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REVIEW ARTICLE

Nature and applications of scorpion venom: an overview

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ABSTRACT

Scorpionism (scorpion sting) is a major public health issue in many regions of the world. Globally, 1.2 million scorpion stings happen annually, specifically in the tropical regions. Mortality due to these venomous stings is serious health problem in absence of suitable medication. Awareness of this problem is fundamental for preventive measures. Scorpion venom is composed of water, mucosa, enzymes, free amino acids, biogenic amines, neurotoxins, low molecular weight peptides, and proteins having maximum molecular activities. Neurotoxins are potent and are highly selective ligands for voltage-gated sodium, potassium, chloride, and calcium ion channels. Therefore, they depict interesting compounds for the development of novel drugs, for example, drugs for cancer, neurological disorders, cardiovascular diseases, and analgesics. Scorpion venom has apoptogenic, cytotoxic, immunosuppressive, and antiproliferative effects. Therefore, scorpion venom can be utilized against various cancers like glioma, leukemia, human neuroblastoma, brain tumor, melanoma, prostate cancer, and breast cancer. This review explains the details of toxin receptor interactions and provides details about opportunities for the development of peptide-based therapeutics.

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Scorpions

Scorpions are the most primitive arachnids that exist on the earth for 430 millions of years (Ortiz *et al*. 2015; Zhang *et al*. 2015). They are the most venomous arthropods that belong to class *Arachnida* of phylum *Arthropoda* (Zhang *et al*. 2015; Xueli *et al*. 2017). These animals are found in all continents except Antarctica. They are adapted to survive in several habitats such as tropical forests, temperate forests, grasslands, savanna, and caves (Chowell *et al*. 2006). All species are nocturnal, hiding during the day under stones, tree barks, in loose tiles of hut, inside empty shoes, crevices of windows and doors (Bawaskar and Bawaskar 2012; Das *et al*. 2013). Scorpions belonging to Buthidae family are more toxic and medically important (Quintero-Hernández *et al*. 2013; Ortiz *et al*. 2015). They cause health problems in subtropical and tropical regions. Scorpion venom is the key to their success which ensures their survival by defending themselves from preys, predators, and competitors. Exploitation of natural resources by expansion of human population increased the interaction with arthropods, which increases the incidents of scorpion stinging (Chippaux and Goyffon 2008; Ortiz *et al*. 2015).

Globally, there are 2231 various scorpion species, consist of 208 genera representing in 20 families (Zhang *et al*. 2015; Cassulini *et al*. 2017; Romero-Gutierrez *et al*. 2017), from which 1500 scorpion species are venomous and approximately 50 species are extremely harmful to humans (Srinivasan *et al*. 2002; Gomes and Gomes 2015; Gomes *et al*. 2016; Ebrahimi *et al*. 2017). Out of these 50 species, some include as *Hemiscorpius*, *Androctonus*, *Tityus*, *Leiurus*, *Buthus*, and *Mesobuthus* (Vazirianzadeh *et al*. 2013; Shahi *et al*. 2015).

Prevalence of scorpion stings

Scorpionism (scorpion stings) is very harmful to humans (Cassulini *et al*. 2017) and cause severe health problem in tropical regions (Bawaskar and Bawaskar 2012; Chippaux 2015; Khatony *et al*. 2015; Maghsoodi *et al*. 2015; Ebrahimi *et al*. 2017). Worldwide there are 1.2 million cases of stings which results in approximately 3250 deaths per year (Chippaux and Goyffon

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2008; Chippaux 2012; Bahloul *et al*. 2013; Khatony *et al*. 2015; Ebrahimi *et al*. 2017). There is a high prevalence of mortality related to scorpionism in developing countries compared to the developed countries due to the low socio-economic status and inadequate health facilities (Natu *et al*. 2006). Chippaux and Goyffon identified seven areas which are at more risk of scorpion envenomation, including Sahelian Africa, Saharan Africa (North), South Africa, Southern India, the Near and Middle-East, Southern Latin America, and Mexico (Dehghani and Fathi 2012; Kassiri *et al*. 2014; Khatony *et al*. 2015; Shahi *et al*. 2015).

Globally, there is a high rate of scorpion stings in Iran (Shahi *et al*. 2015; Ebrahimi *et al*. 2017). Majority of them are related to these three provinces in Iran: Khuzestan, Bueyerahmad, and Kohgiluyeh (Maghsoodi *et al*. 2015; Shahi *et al*. 2016). Scorpions and scorpion sting cases are also found in Saudia Arabia, Turkey, Spain, France, China, and Mongolia due to its climate and geographical location. A plenty of literature is available which describes the regional and epidemiological distribution of scorpions but so far Pakistani literature is nearly nonexistent. In Pakistan, the incidence of scorpion stings is unknown as there is no documentary data present in the literature. Recently, two studies on scorpion stings were reported in Pakistan, one in District Sargodha of Punjab (Ahsan *et al*. 2015) and other in Lasbella District of Balochistan (Khan and Ullaha 2017).

