; Goyffon, M. Correlations between the catalase-like activity and the H₂O₂-ATP production of hæmocyanin and its subunits; implications with the radioresistance of the scorpion *Androctonus australis*. *Comp. Biochem. Physiol.* **1989**, *92*, 17–23. [[CrossRef](#)]

142. Goyffon, M. Hemocyanin. Venoms. Defensins. In *Scorpions of the World*; Stockmann, R., Ythier, E., Eds.; NAP: Verrières-le-Buisson, France, 2010; pp. 91–111.
143. Zabihollahi, R.; Bagheri, K.P.; Keshavarz, Z.; Motevalli, F.; Bahramali, G.; Siadat, S.D.; Momen, S.B.; Shahbazzadeh, D.; Aghasadeghi, M.R. Venom Components of Iranian Scorpion *Hemiscorpius lepturus* Inhibit the Growth and Replication of Human Immunodeficiency Virus 1 (HIV-1). *Iran. Biomed. J.* **2016**, *20*, 259–265. [[PubMed](#)]
144. Farajzadeh-Sheikh, A.; Jolodar, A.; Ghaemmaghami, S. Sequence Characterization of cDNA Sequence of Encoding of an Antimicrobial Peptide With No Disulfide Bridge from the Iranian *Mesobuthus Eupeus* Venomous Glands. *Iran. Red Crescent Med. J.* **2013**, *15*, 36–41. [[CrossRef](#)]
145. Imai, K.; Hiramatsu, A.; Fukushima, D.; Pierschbacher, M.D.; Okada, Y. Degradation of decorin by matrix metalloproteinases: Identification of the cleavage sites, kinetic analyses and transforming growth factor- β 1 release. *Biochem. J.* **1997**, *322*, 809–814. [[CrossRef](#)]
146. Buckley, A. Potential Therapeutic Efficacy of a Novel Metalloproteinase Inhibitor, Extracellular Matrix Protection Factor 1, in Human Osteoarthritic Chondrocyte Primary Cultures. Master's Thesis, Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA, 2016.
147. Kim, B.J.; Hur, J.W.; Park, J.S.; Kim, J.H.; Kwon, T.H.; Park, Y.K.; Moon, H.J. Expression of matrix metalloproteinase-2 and -9 in human ligamentum flavum cells treated with tumor necrosis factor- α and interleukin-1 β . *JNS* **2016**, *24*, 428–435.
148. Giannelli, G.; Falk-Marzillier, J.; Schiraldi, O.; Stetler-Stevenson, W.G.; Quaranta, V. Induction of cell migration by matrix metalloproteinase-2 cleavage of laminin-5. *Science* **1997**, *277*, 225–228. [[CrossRef](#)] [[PubMed](#)]
149. Rudolph-Owen, L.A.; Chan, R.; Muller, W.J.; Matrisian, L.M. The matrix metalloproteinase matrilysin influences early stage mammary tumorigenesis. *Cancer Res.* **1998**, *58*, 5500–5506. [[PubMed](#)]
150. Xia, X.; Ma, Y.; Xue, S.; Wang, A.; Tao, J.; Zhao, Y.; Zhang, Q.; Liu, R.; Lu, S. Cloning and molecular characterization of BumaMPs1, a novel metalloproteinases from the venom of scorpion *Buthus martensi* Karsch. *Toxicon* **2013**, *76*, 234–238. [[CrossRef](#)] [[PubMed](#)]
151. Jahdasani, R.; Rahimi Jamnani, F.; Behdani, M.; Habibi-Anbouhi, M.; Yardehnavi, N.; Shahbazzadeh, D.; Kazemi-Lomedasht, F. Identification of the immunogenic epitopes of the whole venom component of the *Hemiscorpius lepturus* scorpion using the phage display peptide library. *Toxicon* **2016**, *124*, 83–93. [[CrossRef](#)] [[PubMed](#)]
152. Kazemi-Lomedasht, F.; Khalaj, V.; Bagheri, K.P.; Behdani, M.; Shahbazzadeh, D. The first report on transcriptome analysis of the venom gland of Iranian scorpion, *Hemiscorpius lepturus*. *Toxicon* **2017**, *125*, 123–130. [[CrossRef](#)] [[PubMed](#)]
153. Kazemi-Lomedasht, F.; Shahbazzadeh, D.; Behdani, M. Phylogenetic analysis of metalloprotease from transcriptome of venom gland of *Hemiscorpius lepturus*. *Arch. Biotechnol. Biomed.* **2019**, *3*, 006–0010.
