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•Review•

Bioactive peptides from scorpion venoms: therapeutic scaffolds and pharmacological tools

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[ABSTRACT] Evolution and natural selection have endowed animal venoms, including scorpion venoms, with a wide range of pharmacological properties. Consequently, scorpions, their venoms, and/or their body parts have been used since time immemorial in traditional medicines, especially in Africa and Asia. With respect to their pharmacological potential, bioactive peptides from scorpion venoms have become an important source of scientific research. With the rapid increase in the characterization of various components from scorpion venoms, a large number of peptides are identified with an aim of combating a myriad of emerging global health problems. Moreover, some scorpion venom-derived peptides have been established as potential scaffolds helpful for drug development. In this review, we summarize the promising scorpion venoms-derived peptides as drug candidates. Accordingly, we highlight the data and knowledge needed for continuous characterization and development of additional natural peptides from scorpion venoms, as potential drugs that can treat related diseases.

[KEY WORDS] Scorpion venoms; Scorpion venom-derived peptides; Pharmacological properties; Drug development
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Introduction

Scorpions (Phylum Arthropoda, Class Arachnida, Order Scorpionida) are exceptionally successful arachnids; their emergence can be traced back to 400 million years ago [1, 2]. This group of animals consists of about 1500 various species from 15 families, all of which, throughout their evolution, have maintained their morphology largely unchanged [3, 4]. Scorpions are widely distributed worldwide with the exception of the Antarctic and Arctic regions. They have adapted to multiple habitats, including grasslands, tropical forests, caves, temperate forests, and savannas. The medically important scorpion members are largely from the family Buthidae represented by the genera Leirus, Buthus, Parabuthus, Buthotus, Androctonus, and Mesobuthus which are found in the Middle East, India, Asia, and North Africa. *Centruroides* spp. are found in Central America, Mexico, and the Southwest of the United States, while *Tityus* species are mostly from Central and South America, as well as the Caribbean [4, 5]. In these parts of the world and many others, scorpionism (scorpion stings) is an integral health issue, with widespread reports that scorpion stings are lethal [3, 6].

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Scorpionism is often detrimental to human subjects and poses a major health issue [7, 8]. Due to human advancements and population growth, human interaction with these arthropods has increased, often leading to instances when people are stung [3]. Every year, about 1.2 million scorpion envenomation cases are reported worldwide, which results in approximately 3250 deaths [9, 10]. Typically, scorpion envenomation symptoms are primarily determined by the composition of the venom, scorpion species, and the physiological response of the victim to the venom [4, 11]. As soon as a scorpion stings, local pain typically sets in, which may last for minutes, and the maximum severity typically reaches within five hours of envenomation. Nausea, vomiting, and sweating are common during this period due to excessive release of neurotransmitters [4, 12, 13], with typical symptoms in victims such as restlessness, hypersalivation, nystagmus, mydriasis, and dysphagia [12]. Consequently, victims may develop clinical symptoms including stimulation of the autonomic nervous system, an attack on the central nervous system, and, in rare cases, cardiac and respiratory failure, as well as death [14]. A cytotoxin produced by *H. Lepturus* induces psychological problems (mental disorders including schizophrenia, depression, and anxiety), hematuria, cutaneous necrosis, ankylosis of the joints, renal failure, necrotic ulcers, fatal hemolysis, hemoglobinuria, and even death [15]. Notably, there have been reports of scorpion envenomation victims who experienced multi-system organ failure driven by changes in the hormone levels, including a vast secretion of hormones such as cortisol, catecholamine, glucagon, and angiotensin-II (all of which are counter-regulatory hormones) and also elevated blood sugar levels and reduced insulin levels [4].

Scorpions, on the other hand, have been used since time immemorial, especially in traditional Asian and African medicine [6, 16]. Scorpions, their body parts, and venoms have been a remedy for various miscellaneous diseases, including cancer [17]. Interestingly, Cao *et al*. analyzed the genome sequence of *Mesobuthus martensii* [18], the most populous scorpion species from East Asian countries. According to traditional Chinese medicine, *M. martensii* is an essential raw material for the treatment of chronic pain, rheumatoid arthritis, epilepsy, and apoplexy. Its neurotoxic peptides, the active ingredients in their venom, represent a rich resource for drug development in modern medicine. Obtaining the genome of *M. martensii* increases the gene repertoire of the chelicerates and provides a toolkit to investigate this evolutionarily significant organism in a genetic and systemic biology setting [18]. Due to technological advances, numerous peptides from different scorpion species have been identified and characterized, providing excellent evidence that, in tandem with toxins, many other components, including important pharmacological peptides, are present in the venoms of the scorpion. Several studies have demonstrated that scorpion venoms or their components, especially peptides, can potentially treat neurological, immunological, infectious, cardiovascular, and neoplastic conditions [6]. In addition, it has been demonstrated that scorpion venom peptides can be utilized for the development of novel, highly specific medicines due to their distinct structural and functional properties [19]. This review focuses on the pharmacological properties of peptides purified and characterized from scorpion venoms and their possible mechanisms. We also provide the knowledge needed for the continuous development of additional drugs that can treat and manage emerging related ailments.