Scorpion envenomation

Scorpion envenomation is a significant problem for public health and causes a wide range of clinical manifestations in sub-tropical and tropical countries (Chippaux and Goyffon 2008; Ferreira *et al*. 2016; Gomes *et al*. 2016). Scorpion venom contains a wide variety of biomolecules which can disturb physiological activity of the host on envenomation (Ding *et al*. 2014; Bechohra *et al*. 2016). Children and elderly patients have increased chance of complications due to this problem (Shahi *et al*. 2015). Mostly, this is a hazard for farm laborers, farmers, villagers, hunters, and migrating population (Bawaskar and Bawaskar 2012; Das *et al*. 2013). However, age, venom dosage, nutritional state, geographical area, and season of the scorpion, as well as weight and age of the victim, individual sensitivity, and site of sting are important parameters which affect the severity of envenomation (Afshari 2016).

Treatment of scorpion envenomation

Although, most scorpion stings cause death of humans if not treated instantly (Chippaux and Alagon 2008). The treatment which is recommended for scorpion envenomation is therapy with antivenom. Hyperimmune serum is obtained from animals such as horses, after immunizations with the venom (Ferreira *et al*. 2016). World Health Organization approved protocols by which the efficacy of antivenoms is confirmed by injecting animals (usually mice) with different doses of venom (Cassulini *et al*. 2017). The only treatment available for scorpion envenomation is scorpion antiserum, but it is not always effective and sometime induces adverse effects (Chippaux and Goyffon 2008; Zoccal *et al*. 2016). To develop an effective and a specific treatment, it is necessary to understand the pathogenesis of disease induced by scorpion sting (Zoccal *et al*. 2016).

Composition of scorpion venom

Scorpions have been studied extensively due to its venom (AbdulRahman et al. 2016). Scorpion venom contains a wide variety of compounds such as water, mucosa, low molecular weight peptides, enzymes, free amino acids, biogenic amines, nucleotides, mucopolysaccharides, mucoproteins, histamine, serotonin, heterocyclic components, and several unidentified substances, which are described in Figure 1. Scorpion venoms are highly complex mixtures of such molecules, and it is estimated that 100,000 different components are present in the scorpion venom around the world (AbdulRahman *et al*. 2016; Al-Asmari *et al*. 2016; Ferreira *et al*. 2016). Toxins are the thoroughly studied components of scorpion venom. This is due to their pharmacological effect on ion channels and their clinical use as neurotoxins. Both disulfide and

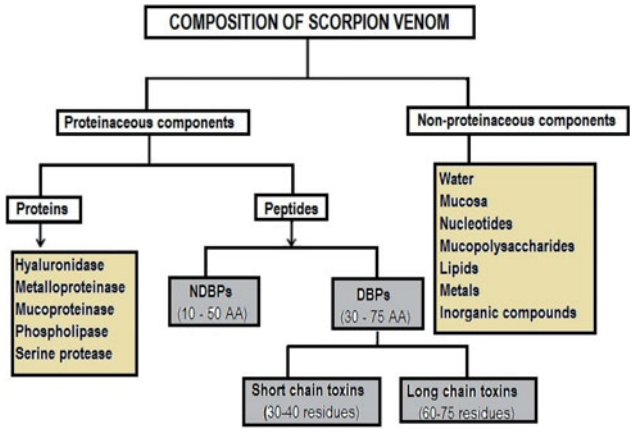

Figure 1. Composition of scorpion venom.

non-disulfide bridged peptides (NDBP) are present in the scorpion venoms whereas NDBP are major components of it (Ortiz *et al*. 2015). Mass-fingerprint analysis revealed that low molecular weight peptides depict more than a third of all the peptides that are determined in the scorpion venom (Rodriguez *et al*. 2010). Such toxins are best known for their deleterious effects on organisms, but paradoxically, they display antimalarial, antimicrobial, anticancer, and immunosuppressing activities that are important for the development of drugs (Ortiz *et al*. 2015).