154. Schaloske, R.H.; Dennis, E.A. The phospholipase A2 superfamily and its group numbering system. *Biochim. Biophys. Acta* **2006**, *1761*, 1246–1259. [[CrossRef](#)]
155. Shimizu, T.; Ohto, T.; Kita, Y. Cytosolic phospholipase A2: Biochemical properties and physiological roles. *IUBMB Life* **2006**, *58*, 328–333. [[CrossRef](#)]
156. De Maria, L.; Vind, J.; Oxenboll, K.M.; Svendsen, A.; Patkar, S. Phospholipases and their industrial applications. *Appl. Microbiol. Biotechnol.* **2007**, *74*, 290–300. [[CrossRef](#)]
157. Rouault, M.; Bollinger, J.G.; Lazdunski, M.; Gelb, M.H.; Lambeau, G. Novel mammalian group XII secreted phospholipase A2 lacking enzymatic activity. *Biochemistry* **2003**, *42*, 11494–11503. [[CrossRef](#)] [[PubMed](#)]
158. Six, D.A.; Dennis, E.A. The expanding superfamily of phospholipase A2 enzymes: Classification and characterization. *Biochim. Biophys. Acta* **2000**, *1488*, 1–19. [[CrossRef](#)]
159. Burke, J.E.; Dennis, E.A. Phospholipase A2 structure/function, mechanism, and signaling. *J. Lipid Res.* **2009**, *50*, S237–S242. [[CrossRef](#)] [[PubMed](#)]
160. Hariprasad, G.; Kumar, M.; Srinivasan, A.; Kaur, P.; Singh, T.P.; Jithesh, O. Group III phospholipase A2 from the scorpion, *Mesobuthus tamulus*: Targeting and reversible inhibition by native peptides. *Int. J. Biol. Macromol.* **2011**, *48*, 423–431. [[CrossRef](#)] [[PubMed](#)]
161. Ramanaiah, M.; Parthasarathy, P.R.; Venkaiah, B. Purification and properties of phospholipase A2 from the venom of scorpion, (*Heterometrus fulvipes*). *Biochem Int.* **1990**, *20*, 931–940. [[PubMed](#)]

162. Hariprasad, G.; Singh, B.; Das, U.; Ethayathulla, A.S.; Kaur, P.; Singh, T.P.; Srinivasan, A. Cloning, sequence analysis and homology modeling of a novel phospholipase A2 from *Heterometrus fulvipes* (Indian black scorpion). *DNA Seq.* **2007**, *18*, 242–246. [[CrossRef](#)]
163. Zamudio, F.Z.; Conde, R.; Arévalo, C.; Becerril, B.; Martin, B.M.; Valdivia, H.H.; Possani, L.D. The mechanism of inhibition of ryanodine receptor channels by imperatoxin I, a heterodimeric protein from the scorpion *Pandinus imperator*. *J. Biol. Chem.* **1997**, *272*, 11886–11894. [[CrossRef](#)]
164. Conde, R.; Zamudio, F.Z.; Becerril, B.; Possani, L.D. Phospholipin, a novel heterodimeric phospholipase A2 from *Pandinus imperator* scorpion venom. *FEBS Lett.* **1999**, *460*, 447–450. [[CrossRef](#)]
165. Valdez-Cruz, N.A.; Batista, C.V.; Possani, L.D. Phaiodactylipin, a glycosylated heterodimeric phospholipase A from the venom of the scorpion *Anuroctonus phaiodactylus*. *Eur. J. Biochem.* **2004**, *271*, 1453–1464. [[CrossRef](#)]
166. Incamnoi, P.; Patramanon, R.; Thammasirirak, S.; Chaveerach, A.; Uawonggul, N.; Sukprasert, S.; Rungsa, P.; Daduang, J.; Daduang, S. Heteromtoxin (HmTx), a novel heterodimeric phospholipase A(2) from *Heterometrus laoticus* scorpion venom. *Toxicon* **2013**, *61*, 62–71. [[CrossRef](#)]
