



Scorpion Venom–Toxins that Aid in Drug Development: A Review

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Abstract

Scorpion venom components have multifaceted orientation against bacterial, viral, fungal infections and other neuronal disorders. They can modulate the ion channels (K^+ , Na^+ , Cl^- , Ca^{2+}) of our body and this concept has been hypothesized in formulating pharmaceuticals. The triumphant achievement of these venom components as formulated anticancer agent in Phase I and Phase II clinical trials allure researchers to excavate beneficial venom components prohibiting DNA replication in malignant tumor cells. This review brings forth the achievements of Science and Technology in classifying the venom components as therapeutics and further application in drug product development.

Keywords Venom toxins · Ion channels · Arthropods · Peptides · Pharmaceuticals

Introduction

Science has always seized attention towards unusual things and if harvested, acts as a potent cure for human disorders. Poisonous, venom producing organisms, being a cause of mortality, have been a source of medicine to human syndrome since time immemorial. History says, in ancient Rome animal venoms were often used to diagnose smallpox, fever, leprosy and wound healing (Utkin 2015). One of the best contributions of animal venom in medical science is the discovery of bradykinin by Rocha e Silva and his team (Rocha e Silva et al. 1949) to reduce contraction of isolated guinea pig ileum upon incubating globulin fraction of dog

plasma with snake venom (obtained from *Bothrops jararaca*). Arthropod envenomation is usually common during the summer months of the year due to increased agricultural activities (Bawaskar and Bawaskar 2012). They secrete venom in response to external stimuli to capture prey, survive from predators and hence build a dynasty on this planet. At optimum concentration, the venom finds application in the field of biotechnology to prevent and cure pharmacological disorders. Venom–toxins exert their effect by interacting with a range of targets which include cellular receptors, membranes, and ion channels. α -Bungarotoxin (venom component of elapid snake *Bungarus multicinctus*), a type of α -neurotoxin proves to be fatal when it binds irreversibly to nicotinic acetylcholine receptor, is one of the best examples of the application of toxin in medical research (Utkin 2015; Young et al. 2003). ‘Tumour Paint’ outlined by natural toxins or peptides from natural organisms (viz. scorpions) and fluorescent molecules by a bunch of scientists from Blaze Bioscience, Fred Hutchinson Cancer Research Centre and the University of Washington to interpret the whereabouts of cancer in the body (Plummer 2017).

Drug resistance, adverse drug reactions in patients have aroused in finding other alternatives for the better living condition of humanity. Investigation to generate derivatives of the active components of animal venoms is ongoing to implement them in the eradication or cure of human disorders. One such example is Kn2-7 obtained by substituting positively charged amino acids in scorpion venom peptide BmKn2 (Investigación y Desarrollo 2015). The climatic

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condition of the originating place is an essential factor influencing concentration and quality of toxins present in arthropods (Utkin 2015). Alteration in living conditions and venom extraction procedure tailors venom toxicity and composition (Utkin 2015). Emerging methods of proteomics and genomics evoke finding of newer compounds that aid in formulating alternative pharmaceuticals (Utkin 2015). Our review elaborates or rather praises the novelty of scorpion venom and its application in pharmaceutical science.

With the breakthrough in research and development in science and technology, novel approaches have been adopted to unveil venom toxins that do not bind antivenoms but can amalgamate to form venom immunization mixtures (Williams et al. 2011; Casewell et al. 2013). The discovery of Captopril (venom from Brazilian snake *Bothrops jararaca*) (Utkin 2015; Escoubas and King 2009), an ACE inhibitor used in the treatment of hypertension, was a remarkable discovery as it was the earliest success in using the concept of ligand-based drug design (Utkin 2015). Research has proven that venom from arachnids decreases risk of heart transplant (Utkin 2015). Blocking N-type calcium channel for analgesic activity is mediated by a venom peptide from snail *Conus magus* (Escoubas and King 2009).

About Scorpion Venom

Scorpions (Class: Arachnida, Order: Scorpiones) are predatory arachnids occupying terrestrial habitat except for Antarctica, of which Buthidae family characteristic of their triangular-shaped sternum is most widely studied and dangerous scorpion among all (Luna-Ramírez et al. 2015). In the earlier days of the twentieth century, scorpion oil had many applications in tumors, infections and inflammatory conditions (Podnar 2015). Incidence of scorpion envenomation is reduced in Asia though established reports hint southern India to be the most affected zone (Bawaskar and Bawaskar 2012). The venom is an amalgamation of peptides, proteins, nucleotides, and amines (Fig. 1) that has emerged as a curative to many disorders