Toxicity of scorpion venom

Scorpion venom contains a large number of toxins which are peptides of low molecular weight (Rodriguez *et al*. 2010; Cao *et al*. 2014; Romero-Gutierrez *et al*. 2017). Scorpion venom is highly toxic because it is composed of neurotoxin, nephrotoxin, cardiotoxin, and hemolytic toxin (Saini *et al*. 2012) which affect ion channels, enzymes, and allergenic compounds (Almeida *et al*. 2012). The toxicity of scorpion venom depends on their contents in neurotoxins. Low molecular weight peptides that interact with ion-channels (Huang and Jan 2014; Rao *et al*. 2015; Cassulini *et al*. 2017) and causing impairment of the proper functions of excitable cells in nerve and muscle tissues which is usually responsible for the known symptoms of envenoming (Andrikopoulos *et al*. 2011; Jian *et al*. 2014; Aboutorabia *et al*. 2016; Cassulini *et al*. 2017). They are able to block the target ion channels in excitable cells (Ortiz *et al*. 2015; Cassulini *et al*. 2017) and cause multiple physiological events associated with metabolic and biological disturbances (Al-Asmari *et al*. 2016). Scorpion toxins are classified into two main categories according to their target site and size: short chain toxins which are composed of 30–40 amino acids and constrained by 3 or 4 disulfide bridges that block the K^+ channels (Ortiz *et al*. 2015), and the long chain toxins which are composed of 60–75 amino acids and cross-linked by 4 disulfide bridges that affect specifically Na^+ channels. These toxins have been used as useful pharmacological probes to study the ion channels because of their high affinity and specificity (Aboutorabia *et al*. 2016).

Physiological effects of scorpion venom

Physiological effects of scorpion sting vary widely from inflammation or local pain to severe complications (Chgoury *et al*. 2011; 2015; Pucca *et al*. 2015) such as pulmonary edema, nervous disorder, and cardiogenic shock (Quintero-Hernández *et al*. 2013; Maghsoodi *et al*. 2015). Scorpion toxins cause massive release of neurotransmitter such as catecholamines which generates a cascade of events that can progress to heart failure, pulmonary edema, arterial hypotension or hypertension, arrhythmia, tachycardia or bradycardia, unconsciousness, and death (Isbister and Bawaskar 2014). The cytotoxin from *H. lepturus* causes psychological problems (Mental disorders, Anxiety, Depression, Schizophrenia, etc.) necrotic ulcers, cutaneous necrosis, hemoglubinuria, renal failure, ankylosis of the joints, fatal hemolysis, hematuria and even death (Rahmani and Jalali 2012; Shahi *et al*. 2015). Scorpion venom is linked to dysfunctions of the immune system by recruiting inflammatory cells, leukocytes, platelet activating factor, adhesion molecules, immunoglobulins, and cytokines (Petricevich 2004).

Diverse functions of toxins

Ion channels permit specific ions to move across the cell membrane (Chen and Chung 2015). They are associated with a series of physiological processes, that is, electrical signaling in neuron and muscle cells, and their malfunction cause different human diseases so such ion channels are important targets for the drug discovery (Bagal *et al*. 2013). Scorpion venom mainly consists of toxins which target various ion channels (K^+, Na^+, Ca^{++}, Cl^-) located in neuronal and muscle cells (Rao *et al*. 2015).

Scorpion venom is a rich source of biomolecules which block or modulate the various ion channels in excitable cells (Rao *et al*. 2015). Many short chain peptides (30–40 residues) are specific and potent blockers of K^+ channels, that is, charybdotoxin isolated from the scorpion venom is a specific blocker of two isoforms (KCa3.1 and Kv1.3) of potassium (K^+) channel, which are target for the immunosuppression (Chandy *et al*. 2004; Chen and Chung 2015). Similarly, long chain peptides (60–75 residues) are potential blockers of sodium (Na^+) channels, which are target for the treatment of pain (Knapp *et al*. 2012; Chen and Chung 2015). These peptides are used for the development of different drugs (Ortiz *et al*. 2015).

K^+ channel blockers

Scorpion toxins which block different K^+ channels have been widely studied and are referred to as "K^+ channel toxins" (González *et al*. 2012; Quintero-Hernández *et al*. 2013). They are shorter than Nav toxins but are closely related to them (Ortiz *et al*. 2015).

Previous studies demonstrated that many KTxs from *M. eupeus* and *M. martensii* scorpions were isolated which block different K^+ channels (Shi *et al*. 2008) such as maurotoxin acting on the Kv1.2 channel (Yi *et al*. 2008), BeKm-1 block hERG channel (Yi *et al*. 2007; 2008), Kunitz-type toxins block the Kv1.3 channel (Chen *et al*. 2012), charybdotoxin acting on the BKCa channel (Qiu *et al*. 2009), and BmP05 block the SKCa3 channel (Han *et al*. 2008; 2010; Yin *et al*. 2008). Several active components of scorpion venom that act on Ca^{++} and Cl^- channels have also been described (Possani *et al*. 2000; Gueguinou *et al*. 2014; Zamponi and Simms 2014; Rao *et al*. 2015).