167. Jridi, I.; Catacchio, I.; Majdoub, H.; Shahbazeddah, D.; El Ayeb, M.; Frassanito, M.A.; Ribatti, D.; Vacca, A.; Borchani, L. Hemilipin, a novel *Hemiscorpius lepturus* venom heterodimeric phospholipase A2, which inhibits angiogenesis in vitro and in vivo. *Toxicon* **2015**, *105*, 34–44. [[CrossRef](#)] [[PubMed](#)]
168. Louati, H.; Krayem, N.; Fendri, A.; Aissa, I.; Sellami, M.; Bezzine, S.; Gargouri, Y. A thermoactive secreted phospholipase A(2) purified from the venom glands of *Scorpio maurus*: Relation between the kinetic properties and the hemolytic activity. *Toxicon* **2013**, *72*, 133–142. [[CrossRef](#)] [[PubMed](#)]
169. Borchani, L.; Sassi, A.; Shahbazzadeh, D.; Strub, J.; Tounsi-Guetteti, H.; Boubaker, M.; Akbari, A.; Dorsselaer, A.; El Ayeb, M. Heminecrolysin, the first hemolytic dermonecrotic toxin purified from scorpion venom. *Toxicon* **2011**, *58*, 130–139. [[CrossRef](#)] [[PubMed](#)]
170. Jridi, I.; Catacchio, I.; Majdoub, H.; Shahbazeddah, D.; El Ayeb, M.; Frassanito, M.A.; Solimando, A.; Ribatti, D.; Vacca, A.; Borchani, L. The small subunit of Hemilipin2, a new heterodimeric phospholipase A2 from *Hemiscorpius lepturus* scorpion venom, mediates the antiangiogenic effect of the whole protein. *Toxicon* **2017**, *126*, 38–46. [[CrossRef](#)] [[PubMed](#)]
171. Craik, C.S.; Page, M.J.; Madison, E.L. Proteases as therapeutics. *Biochem. J.* **2011**, *435*, 1–16. [[CrossRef](#)] [[PubMed](#)]
172. Cao, Z.J.; Di, Z.Y.; Wu, Y.L.; Li, W.X. Overview of Scorpion Species from China and Their Toxins. *Toxins* **2014**, *6*, 796–815. [[CrossRef](#)] [[PubMed](#)]
173. Duffy, M.J.; McGowan, P.M.; Gallagher, W.M. Cancer invasion and metastasis: Changing views. *J. Pathol.* **2008**, *214*, 283–293. [[CrossRef](#)]
174. Hakim, M.A.; Yang, S. Discoveries of Serine Protease Inhibitors from Scorpions. *J. Proteom. Bioinform.* **2016**, *9*, 101–106. [[CrossRef](#)]
175. Laskowski, M., Jr.; Kato, I. Protein inhibitors of proteinases. *Annu. Rev. Biochem.* **1980**, *49*, 593–626. [[CrossRef](#)]
176. Ranasinghe, S.; McManus, D.P. Structure and function of invertebrate Kunitz serine protease inhibitors. *Dev. Comp. Immunol.* **2013**, *39*, 219–227. [[CrossRef](#)]
177. Wan, H.; Lee, K.S.; Kim, B.Y.; Zou, F.M.; Yoon, H.J.; Je, Y.H.; Li, J.; Jin, B.R. A Spider-derived Kunitz-Type Serine Protease Inhibitor that acts as a Plasmin Inhibitor and an Elastase Inhibitor. *PLoS ONE* **2013**, *8*, e53343. [[CrossRef](#)] [[PubMed](#)]
178. Gronenborn, A.M.; Nilges, M.; Peanasky, R.J.; Clore, G.M. Sequential resonance assignment and secondary structure determination of the ascaris trypsin inhibitor, a member of a novel class of proteinase inhibitors. *Biochemistry* **1990**, *29*, 183–189. [[CrossRef](#)] [[PubMed](#)]
179. Chen, Z.Y.; Hu, Y.T.; Yang, W.S.; He, Y.W.; Feng, J.; Wang, B.; Zhao, R.M.; Ding, J.P.; Cao, Z.J.; Li, W.X.; et al. Hg1, novel peptide inhibitor specific for $k_v1.3$ channels from first scorpion kunitz-type potassium channel toxin family. *J. Biol. Chem.* **2012**, *287*, 13813–13821. [[CrossRef](#)] [[PubMed](#)]