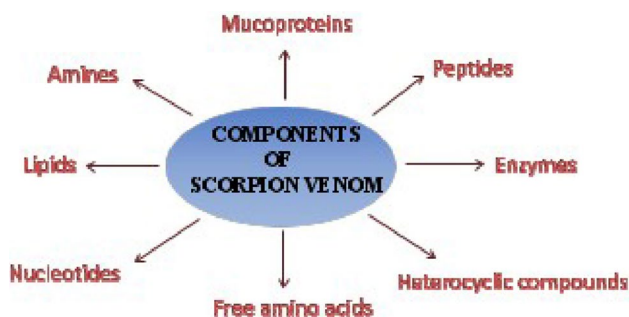


Fig. 1 Components present in scorpion venom

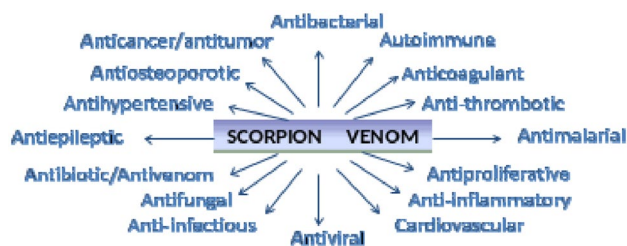


Fig. 2 Pharmacological characteristics of scorpion venom toxin

including cancer (Fig. 2). Often they lack enzymes in their venom except for *Mesobuthus tamulus*, *Centruroides exilicauda* and scorpions belonging to *Heterometrus* sp. (Gwee et al. 2002). The autonomic nervous system is perturbed during scorpion envenoming that elevate insulin and release glucagon, cortisol, angiotensin II (Krishnamurthy 2000). Scorpion venom toxins (SVTs) exert their pharmacological activities on human ion channels (Na^+ , K^+ , Ca^{2+} , Cl^-) (Kastin 2006) by blocking potassium and chloride channels (short chain peptides) or acting upon sodium and calcium channels (long chain peptides) (Smith et al. 2012; Petricevich 2010; Possani et al. 2000). Sodium channel acting toxins have shown to be most effective in mammals including humans (Ortiz et al. 2014). Venoms containing structurally diverse peptides with disulphide bridges exhibit multiple pharmacological properties and are very stable (Ortiz et al. 2014). The peptide mixture is known to trigger cell death (Ortiz et al. 2014) forming pores in biological membranes; a novel concept to destroy unwanted cells or initiate apoptosis.

Scorpion toxins are classified according to (a) the ion channels exhibiting pharmacological activity, (b) their three-dimensional structure (c) the respective receptors they bind to and (d) the action delivered upon the receptors (Gomes et al. 2010; Petricevich et al. 2013). Genus and species of a scorpion, its age, physiology, feeding state and region it inhabits are the factors governing venom toxicity (Oukkache et al. 2013). Adopting the fruitful extraction procedure to collect high-quality venom is very crucial (Oukkache et al. 2013). Stimulating the abdomen yields less toxic, transparent venom rather a pre-venom (a combination of salts and peptides) that can only elicit pain but an external stimulation applying electric shock to the scorpion generate highly concentrated toxin (Gomes et al. 2010; Oukkache et al. 2013; Inceoglu et al. 2003). The pre-venom differs from the venom in having (varied physical and chemical characteristics) a greater concentration of K^+ salt that can modulate or excite K^+ channels of the target organism (Oukkache et al. 2013; Inceoglu et al. 2003). pH of the freshly collected venom ranges from neutral to alkaline (Oukkache et al. 2013). A team of researchers from Ben M'sik Hassan II University, Morocco, have designed VES-4, a portable robot to milk

scorpion lessening the risk of venom gland puncture (Plummer 2017).

Scorpion Venom in Medicine

Disulphide-bridged peptides (DBPs/DBs) and non disulphide-bridged peptides (NDBPs/NDBs) are the important constituents of scorpion venom that display various pharmacological activities (Ortiz et al. 2014; Zeng et al. 2005) (Table 1). Several advancements to characterize the structure, properties and pharmacological activities of disulphide-bridged neurotoxic peptides have been carried out successfully till date (Ortiz et al. 2014). NDBPs were out of the limelight till the last decade and henceforth with their remarkable activities have mustered enough attention from researchers (Ortiz et al. 2014; Zeng et al. 2005). These peptides are flexible, usually cationic, potent antimicrobials, α -helical and amphipathic (Machado et al. 2016).

As Antimicrobial

Mucroporin, scorpine, hadrurin etc. are some antimicrobial peptides (AMP) obtained from scorpions (Ortiz et al. 2014) that have broad-spectrum activity against viral pathogens namely rotavirus, measles virus, adenovirus etc (Ortiz et al. 2014; Petricevich et al. 2013). Mucroporin derivative

mucroporin-M1 (from the venom of scorpion *Lychas mucronatus*) has proven to possess antimicrobial activity against bacteria and measles virus (Ortiz et al. 2014; Petricevich et al. 2013) and Hadrurin (from scorpion *Hadrurus aztecus*) (Heinen and da Veiga 2011) inhibits the growth of gram positive and gram negative bacteria (Petricevich et al. 2013; Zeng et al. 2005). Antibiotics (amoxicillin, cefuroxime, and erythromycin) in combination with Parabutopporin (from scorpion *Parabuthus schlechteri*) and Opistopporin1 (derived from African yellow leg scorpion *Opisththalmus carinatus*) display synergistic antibacterial activity (Zeng et al. 2005). Parabutopporin is an antibiotic peptide obtained from scorpions with significant immuno-regulatory effects (Remijsen et al. 2010; Willems et al. 2004). BmKn2, another NDBP identified in *Buthus martensii* Karsch established itself of being a satisfactory antimicrobial candidate against both gram negative and positive bacteria (Zeng et al. 2004). Stigmurin and TsAP-2, two NDBPs from scorpion *Tityus stigmurus* exhibited bactericidal and bacteriostatic activity in a study conducted by Daniele-Silva et al. (2016) and both were potent in controlling sepsis in lung and caecum of animals (Daniele-Silva et al. 2016).