Mechanism of K^+ channel function

Pore blocking peptides bind tightly with the outer vestibule of K^+ channel and obstruct the selectivity filter of ion channel and inhibiting the transport of potassium ions (Chen and Chung 2015; Oukkache *et al*. 2015). Mechanism of K^+ channel activity depends on the conformational changes in the channel protein (Figure 2). Ion channel is closed at the resting membrane potential and does not conduct ions at that time. When membrane potential is increased it affects the voltage sensor which causes the opening of the channel (Bezanilla 2000). Due to the high sensitivity of the voltage sensor, the ion channel responds even to slight membrane potential change and the open channel conducts ions until it enters into inactivation phase (Kuzmenkov *et al*. 2015).

Kv channel is inactivated by two mechanisms: (1) N-type and (2) C-type (Figure 2). In N-type of inactivation, channel remains in the open conformational state, but the pore is blocked by N terminal of the alpha subunit of channel. In N-type mechanism, removal of N terminal fragment abolishes this inactivation and addition of this fragment in the form of peptide restores the inactivation. Whereas in C-type of inactivation, N terminal is not involved. Structural elements located in the vestibule of selectivity filter are responsible for this type of inactivation (Kuzmenkov *et al*. 2015).

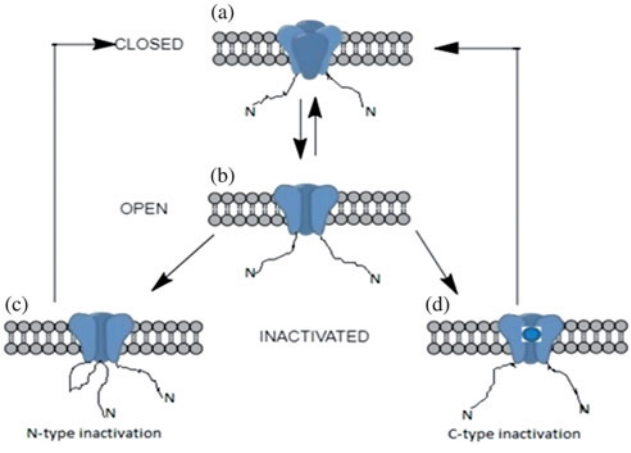

Figure 2. Mechanism of K^+ channel activity: (a) closed state; (b) open state; (c) N-type inactivation; (d) C-type inactivation.

Na^+ channel modulators

Voltage-gated sodium channels (VGSCs) are accountable for the quick influx of Na^+ ions that increases the action potential in muscle, nerve, and endocrine cells (Catterall *et al*. 2007). Isoforms of VGSCs are distributed throughout the excitable cells (muscles, neurons, and endocrine cells) of the body, which associate with different properties in the corresponding cells and tissues. Nav1.6, 1.3, 1.2, and 1.1 isoforms are present in the central nervous system; On contrary, Nav1.9, 1.8, and 1.7 isoforms are expressed in the peripheral nervous system and the last, Nav1.5 and 1.4 are highly expressed in the heart muscle and skeletal muscle, respectively (Stevens *et al*. 2011).

Toxins that are highly lethal modify voltage-gated Na^+ channel (Nav) and known as "Nav channel long-chain toxin" (Rodrıguez *et al*. 2005; Andrikopoulos *et al*. 2011; Davis *et al*. 2012; Aboutorabia *et al*. 2016). Nav channel long-chain toxins modulate the activation and inactivation of sodium channels by β-NaTxs and α-NaTxs, respectively (Rodrıguez *et al*. 2005; Cao *et al*. 2014). Sodium toxin (BmKIM) isolated from the scorpion *M. martensii*, is found to inhibit the sodium currents in rat ganglion neurons and myocytes and protect against the cardiac arrhythmia in mice model (Peng *et al*. 2002).

Structure of sodium channel

Like other ion channels, sodium channels are also transmembrane complexes. They consist of two subunits; first one is the α-subunit, a large core protein (220–260 kDa), associated with another small regulatory β-subunit (22–36 kDa). Alpha subunit contains the pore that is selectively permeable for Na^+ ions. α-subunit is composed of four homologous domains (DI–DIV), all of which contains six segments (S1–S6) which are transmembrane (Yu and Catterall 2003). These four domains are joined together by three cytoplasmic loops and form a bell-shaped protein (Figure 3). All of the four domains (DI–DIV) contains two modules, first one is the voltage sensing module developed by S1–4, second is the pore forming module, developed by the S5, S6, and the connecting loop (Sato *et al*. 2001).