Composition of Scorpion Venoms

Scorpions utilize their venoms to forage and defend themselves from predators and rivals [20, 21]. The composition of scorpion venoms is heterogeneous and highly complex; it is composed of different concentrations of hemolytic toxin, cardiotoxin, nephrotoxin, neurotoxin, phosphodiesterases, glycosaminoglycans, cytokine releasers, phospholipases, hyaluronidases, histamine, serotonin, tryptophan, among others [22]. Classifying scorpion toxins is essential in order to understand the structure-function relationship of each individual group. In the scientific literature [23-26], it is common to find that the toxins are classified based on the following criteria: the specific receptor to which the toxin binds, the ion channel involved (calcium, sodium, chlorine, and potassium), peptide length (long chain and short chain), the type of response induced (activation/inactivation of the receptor) and the three-dimensional structure of the toxin. Since scorpion-derived venom peptides are diverse and have an extensive variety of pharmacological properties [6], they have been the most investigated scorpion venom components to date. These peptides are generally categorized into two classes based on their structure and effect: disulfide-bridged peptides (DBPs) and non-disulfide-bridged peptides (NDBPs) [27-29]. Besides, enzymes (larger proteins), amines, free amino acids, mixtures of inorganic salts, lipids, and nucleotides are also present in the venoms of scorpions.

Disulfide bridged peptides (DBPs)

The DBPs usually contain 31 to 70 amino acids cross-linked with 3 or 4 disulfide bridges [30]. Throughout the structure of DBPs, there are at least two cysteines that interact and form a disulfide bridge [23]. Amongst the families of scorpion toxins with these bridges are calcium channel bound toxins (CaTx), sodium channel bound toxins (NaTx), chloride channel bound toxins (ClTx), and potassium channel bound toxins (KTx) [31]. DBP binds more specifically to their target structures, predominantly voltage-dependent ionic channels. Its secondary structure consists of an α-helix next to a double or triple antiparallel chain β-sheet supported by four disulfide bridges for those functioning on sodium and chloride channels and three bridges for those working on calcium and potassium channels. They have two positive basic amino acid poles. While some DBPs affect mammals, others are reported to be toxic to crustaceans or insects. In light of their exceptional specificity and potency, these peptide probes are extremely useful in investigating the functions and structures of various ion channels, and present potential lead molecules for pharmaceutical research and novel drug development for the treatment of a variety of ion channel-related conditions,

such as chronic pain, autoimmune diseases, glioma, neurological diseases, and epilepsy [27]. According to their structural characteristics, the members of this superfamily can be further classified into long-chain and short-chain scorpion toxins.

Long-chain scorpion toxins

These toxins are typically larger molecules with 56–76 residues [19]. They are also referred to as sodium channel toxins (NaTxs) as they selectively target Na^+ channels [32]. Notably, these toxins have been crucial in mapping Na^+ channel proteins, both structurally and functionally [33, 34]. Long-chain scorpion NaTxs are further subdivided into α-toxins and β-toxins based on their effects on the opening and closing dynamics of Na^+ channels. Through binding to site 3 of the channel receptor, scorpion α-toxins inhibit or slow down the inactivation of the Na^+ current. For instance, the α-toxin LqhIII from the deathstalker scorpion inhibited the fast inactivation of cardiac $Na_V1.5$ channels with IC_{50} value of 11.4 $nmol \cdot L^{-1}$. LqhIII anchored on top of voltage-sensing domain IV, wedged between the S1-S2 and S3-S4 linkers, which trapped the gating charges of the S4 segment in a unique intermediate-activated state stabilized by four ion-pairs [35]. In contrast to α-toxins, by binding to site 4 of the channel receptor, scorpion β-toxins modify the Na^+ channel activation dynamics [32]. With a deepened understanding of α- and β-toxins, it has been found that they can bind to multiple positions in the sodium channels. Binding of scorpion α- and β-toxins to two distinct, pseudo-symmetrically organized receptor sites on Na_V channels acted synergistically to modify channel gating and paralyze prey [33]. There are three subgroups of scorpion α-toxins, namely insect α-toxins, classical α, and α-like. Additionally, the β-toxins can also be subdivided into subgroups. The first subgroup consists of classical β-toxins, which are selective to mammals. The second subgroup is insect- and mammal-targeted. Additional subgroups of NaTx include New World toxins that target crustaceans and insects [26]. These molecules have four disulfide bridges and fifteen non-cysteine residues that are identical. Consequently, their 3D structure is remarkably preserved, consisting of an α-helix and β-sheet with three strands [26].

Short-chain scorpion toxins

These molecules are 23–64 amino acids in length, comprising 3 to 4 disulfide bridges. They are commonly described as potassium channel toxins (KTxs), as they predominantly inhibit potassium ion channels. Exceptionally, a short-chain toxin, BmP01, was reported to target the TRPV1 channel to cause a painful sensation [36]. Generally, based on their cysteine pairs as well as the length of the sequences, KTxs can be classified into α-KTx, β-KTx, γ-KTx, κ-KTx, δ-KTx, and λ-KTx groups [37].