As Antiviral

Hp 1090 was the first reported antiviral peptide collected from the venomous gland of scorpion *Heterometrus petersii*.

Table 1 Major peptides in different scorpions and their pharmaceutical properties

Scorpion	Major peptide(s)	Type of peptide	Uses
<i>Hadrurus aztecus</i>	Hadrurin	Non disulphide bridged peptide	As antimicrobial against <i>K. pneumoniae</i> , <i>S. typhimurium</i> , <i>E. coli</i> , <i>E. cloacae</i> , <i>P. aeruginosa</i> and <i>S. marcescens</i> ; hemolysis of human erythrocytes
<i>Parabuthus schlechteri</i>	Parabutopporin	Non disulphide bridged peptide	Antibiotic, immuno-regulatory effects
<i>Heterometrus petersii</i>	Hp1090	Non disulphide bridged peptide	Antiviral against hepatitis B and C infection
	Hp 1036	Non disulphide bridged peptide	Inhibits replication of HSV-1 virus
	Hp 1239	Non disulphide bridged peptide	Inhibits replication of HSV-1 virus
	Hp 1404	Non disulphide bridged peptide	Antibacterial
<i>Lychas mucronatus</i> (Chinese swimming scorpion)	Mucroporin	Non disulphide bridged peptide	Antiviral, antibiotic, antimicrobial
<i>Pandinus imperator</i> (emperor scorpion)	Scorpine	Disulphide and Non disulphide bridged peptide	Antibacterial, antiparasitic Potassium channel modifier
	Pandinin-2	Non disulphide bridged peptide	Antibiotic, antimicrobial, fungicide
<i>Opisththalmus carinatus</i>	Opistopporin	Non disulphide bridged peptide	Antibacterial against gram negative bacteria, antifungal
<i>Tityus serrulatus</i>	Stigmurin, TsAP1, TsAP2, T	Non disulphide bridged peptide	Antimicrobial, anticancer, Bradykinin potentiating activity
<i>Buthus martensii</i> Karsch	Bmka1, Bmka2, Bmkb1, Bmkn2	Disulphide bridged peptide	Antimicrobial
<i>Buthus occitanus</i>	K12	Non disulphide bridged peptide	Bradykinin potentiating activity
<i>Tityus discrepans</i>	Neopladine 1, Neopladine 2		Anticancer

Hp 1090 and Hp 1035 are structurally homologous but functionally distinct as the former is a successful candidate inhibiting in-vitro hepatitis C virus (HCV; a virus that resists all other antiviral agents) infection (Ortiz et al. 2014; Gomes da Mata et al. 2017; Yan et al. 2011). Venom peptides exert their activity either by disrupting the viral coat or preoccupy receptors preventing viral entry into the cell (Gomes da Mata et al. 2017). Kn2-7, an antimicrobial peptide was designed to amplify the α -helical structure and net positive charge of BmKn2 by replacing glycine, alanine and serine with lysine and arginine (Chen et al. 2012) and its hemolytic value was substantially decreased (Ortiz et al. 2014). The peptide directly targets the HIV-1 particle thus ceasing its viral activity. Assumptions made by Chen et al. (2012) on its mode of action indicate that the peptide on entering the viral coat dismantles the two segments (hydrophilic and hydrophobic) as the hydrophilic part form the innermost region along with the positive charge on the peptide (Chen et al. 2012). It also has a significant inhibitory role in replication-competent virus HIV-1 (Gwee et al. 2002; Chen et al. 2012; Hmed et al. 2013). To substantiate its inhibitory activity an anti-HIV assay was done by adopting a “replication-competent” HIV-1 virus; the peptide interacted with viral particles and strongly inhibited the “replication-competent” HIV-1 virus (Quintero-Hernández et al. 2013). This compound can also resist the growth of gram negative and gram positive bacteria and bacterial strains that have become resistant to antibiotics (Ortiz et al. 2014). Another peptide mucroporin S1 too revealed potent anti-HIV activity preventing chemokine receptor CCR5 and CXCR4 activity (Hmed et al. 2013). Kn2-7 was even successful when applied topically on *S. aureus* infection (Ortiz et al. 2014). Mucroporin-M1 substantiated of being an antiviral agent showing activity against measles virus, SARS coronavirus and Influenza A virus (subtype H5N1) and inhibited amplification of hepatitis-B virus (Ortiz et al. 2014; Gomes da Mata et al. 2017). An NDBP from scorpion *Chaerilus tryznai* initially inactivated viral particles of HCV in Huh7.5.1 cells but owing to its low bioavailability was unsuccessful in inhibiting ‘established infections’. This led to further designing of effective, histidine-rich peptides using the source peptide as template and these peptides proved to be efficient against HCV infection (Gomes da Mata et al. 2017). Crude venoms of Egyptian scorpions *Scorpiomaurus palmatus* and *Androctonus australis* delivered antiviral activity against HCV in an in vitro cell culture experiment carried out by El-Bitar et al. (2015), Gomes da Mata et al. (2017), El-Bitar et al. (2015). Further, they concluded that the antiviral activity of *Scorpiomaurus palmatus* remained consistent post-treatment with 1,10-phenanthroline or heat at 60 °C (El-Bitar et al. 2015) and paved the way for future antiviral therapeutics. Recent discoveries indicate two venom peptides (Hp 1036, Hp 1239) from *H. petersii* have destructive activity