Mechanism of neurotoxin binding with sodium channel

Toxins interact with VGSCs in two ways. It either results in a blockage of pore when the neurotoxin physically obstructs the pore and inhibits the conductance of sodium ions, or in a modification of the gating, that altered the voltage-dependence and gating kinetics of the ion channels. Toxins that interact with the site 1 use first mechanism. For example, tetrodotoxin (TTX) and sexitoxin (STX) are pore blockers of site 1. Grayanotoxin and batrachotoxin are site 2 toxins which prevent inactivation and therefore, channel remain persistently active (Stevens *et al*. 2011). Scorpion α-toxins and sea anemone toxins bind to site 3 and inhibit the inactivation (Possani *et al*. 2000). Scorpion β-toxins and spider β-toxins are site 4 toxins which shift the activation toward hyperpolarized state (Shichor *et al*. 2002). Site 5 toxins like ciguatoxins and brevetoxins display a real effect upon binding with VGSC, for example, inhibition of activation and the hyperpolarizing shift of voltage-dependence activation. Finally, δ-conotoxins interact with site 6 and produce similar outcomes as the site 3 neurotoxins by inhibiting inactivation (Figure 3) (Stevens *et al*. 2011).

In addition to these neurotoxins, some other components such as proteases and protease inhibitors have also been identified from scorpion venoms (Hargreaves *et al*. 2014; Xueli *et al*. 2017). Few scorpion-derived peptides have revealed enzymatic activities similar to lysozyme C (Baradaran *et al*. 2011), phospholipase A2 (Incamnoi *et al*. 2013), and hyaluronidase (Feng *et al*. 2008).

Venoms of spiders, snakes, cone snails, and sea anemones also have a complex mixture of peptides and proteins that have evolved for defense. Ion channels have emerged as targets and potent molecular probes for such venom peptides (Dutertre and Lewis 2010). Like scorpions, spiders, snakes, cone snails, and sea anemones also have a diversity of Na^+ and K^+ channel peptide inhibitors. Guangxitoxin (GxTx1E), dendrotoxins, κ-conotoxin, and BDS-I (Blood depressing substance) are potassium channel inhibitors which are isolated from spiders, snakes, cone snails, and sea anemones, respectively whereas δ-hexatoxins and μ-conotoxins are gating modifier of sodium channel isolated from spiders and snails (Dutertre and Lewis 2010).

Scorpion venom and medical science

Medically important species belong to the genera *Buthus*, *Mesobuthus*, *Parabuthus*, *Androctonus*, *Tityus*,