180. Van Gent, D.; Sharp, P.; Morgan, K.; Kalsheker, N. Serpins: Structure, function and molecular evolution. *Int. J. Biochem. Cell Biol.* **2003**, *35*, 1536–1547. [[CrossRef](#)]
181. Mourão, C.B.; Schwartz, E.F. Protease inhibitors from marine venomous animals and their counterparts in terrestrial venomous animals. *Mar. Drugs* **2013**, *11*, 2069–2112. [[CrossRef](#)]
182. Chen, Z.; Wang, B.; Hu, J.; Yang, W.; Cao, Z.; Zhuo, R.; Li, W.; Wu, Y. SjAPI, the first functionally characterized Ascaris-type protease inhibitor from animal venoms. *PLoS ONE* **2013**, *8*, e57529. [[CrossRef](#)]

183. Celis, A.; Gaxiola-Robles, R.; Sevilla-Godinez, E.; de Orozco Valerio, M.J.; Armas, J. Tendencia de la mortalidad por picaduras de alacran en Mexico, 1979–2003. *Rev. Panam. Salud Publ.* **2007**, *6*, 373–380. [[CrossRef](#)]
184. Mion, G.; Larreche, S.; Goyffon, M. *Aspects Cliniques et Thérapeutiques des Envenimations Graves*; Urgence Pratique: Ganges, France, 2010; Volume 1, p. 255. (In French)
185. Chowell, G.; Hyman, J.M.; Diaz-Duenas, P.; Hengartner, N.W. Predicting scorpion sting incidence in an endemic region using climatological variables. *Int. J. Environ. Health Res.* **2005**, *15*, 425–435. [[CrossRef](#)]
186. Mirdehghan, M.M.; Motlagh, M.I. Scorpion stings survey (including: Residence, sex and age) and treatment strategy in Abuzar hospital- Ahvaz, Khuzestan during 1994–1999, Iran. *J. Trop. Med. Hyg.* **2001**, *14*, 62–64. (In Persian)
187. Ward, M.J.; Ellsworth, S.A.; Nystrom, G.S. A global accounting of medically significant scorpions: Epidemiology, major toxins, and comparative resources in harmless counterparts. *Toxicon* **2018**, *151*, 137–155. [[CrossRef](#)]
188. Dehghani, R.; Fathi, B. Scorpion sting in Iran: A review. *Toxicon* **2012**, *60*, 919–933. [[CrossRef](#)] [[PubMed](#)]
189. Jalali, A.; Rahim, F. Epidemiological review of scorpion envenomation in Iran. *Iran. J. Pharm. Res.* **2014**, *13*, 743–756. [[PubMed](#)]
190. Shahbazzadeh, D.; Amirkhani, A.; Dinparast Djadid, N.; Bigdeli, S.; Akbari, A.; Ahari, H.; Amini, H.; Dehghani, R. Epidemiological and clinical survey of scorpionism in Khuzestan province, Iran (2003). *Toxicon* **2009**, *53*, 454–459. [[CrossRef](#)] [[PubMed](#)]
191. Baradaran, M.; Jalali, A.; Naderi-Soorki, M.; Jokar, M.; Galehdari, H. First Transcriptome Analysis of Iranian Scorpion, *Mesobuthus Eupeus* Venom Gland. *Iran. J. Pharm. Res.* **2018**, *17*, 1488–1502. [[PubMed](#)]
192. Lourenço, W.R. A new species of *Apistobuthus* Finnegan, 1932 (Scorpiones, Buthidae) from Iran. *Ent. Mitt. Zool. Mus. Hamburg.* **1998**, *12*, 237–244.
193. Navidpour, S.; Lowe, G. Revised diagnosis and redescription of *Apistobuthus susanae* (Scorpiones, Buthidae). *J. Arachnol.* **2009**, *37*, 45–59. [[CrossRef](#)]



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