on herpes simplex virus type-1 (HSV-1) (Ortiz et al. 2014) and venom components of Italian Scorpion *Hemiscorpius lepturus* proved to be active against HIV infection with IC₅₀ value 20 μ g/ml (Zabihollahi et al. 2016).

As Neurotoxins

Scorpion neurotoxins can bind effectively for a long time because they have a three-dimensional backbone that is highly stable by the presence of three or four DBs (Hmed et al. 2013). Compounds present in scorpion venom mostly target the nervous system (Podnar 2015). *Buthus martensii* Karsch (BMK, Family: Buthidae) scorpion or Chinese scorpion has been widely used as “ethnomedicine” in China in the treatment of neurological diseases that includes cerebral palsy, epilepsy and apoplexy (Hmed et al. 2013). Antinociceptive effect had been observed with Bmk AS (obtained from *Buthus martensii* Karsch) in sensory nerves (Hmed et al. 2013). Other scorpion derived toxins that exhibit antinociceptive activity include α -anatoxin, Amm VIII and β -toxin LqqIT2 (Hmed et al. 2013). Envenomation associated death of individuals is due to cardiovascular toxicity causing catecholamine release which initiates pulmonary oedema finally cardiac arrest (Gwee et al. 2002). The venom of scorpion *Leiurus quinquestriatus* develops synergistic effect along with alkaloid neurotoxins like veratridine, batrachotoxin and aconitine in the regulation of action potential (Heinen and da Veiga 2011; Catterall 1976). Reversible heterotrophic cooperation between the site of action of the neurotoxins and venom toxin (Catterall 1976) reorients the properties of Na⁺ ionophore by non-covalent interactions (Heinen and da Veiga 2011; Catterall 1976). Presently, researchers at the University of Collima (UCOL) have investigated on animal model that scorpion venom toxins have an effect on the release of dopamine when attached to receptors on dopaminergic neurons (Investigación y Desarrollo 2015). This release of dopamine can be a cure for Parkinson’s disease (Investigación y Desarrollo 2015; Lorenzo et al. 2012) (a condition when dopamine release is inhibited and muscle movement is prevented).

As Antimalarial

Antimalarial activity is exhibited by peptides that have cytolytic and K⁺ channel blocking activity at the N- and C-terminus respectively (Luna-Ramírez et al. 2016). Scorpine, a DBP, was the first described antimalarial peptide isolated from the venom of Emperor Scorpion, *Pandinus imperator* (family: Scorpionidae) (Ortiz et al. 2014). This peptide at 15 and 5 mM concentrations respectively displayed 98% death in sexual staged *Plasmodium berghei* and 100% depletion of *Plasmodium falciparum* parasites (Luna-Ramírez et al. 2016). AMPs meucin-13 and

meucin-18 reveal cytolytic activity on bacteria, fungi and yeasts while meucin-24 and meucin-25 (obtained from genetic sequences in venom gland) have intense activity in the inhibition of malarial parasites without impairing normal functioning of mammalian cells (Gao et al. 2009, 2010). Meucin-18, pandinin 2, ctriporin are some NDBPs that have an inhibitory role in the growth of fungus *Candida albicans* (responsible for candidiasis infection in humans); yeast *Saccharomyces cerevisiae* can be inhibited by parabutopporin, opistopporin 1 and meucin-18 (Ortiz et al. 2014).

Bradykinin Potentiating Activity

Bradykinin potentiating scorpion venom peptides are devoid of disulphide bridges and enriched with proline residues at the C-terminus (Goudarzi et al. 2017). Studies report that proline enrichment at the C-terminal end contributes in its increased bradykinin potentiating activity (Goudarzi et al. 2017). A unique characteristic of these peptides is that their functioning involves a synergistic action or bradykinin proteolysis prevention (Rioli et al. 2008). The thirst to excavate bradykinin potentiating arthropod venom peptides that activate argininosuccinate synthetase is ongoing as they can act as potential targets to reduce arterial blood pressure (Camargo et al. 2012). Venom extracted from scorpions *T. serrulatus* and *B. occitanus* contain bradykinin-potentiating peptides (peptide T and K12 respectively) (Petricevich et al. 2013; Zeng et al. 2005). Peptide T was the first discovered NDBP that was capable of initiating in-vivo bradykinin activity (Petricevich et al. 2013; Zeng et al. 2005). These peptides are notable for being strong hypotensive agents (Petricevich et al. 2013). Further studies on *T. serrulatus* reveal that its bradykinin potentiating activity regulates blood pressure as bradykinin receptor synthesis and ACE activity is averted (Goudarzi et al. 2017). The first member of *T. serrulatus* hypotension family, TsHpt1, achieved success as an initiator of hypotensive effect of bradykinin in normal rats (Verano-Braga et al. 2008). TsHpt1 ([17–25]), a synthetic analog designed using the C-terminal peptide of the native member and both compounds showed bradykinin independent hypotensive activity (Verano-Braga et al. 2008). Bmkbpp, a bradykinin potentiating peptide was identified by cDNA cloning from scorpion *B. martenisii* Karsch (Zeng et al. 2005). Goudarzi et al. (2017) conducted a study to illustrate the bradykinin potentiating activity of three Iranian scorpions namely *Hottentotta saulcyi*, *Odontobuthus doriae* and *Mesobuthus eupeus* and demonstrated their effect using organ bath instrument on Guinea pig ileum and rat uterus tissues (Goudarzi et al. 2017).