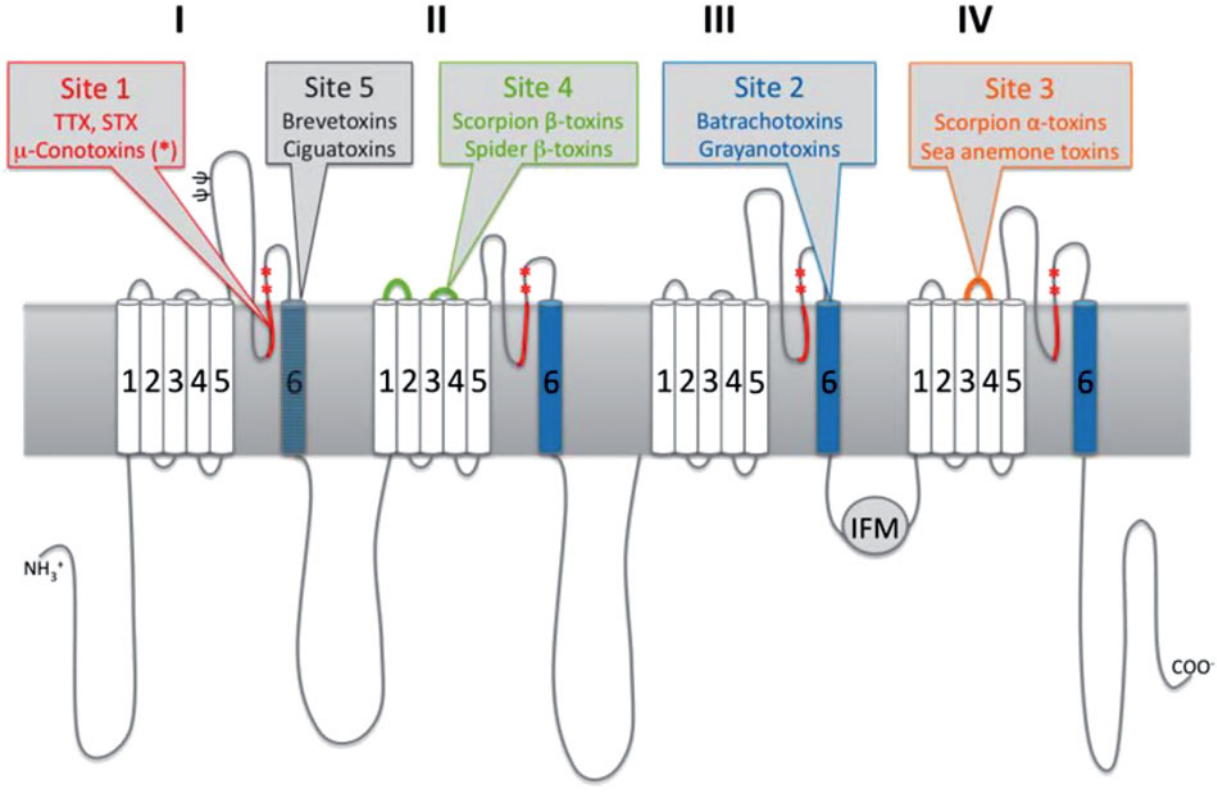

Figure 3. Schematic diagram of α-subunit of voltage-gated sodium channel (VGSC) and identification of the neurotoxin binding areas (Stevens *et al*. 2011).

Leiurus, and *Centruroides* from the Buthidae family (Sadeghian 2003; Ozkan *et al*. 2008). Among these, most important species are *T. bahiensis*, *T. serrulatus*, *T. trivittatus*, and *T. stigmurus* in South America; (Pardal *et al*. 2003; Ozkan *et al*. 2008); *C. suffusus*, *C. limpidus*, *C. sculpturatus*, and *C. infamatus* in Mexico (Osnaya-Romero *et al*. 2001; Chowell *et al*. 2006); *L. quinquestriatus*, *B. occitanus*, *A. crassicauda*, *A. amoreuxi*, *A. mauretanicus*, and *A. australis* in the Middle East and North African countries; (Dittrich *et al*. 1995; Farghly and Ali 1999; Hammoudi-Triki *et al*. 2004; Ozkan *et al*. 2008); *P. transvaalicus* and *P. granulates* in the South African countries (Bergman 1997); *P. swammerdami* and *M. tamulus* in India (Bawaskar 2005); and *A. finitimus*, *H. tamulus* and *O. odonturus* in Pakistan (Ahsan *et al*. 2016).

Scorpions have been used in traditional medicine in Asia and Africa since the ancient cultures (Shao *et al*. 2007; Gomes *et al*. 2010; Ding *et al*. 2014; Ortiz *et al*. 2015; Bechohra *et al*. 2016). Scorpions, their venoms, and body parts are very effective for the treatment of many diseases, specifically for cancer (Das *et al*. 2007; Diaz-Garcia *et al*. 2013). With the help of novel methodologies components of scorpion venom are characterized which revealed that along with peptides, many toxins are present in the scorpion venoms. Several of these toxins and peptides are valuable tools for the development of therapeutic drugs for the treatment of many diseases (Feng *et al*. 2013; Smith *et al*. 2013; Cordeiro *et al*. 2015; Ortiz *et al*. 2015; AbdulRahman *et al*. 2016; Romero-Gutierrez *et al*. 2017). In clinical trials, Vidatox (venom extracted from the *Junceus Rhopalurus* scorpion) is used for hepatocellular carcinoma (Giovannini *et al*. 2017).

The venom peptides are used to cure different diseases like cardiovascular diseases (Wang *et al*. 1994; Hmed *et al*. 2013; Attarde and Pandit 2016), HIV (El-Bitar *et al*. 2015; Zabihollahi *et al*. 2016), epilepsy (Wang *et al*. 2001), autoimmune diseases (Attarde and Pandit 2016), lung cancer (Roger *et al*. 2007; Jahchan *et al*. 2013; Bechohra *et al*. 2016), oral cancer (Tong-ngam *et al*. 2015), human leukemia cell lines (Heinen and Veiga 2011; Ding *et al*. 2014; Rashidi *et al*. 2016), brain tumor (Dardevet *et al*. 2015), glioma (Cheng *et al*. 2014), neuroblastoma (Dardevet *et al*. 2015), kidney tumor (Scholl *et al*. 2013), prostate tumor (Diss *et al*. 2005; Nakajima *et al*. 2009; Al-Asmari *et al*. 2016), breast cancer (Lansu and Gentile 2013; Perez-Neut *et al*. 2015; Al-Asmari *et al*. 2016), and pancreatitis (El-Ghlban *et al*. 2014). These observations have provided insight into the application of scorpion venom peptides and toxins as a novel therapeutics for different diseases (Ding *et al*. 2014; Tong-ngam *et al*. 2015).

Scorpion toxins for analgesic

Many Asian scorpions are used in the medicine to treat acute and chronic pain, that is, *Buthus martens* Karsch (BmK). BmK-AS and BmK dIT-AP3 toxins isolated from BmK scorpion showed antinociception and antihyperalgesia for the inflammation induced by carrageenan in the mice by blocking or modulating the Na^{+} channel of nociceptors (Xiong *et al*. 1999; Chen and Ji 2002; Joseph and George 2012).