As Antineoplastic Agent

Natural therapy, be it plant or animal derived, is occupying a vast section gradually as antineoplastic or cytotoxic agent due to the increasing uncontrollable adverse effects and ineffectiveness (possibly in metastasis and recurrence conditions) of chemotherapy and radiotherapy. The last three decades have seen attempts at detecting promising anticancer activity of animal venoms and toxins, some of which are presently under clinical trial (Lorenzo et al. 2012). Scorpion venom can be an amazing therapeutic agent against cancer as it inflicts upon cancer cells by arresting cell cycle at the S-phase thereby acting as a proliferative curb (Lorenzo et al. 2012; Ahluwalia and Shah 2014). SVTs are an inducer of apoptosis, aggravates neoplastic cells by amplifying production of nitric oxide, shows caspase-3 activity and depolarizes mitochondrial membrane (Ahluwalia and Shah 2014). Presently, positive results from in-vivo, in-vitro examination and Phase I and II clinical trials have proven SVTs as anticancer therapeutic agent (Kastin 2006). Cuba and Dominican Republic islands dwelling Blue (or Red) Scorpion (*Rhopalurus junceus*) is steadily gaining fame as an antineoplastic (Podnar 2015; Lorenzo et al. 2012) and is the thrust area for inquisitive researchers as numerous experiments are being executed on this arthropod to evaluate its pharmacological aspects. A protein constituent of this scorpion can abolish cancer cell proliferation (Ahluwalia and Shah 2014). Natives of the Caribbean island have been using this venom as an antitumor agent since 1997 (Podnar 2015). Novel discovery elucidates venom of this scorpion acts as a pain reliever and replenisher of energy in cancer patients (Lorenzo et al. 2012). A recent research work proposed by Díaz-García et al. (2017) on treatment recalcitrant Triple Negative Breast Cancer (TNBC) cell line (MDA-MB-231) demonstrated high cytotoxic activity of this arthropod venom breaking grounds for new therapeutic approaches (Díaz-García et al. 2017).

Traditionally used, venom of BMK scorpion is a possessor of multiple pharmacological activities including cancer and brain tumor (found effective against brain tumor cell line U251-MG) (Gomes et al. 2010; Díaz-García et al. 2013). Antitumor-analgesic peptide (AGAP) obtained by the application of recombinant DNA technology from this scorpion venom and expressed in *Escherichia coli* have confirmed to have both analgesic and antitumor activity in mice (Hmed et al. 2013). This peptide in a much lower dose compared to other antineoplastic agents has revealed of increasing antitumor activity with very few adverse effects (Oukkache et al. 2013). It can inhibit glioma cell proliferation by regulating their ion channels (Gomes et al. 2010). A peptide isolated from this scorpion has proven to be an anti-thrombotic (Petricevich et al. 2013) and another polypeptide having dose-dependent inhibitory activity arrested cell cycle of prostate cancer cell line DU-145 at G1 phase (Mishal et al.

2013; Zhang et al. 2009). Antiapoptotic role of this polypeptide can be due to highly expressed Bax (proapoptotic) or downregulated Bcl-2 (antiapoptotic) (Zhang et al. 2009). BMHYA1, an enzyme procured by extraction and purification from this scorpion hampers overexpression of CD44 surface marker in cancer cells (Hmed et al. 2013).

Indian black scorpion (*Heterometrus bengalensis* Koch) venom showed cell growth inhibition, cell cycle arrest, apoptogenic features and antiproliferative role when explored on human leukemic cells (U937 and K562) (Das Gupta et al. 2007). Peptides neopladine 1 and neopladine 2 (venom obtained from scorpion *Tityus discrepans*), when tested on SKBR3 cells (human breast cancer cells) bind them inducing apoptosis as FasL and Bcl-2 is expressed and the effect is found proportional to time (Ahluwalia and Shah 2014; D'Suze et al. 2010). Ning et al. (2012) had conducted an in vivo study by successfully implanting Lewis Lung cells onto the subcutaneous layer of C57BL/6 mice to explore the apoptotic effect of a scorpion venom derived polypeptide on tumor cells (Ahluwalia and Shah 2014; Ning et al. 2012). Their target hints that the polypeptide, when compared to cyclophosphamide (an alkylating agent) shows improved apoptotic activity, can inhibit VEGF and TGF β -1 expressions and assists in the maturation of dendritic cells (Ahluwalia and Shah 2014; Ning et al. 2012).