Scorpion toxins for epilepsy

Antiepileptic drugs (AEDs) are most widely used to cure the epileptic seizures. But these drugs produce very severe side-effects, such as cognitive impairment, chronic toxicity, teratogenesis, and sedation. Therefore, there is a need to develop new AEDs for epilepsy (Raza *et al*. 2001). *Buthus martensi* Karsch is a Buthid scorpion, whose crude venom and peptides have been used for epilepsy. In Chinese medicine, the body of scorpions and especially its tail has been used to cure the several neurological disorders such as apoplexy, paralysis, and epilepsy (Villetti *et al*. 2001).

Scorpion toxins for malaria

Different antimalarial drugs are employed for the prevention and treatment of malaria. Meucin-25 and Meucin-24 were first isolated from *Mesobuthus eupeus* scorpion which specifically kill the *Plasmodium falciparum* and retard the growth of *Plasmodium berghei*, and do not damage the mammalian cells. Different antimalarial drugs are developed from these two venom-derived peptides (Gao *et al*. 2010).

Scorpion toxins for cardiovascular diseases

Many toxins, for example, desintegrins and integrins extracted from different sources of venom, act on the cardiovascular system by disrupting coagulation cascade (Joseph and George 2012). A toxin isolated from the venom of *Androctonus australis* is able to stimulate the secretion of atrial natriuretic peptide, similarly BmK I toxin extracted from *Buthus martensi*, is able to change the cardiac contraction (Lu *et al*. 2006; McLane *et al*. 2008).

Scorpion toxins for autoimmune diseases

Peptides derived from scorpions are blockers of potassium channel (Kv1.3) in memory T cells, and are able to utilize for the treatment of bone resorption, rheumatoid arthritis, multiple sclerosis, and other autoimmune diseases. For example, Kaliotoxin (KTX) and OSK1 toxins are immunosuppressive agents, which are isolated from the *Androctonus mauretanicus* and *Orthochirus scrobiculosus* scorpions, respectively (Crest 1992). Both of the toxins block the K^+ channel (Kv1.3), which is a suitable pharmacological target for the immunosuppressive therapy (Chen and Chung 2012).

Scorpion venom for treatment of diabetes

It has been demonstrated that scorpion venom combined with Chinese medicines, is very effective in diabetes treatment (Xie and Herbert 2012; Bouafir *et al*. 2016). Previous studies have exhibited that scorpion had antidiabetic effects and are able to activate b-islets (Xie and Herbert 2012; Bouafir *et al*. 2016). The observation demonstrated that scorpion peptide from *Tityus bahiensis* and *Tityus serrulatus* caused the increased proliferation of β cells in pancreas (El-Ghlban *et al*. 2014; Bouafir *et al*. 2016).

Scorpion venom and microbial infections

Scorpion has innate immune system which enables them to resist microbial infections, which revealed that there are different antimicrobial peptides in scorpion (Cao *et al*. 2014). Different toxins were isolated from the scorpion venom (*M. martensii*), which have antimicrobial activity, such as BmKn1 and BmKn2. BmKn2 inhibits the growth of bacteria (Zeng *et al*. 2004; Cao *et al*. 2014). Mucoporin is another antibacterial peptide which specifically inhibits the Gram-positive bacteria (Dai *et al*. 2008). Ctriporin is a new peptide extracted from the *Chaerilus tricostatus* scorpion which specifically resists the *Staphylococcus aureus* (Fan *et al*. 2011).

Scorpion toxins for cancer

It has been suggested that the potential of scorpion venom for the treatment of diseases is due to the presence of pharmacologically important substances, such as amino acids, nucleotides, inorganic salts, biogenic amines, enzymes, and toxic peptides (Ortiz *et al*. 2015; Al-Asmari *et al*. 2016; Xueli *et al*. 2017). Despite huge efforts, current treatments for cancer such as radiotherapy and chemotherapy are not satisfactory

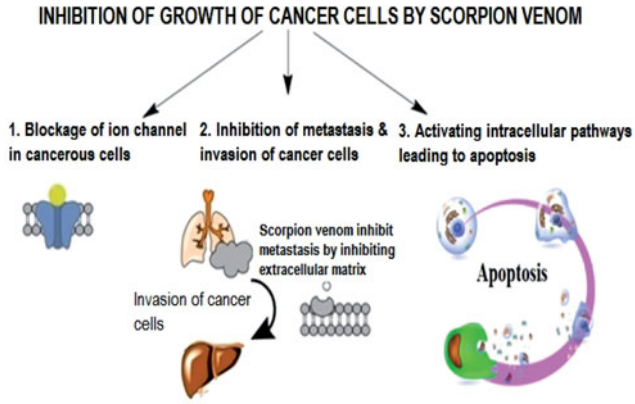

Figure 4. Mechanism of inhibition of growth of cancer cells by scorpion venom.