Chlorotoxin, a small protein containing 36 amino acids, results in paralysis of normal cells when a scorpion defends an aggressor or captures its prey (Dardevet et al. 2015) but this toxin ceases metastasis invasion and checks mobility of cancer cells (Chen et al. 2012). The inability of chlorotoxin to bind normal human cells was suggestive of its nontoxic effect (Podnar 2015; Gomes et al. 2010). Under in-vitro conditions, this peptide has shown impairment of glioma invasion by inhibiting gelatinase activity (Gomes et al. 2010) of MMP-2 (matrix metalloproteinase 2). Chlorotoxin is mixed with a type of IgG antibody to obtain the required structure that can be capable of targeting tumor cells (Bancroft 2016). Further, Sun et al. (2008) had selected chlorotoxin as a measure to screen the early detection of cancers of skin, esophagus, colon and lungs (Gomes et al. 2010). The toxin is found competent in quicker identification of positive lymph nodes in breast, prostate and testicular cancers and hence prognosis can be done faster (Heinen and da Veiga 2011).

Scorpion venom component III (SVC III) has profound activity on the NF κ B signaling pathway (has role on immune cell generation, lymphocyte development and cell apoptosis) and thus selectively act upon human leukemia Jurkat cell line and THP-1 cells (Mishal et al. 2013). SVC III prevents cyclin D1 production and inhibits cell cycle at G1 phase (Mishal et al. 2013). Venom derived from *Odontobuthus doriae* is capable of platelet aggregation and possesses proteolytic enzymes (Mishal et al. 2013). It is a cytotoxic and apoptogenic agent as it has lactate dehydrogenase (LDH)

(Mishal et al. 2013). This LDH can lower cell viability activating caspase-3 and mitochondrial depolarization (Ahluwalia and Shah 2014). Proteases derived from scorpion *Mesobuthus gibbosus* are proteolytic and gelatinolytic against human lung adenocarcinoma cell line (A549) (Mishal et al. 2013). An extensive research on venom from Blue Scorpion has drawn a conclusion that it can be an analgesic, anti-inflammatory and antitumor agent (Podnar 2015). To support this research, a drug named Vidatox 30CH has been formulated by Labiofam (a Cuban company) which reports of lessening the spread of cancer cells, increase life expectancy among cancer patients and has negligible side effects on patients (Podnar 2015). This scorpion venom induces apoptosis in HeLa cell line via both extrinsic and intrinsic pathway as p53 upregulation stimulates bax and downregulates bcl-2 (Díaz-García et al. 2013). A549 cell necrosis, as demonstrated by Díaz-García et al. (2013) was noticed along with p53 and bax downregulation when this scorpion venom was further examined (Díaz-García et al. 2013). Demetrio Rodriguez Fajardo, a 17-year-old Mexican has gained enough recognition by discovering a low molecular weight protein from scorpion venom and has developed a prodrug that can be used as a treatment against breast cancer (Takahashi 2014). He has even quoted that this protein has profound inhibitory activity on uterine cancer cells. This protein as a drug substance in the treatment of cancer is efficacious than conventional therapy even for diabetic patients (Takahashi 2014).

Zargan et al. (2011) conducted a study on human breast cancer cell lines (MCF-7) putting into practice the venom of *Odontobuthus doriae* (family: Buthidae) or yellow Iranian Scorpion (Zargan et al. 2011) that confirmed venom a suppressor of DNA synthesis by arresting S-phase (Zargan et al. 2011). Furthermore, it can induce apoptosis by increasing reactive nitrogen intermediates, depolarization of mitochondrial membrane and caspase-3 activity (Ahluwalia and Shah 2014; Zargan et al. 2011). Reduction in tumor size and antiproliferative activity was observed in a study conducted on mice with venom peptide (also a potassium channel blocker) extracted from *Centruroides margaritatus* (Chaisakul et al. 2016). Pan and his fellow co-workers at the University of Illinois have initiated in-vitro targeting of cancer cells by constructing nanoparticle encapsulated (named Nano Venin) SVT peptide (TsAP-1) (Liu et al. 2003). A research team of UCOL (though at primary stage of their research) says that venom toxins contain peptides that can bind to ion channels of cancer cells inducing death (Investigación y Desarrollo 2015; Gomes et al. 2010).

In Other Fields of Medicine

Scorpions, the age-old arthropods possessing venoms were first utilized in the field of medicine in 1909 as antivenom or

rather antibody to scorpion stings (Petricevich et al. 2013). Highly toxic venoms with elevated LD₅₀ value are considered effective when formulated as antivenoms (Oukkache et al. 2013). Further investigations on this ejected fluid have turned fruitful in its manifold application in medicine. Doctors prefer using the venom as an anaesthetic by paralyzing the body when performing long-term surgery (Podnar 2015). The venom of *Uroplectes lineatus* finds clinical application in the field of dermatology (Rapini et al. 2007). A possessor of hyaluronidase, scorpion venom inhibits hyaluronan (important because of its metastasis causing capacity) present in breast cancer cell lines (Mishal et al. 2013). Increase in calcium ion influx or rather an immunomodulatory role of NDBPs is another notable activity of SVTs (Daniele-Silva et al. 2016). Examples include peptides paratuboporphin and opistoporphin that indulges in modifying productivity of superoxide, chemotaxis at concentration 10⁻⁷ to 10⁻⁶ M (Daniele-Silva et al. 2016). Pantinin-3, a cysteine-free peptide from venom of scorpion *Pandinus* can inhibit the growth of pathogen S13, a vancomycin-resistant *Enterococcus* (VRE) and causative organism of many human infections; thus gaining notice in the treatment of VRE infections (Zeng et al. 2013). Toxins with short-chains act as potassium voltage-gated channel blockers thereby reducing T-lymphocyte (T-cell) proliferation and this principle is applied in the treatment of autoimmune disorders like rheumatoid arthritis (Chandy et al. 2004). These toxins are sources of peptidyl inhibitors of potassium channels of which some possess anti-inflammatory and antiproliferative role by depolarizing human T cells (Petricevich et al. 2013).

Future Prospects in Drug Discovery

The increment in newer techniques in the field of Research and Development (R&D) have led scientists to brood over to find cure from nature be it from plant or animal. A rough estimate brings forth the fact encompassing constant usage (nearly 40%) of Nature in the formulation of pharmaceuticals (Burke 2015). With the evolution of proteomics, genomics and transcriptomics, drug discovery from Nature and her resources has been a splendid approach. Though only a handful of 'biologically important' toxins could be derived from toxin-secreting animals still it calls for a revolution to fetch cure from these animals. Thus, it is mandatory to gain a thorough knowledge of the evolutionary history and the ecology of these animals before putting them into practice for the development of future pharmaceuticals (Casewell et al. 2013).

The process of establishing a chemical entity as a clinical candidate is an enormous and time-consuming process. Thousands of potential candidates are screened and only a few with potentialities emerge to face challenges in the

pharmaceutical market. Till date, only a few venom peptide derived drugs have been approved by the FDA and furthermore are undergoing clinical trials or at the stage of pre-clinical development (Henney 2015). Captopril, ziconotide, atracurium, eptifibatid are some of the established drug products formulated from venom toxins (Harvey 2014). The synergistic property exhibited by K⁺ salt and peptide (scorpion pre-venom and venom constituents) indicates the discovery of effective pharmaceuticals in the near future (Inceoglu et al. 2003).

Drugs and pharmaceuticals tend to have an affinity towards the ion channels of our body in conserving human physiology and usually, therapeutic advancement is being made by targeting these channels (Bennett and Guthrie 2003; Kaczorowski et al. 2008). Venom peptides being reservoir of chemical components are the tools to identify or characterize the function and structure of ion channels of our body. The rationale underlying the choice in targeting ion channels lies in their increased accessibility and success in delivering intended pharmacological activity upon being targeted by traditional or novel drug (Kaczorowski et al. 2008; Niemeyer et al. 2001). The failure of a drug candidate or an new drug application (NDA) often lies in the interaction with unrelated targets or channels (Kaczorowski et al. 2008). The key to ion channel drug discovery is embedded in the approaches that include in-vivo, in vitro targeting by the candidate drug product and other traditional drugs. Ziconotide, one such example, was developed to treat pain induced by intrathecal administration and by in vivo methods, was hence confirmed to treat pain as a calcium channel blocker (Kaczorowski et al. 2008).

Voltage-gated sodium channels have enormous contribution in blooming of metastasis as many cancers are enriched with these channels (Hmed et al. 2013). It is said that potassium channel has ardent activity in promoting proliferation of tumour cells (Villalonga et al. 2007) and SVTs being bona fide blockers of the K⁺ channels can be highly efficacious as active pharmaceutical agents (Petricevich et al. 2013; Cremonese et al. 2016). This channel seldom acts as therapeutic target in the diagnosis of cardiovascular diseases, autoimmune disorders and inflammation (Bergeron and Bingham 2012). Reports confirm that Ca²⁺ signalling and Ca²⁺ channel expression are often associated with cancer proliferation and metastasis (Monteith et al. 2012). Innumerable Ca²⁺ channels mark heart diseases and migraine (Niemeyer et al. 2001). Venomous animals are enriched with diverse venom components and are proficient in targeting voltage-gated ion channels; favouring analysis of these channels and their isoforms (Israel et al. 2017).

Noxiustoxin, the first K⁺ channel blocker isolated from scorpion *Centruroides noxius* dates back to more than 30 years (Dutertre and Lewis 2010). SVT components that modify sodium channels were first identified as neurotoxins