(DeSantis *et al*. 2014; Rao *et al*. 2015) and have many side effects on healthy tissue surrounding tumors. Furthermore, tumor cells develop resistance to these therapies (DeSantis *et al*. 2014; Rao *et al*. 2015). Recently, it has been demonstrated that scorpion venoms inhibit the growth of different cancer cell lines through distinct mechanisms (Figure 4): (1) blockage of specific ion channels or bind to the specific targets in the membranes of cancer cells (Rao *et al*. 2015) (2) inhibiting metastasis and invasion of cancer cells (Turner and Sontheimer 2014; Salem *et al*. 2016); (3) activating intracellular pathways leading to apoptosis and cell cycle arrest (Gupta *et al*. 2010; Pedersen and Stock 2013; Ding *et al*. 2014; Djamgoz *et al*. 2014; Salem *et al*. 2016).

In vitro, apoptogenic, cytotoxic, and antiproliferative effects have been demonstrated by use of crude venom of scorpion species (Biswas *et al*. 2012; Ding *et al*. 2014; Al-Asmari *et al*. 2016). SH-SY5Y (neuroblastoma cells) (Zargan *et al*. 2011; Dardevet *et al*. 2015) and MCF-7 (breast cancer) (Zargan *et al*. 2011; Perez-Neut *et al*. 2015) cell lines treated with venom of *Odontobuthus doriae* accelerate cell death and increase nitric oxide production which is related to caspase activation and mitochondrial depolarization, present in apoptosis. It has been studied that *Odontobuthus doriae* venom not only induces antiproliferation and apoptosis in cancer cells but also inhibits the DNA synthesis in cancer cell lines (MCF-7 breast cancer) (Feng *et al*. 2008; Lansu and Gentile 2013; Perez-Neut *et al*. 2015; Al-Asmari *et al*. 2016). ICD-85 is another venom peptide that exhibited potential antiproliferation effects against breast cancer (Koohi *et al*. 2009).

Venom peptides of *Rophalurus junceus* revealed remarkable antiproliferative and cytotoxic effects on myeloma cell line P3-X63 (Betancourt *et al*. 2009). Venom peptides of *Heterometrus bengalensis* exhibited

apoptosis-inducing and antiproliferative properties on K562 and U937 leukemia cell lines (Das *et al*. 2007; Heinen and Veiga 2011; Ding *et al*. 2014; Rashidi *et al*. 2016). Venom peptides of *Leirus quinquestriatus* inhibit the growth of brain tumors (Veiseh *et al*. 2007; Dardevet *et al*. 2015). Additionally, venom of *Buthus martensi* induced cell death by antiproliferative and apoptosis effect, and reduces the growth of glioma cells (U251-MG) (Wang and Ji 2005; Cheng *et al*. 2014). It has been demonstrated that peptide extract from the scorpion venom is potential therapeutic agent against prostate cancer (Diss *et al*. 2005; Nakajima *et al*. 2009; Zhang *et al*. 2009; Al-Asmari *et al*. 2016). A polypeptide extracted from *Buthus martensi Karsch* (Bmk) has also cytotoxic, apoptosis, and antiproliferative activities against prostate cancer and suppression of S180 sarcoma (Zhang *et al*. 2005).

These findings indicate the presence of compounds in the scorpion venom that can bring about apoptosis and antiproliferation. It is clear that apoptosis and antiproliferation of cells are widely recognized common factors in biological response of cancer and key mechanism to a variety of therapeutic drugs. Several previous studies have been attempted to find out the antiproliferative and apoptotic properties of scorpion's venoms (Wang and Ji 2005; Das *et al*. 2007; Petricevich 2010; Biswas *et al*. 2012; Almaaytah *et al*. 2013; Caliskan *et al*. 2013; Ding *et al*. 2014; Tong-ngam *et al*. 2015; Al-Asmari *et al*. 2016).

Conclusion

The scorpion venom is a highly complex mixture of molecules with high molecular activities. It is a rich source of bioactive peptides that offer promising biomolecules that may lead to the discovery and development of new drugs against a variety of diseases, that is, epilepsy, malaria, cardiovascular diseases, diabetes, and autoimmune diseases. It induces antiproliferative, apoptogenic, cytotoxic, and immunosuppressive effects which are achieved mainly through the inhibition of cancer growth, arrest of cell cycle, induction of apoptosis, and suppression of cancer metastasis. Therefore, scorpion venom can be used against a vast variety of cancers like, human neuroblastoma, glioma, brain tumor, leukemia, breast cancer, prostate cancer, and lung adenocarcinomas.

Disclosure statement

No potential conflict of interest was reported by the authors.

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