that abolish specific channel activity (Zhu and Gao 2006). The sodium and potassium channel aiming SVTs are composed roughly of 60–76 amino acids with disulphide bridges and 30–39 amino acids respectively (Petricevich et al. 2013). Long-chain SVTs that exert their effect on vertebrate voltage-gated sodium channel (Gwee et al. 2002; Petricevich et al. 2013) are of two types— α -toxins and β -toxins (Petricevich et al. 2013) (Fig. 3); α -toxins bind to receptor site 3 lingering the inactivation of the channel (Gwee et al. 2002) and β -toxins to receptor 4 that boosts up the activation of the channel (Gwee et al. 2002). The K^+ channel toxins are accordingly classified into α , β and γ potassium toxins on the basis of their cysteine pairing and sequence identity (Duttre and Lewis 2010). K^+ channel SVTs bind reversibly to the exterior portion of the channel hindering the passage of ions through the membrane (Gwee et al. 2002; Petricevich et al. 2013). The sole selective inhibitor of K^+ channel is iberiotoxin (obtained from the scorpion *B. tamulus*) (Gwee et al. 2002). Peptide components of venom collected from the scorpion *Buthotus hottenta* were the first to exert activity over the ryanodine receptor (receptors that release stored calcium from endoplasmic or sarcoplasmic reticulum) (Quintero-Hernández et al. 2013). Ryanotoxin, another peptide that can induce the receptors to a subconductance state, was purified from scorpion *Buthotus judaicus* (Quintero-Hernández et al. 2013). Venom peptides from *Pandinus imperator* have high affinity for the ryanodine receptor (Quintero-Hernández et al. 2013).

Researchers persistently ponder over to reshape a drug candidate to act as ligand to other receptors and a new therapeutic approach is thus achieved (Burke 2015). A venom toxin with therapeutic approach can be modified by making amendments in its outer coating or by orienting its release kinetics such that it acts as a prodrug at the time of administration and upon contact with its substrate exhibits its activity (Zargan et al. 2011). In spite of being a potent bradykinin potentiator, TsHpt1 (Ts14), on further examination was found to exert anti-inflammatory, proangiogenic and anti-fibrogenic activities thereby proposing to be a drug candidate for chronic diseases (Cassini-Vieira et al. 2017)

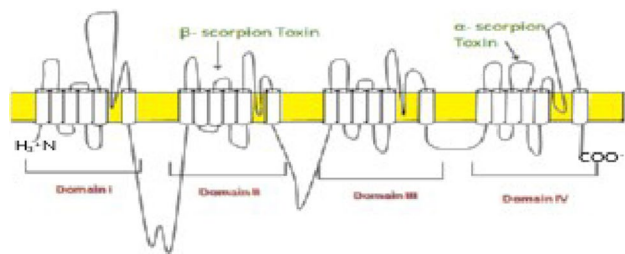


Fig. 3 Voltage-gated sodium channel specific α - and β -scorpion toxins. Reproduced with permission from Zhang et al. (2013), Stevens et al. (2011) and Catterall (2000)

.Subsequently, this approach in drug delivery is clinically beneficial as healthy, normal cells loose communication with the toxin, their proliferation less hampered and the victim too gets relieved from the disease.

Conclusion

Diversity of nature's medicinal properties has served as a healer and man has embraced her potentialities since evolution. Arthropods secrete venom in order to protect themselves from predation and this venom upon contact with man delivers change in physiologic activity which can be harnessed as therapy. Thus arthropod venoms have occupied a niche in the pharmaceutical industry. Application of the recombinant DNA technology (especially using *E. coli* system due to its simplicity and high effectiveness) in the synthesis of peptides is becoming popular with every passing day (Zhang et al. 2014). AMPs derived from scorpion venom are cytotoxic against eukaryotic cells (Ortiz et al. 2014), the minimum inhibitory concentration (MIC) of scorpion NDBPs against microorganisms and the concentration at which it is cytotoxic to human cells is very close (Ortiz et al. 2014). Still, these AMPs find application topically when applied on skin infections, inhibiting of growth of oral bacteria (associated with plaque formation) (Ortiz et al. 2014; Zeng et al. 2005). Pantinin1 (obtained by cloning cDNA of *P. imperator*), Pantinin1, BmKbpp (from scorpion *Mesobuthus martensii* Karsch), VmCT1 (synthesized from cDNA library of *Vaejovis mexicanus smithi*) are some AMPs that can inhibit growth of gram negative and positive bacteria at an MIC preferably non toxic to human erythrocytes (Ortiz et al. 2014) confirming as antimicrobials in the pharmaceutical industry. Peptides derived from scorpion venom or by the application of biotechnology have shown amazing results as pharmaceuticals. When synthetically derived drug products fail to generate their task in being static or cidal towards pathogens, these peptides come into action. Examples include imcorporin (from scorpion *Isometrus maculatus*), ctriporin (from scorpion *Chaerilus tricostatus*), Vejovine (from *V. mexicanus smithi*) (Ortiz et al. 2014). Antibiotics in combination with AMPs show synergistic inhibitory activity towards resistant strains of microbes (Ortiz et al. 2014).

The alarming rise in pharmaceuticals to formulate cure to epidemic, endemic and pandemic diseases evokes the hope that SVTs, the possessor of multi-potential components are sure to become the heir in the near future. These molecules are drawing attention as precious tools in the research and development of newer pharmaceutical formulations (Zargan et al. 2011). SVTs and their outstanding performance in Phase I and Phase II clinical trial as effective therapeutic agent is a huge success (Heinen and da Veiga 2011). Research to accomplish the benefits of scorpion venoms is

ongoing in all corners of the world and is sure to hit the benchmarks by the next decade to establish a better world.

Compliance with Ethical Standards

Conflict of interest Authors disclose no conflict of interest.

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