Non-disulfide bridged peptides (NDBPs)

The NDBPs are small peptides consisting of 13 to 56 amino acids and unique sequences [6, 38]. Few NDBPs have been isolated and characterized from scorpion venoms, unlike DBPs [39]. Most of the reported NDBPs have an α-helical structure and fall into three distinct groups based on the arrangement of their α-helical regions within the main peptide [38]. Group one entails two random coils at the C and T ends and a single α-helical domain. Examples of peptides with such organizations include Mauriporin, HsAP, Im-1, Pandinin 2, Meucin-24, BmKb1, BmKn2, IsCT, IsCT2, AamAP1, and AamAP2 [38]. In the second group, two α-helical segments are present within the main peptide structure, divided by a randomized looped sequence, as in Pandinin 1, Parabutoporin, Hadrurin, and Opistoporin 1 [38]. The third group of peptides has been described to have complete helicity, only seen in a limited number of NDBPs like StCT2 and Imcroporin [40, 41].

The NDBPs appear to have no conserved function-sequence association. These peptides may regularly have multipurpose effects unrelated to their targets, unlike scorpion DBPs, which have membrane-bound channels as their target and have precise functions predicted from the analysis and studies of their mature peptide sequences.

Enzymes (larger proteins)

In scorpion venoms, enzymes (larger proteins) have rarely been identified, partly because previous researches mainly focused on peptides and small proteins. In recent years, however, serine proteases, metalloproteases, phospholipases, hyaluronidases, and other enzymes have been reported in the venoms of different scorpion species [19].

Phospholipases are lipolytic enzymes known for hydrolyzing phospholipid substrates at specific ester bonds [42]. In light of their ability to hydrolyze phospholipids, they are recognized as potent hemolytic agents. Additionally, these enzymes are capable of causing tissue necrosis and bleeding. In recent decades, phospholipases structures and functions have been studied with remarkable progress. Phospholipase action has been recorded in numerous scorpions, including *Heterometrus laoticus* [14] and *Opisthacanthus cayaporum* [43].

Hyaluronidases are primarily responsible for the degradation of hyaluronan, the main glycosaminoglycan of the interstitial matrix. Scorpion venom hyaluronidases were first described in 1975 in the venom of *Heterometrus scaber* [44] from South India. Although numerous studies have demonstrated the availability of hyaluronidases in scorpion venoms, only a few studies have shown their isolation from these sources [45]. This may occur because hyaluronidases are challenging to isolate due to their relatively small quantities in venoms (relative to other toxins), and their enzymatic activity is efficiently inhibited [46]. Six hyaluronidases have been isolated from the venoms of *M. martensii* [47], *T. serrulatus* [48], *H. fulvipes* [49], *T. stigmurus* [50], and *P. gravidus* [51] and biochemically and structurally characterized. It was reported that these hyaluronidases increased the toxicity of venoms by distorting the connective tissues that encompass blood vessels at the sting site, thus facilitating the widespread permeation of other scorpion toxins [52]. Oliveira-Mendes *et al.* demonstrated that these enzymes played a vital role in the dispersion of venoms from the blood system to the target organs [53].

Proteolytic enzymes and their inhibitors perform a cru-

cial function in host-pathogen interactions. Notably, metalloproteases naturally produced by harmful microbes play a vital role in the destruction of not only host tissues but also their immune proteins [54]. Also, serine proteases have been known for a long time to regulate inflammatory reaction and coordinate numerous physiological processes. The very first metalloprotease was identified from the venom of *T. serrulatus* [55]. Metalloproteases and serine proteases have also been identified in the venoms of *T. discrepans* [56] and *Hemiscorpius lepturus* [57]. Proteases are presumed to perform an essential function in the post-translational activation of toxin precursors [58]. These enzymes also regulate the production of cytokines and complement system activation, and inhibit platelet aggregation [59, 60]. Overall, these implications enable the diffusion of scorpion venom toxins through matrix protein degradation [19].

Other scorpion venom components

The number of reports concerning non-proteinous elements in scorpion venoms is somewhat limited. However, adenosine, a compound with anticoagulant effect and a well-known platelet aggregation inhibitor, has been identified from the venom of *Heterometrus laoticusv* [61]. Al-Asmari *et al.* cataloged numerous elements available in the venoms of scorpions [62]. Chemical elements including arsenic, magnesium, copper, calcium, iron, lead, manganese, nickel, and zinc ions were present in the venoms of *Leiurus quinquestriatus*, *Androctonus crassicauda*, and *Androctonus bicolor* [62]. Serotonin is a monoamine responsible for the significant pain and vomiting experienced by patients after a scorpion sting. Tiwari *et al.* reported that serotonin is present in some scorpion venoms, including *M. cumulus* [63]. Moreover, two 1,4-benzoquinone derivatives were characterized from the venom of *Diplocentrus melici*. These compounds were found to have antimicrobial effect [64].

Diverse pharmacological activities reported for scorpion venom-derived peptides

The enormous diversity of scorpion venom peptides has sparked investigations on these molecules for their potential in drug development and medical applications. Due to the pressing need to identify or improve current treatments for various medical conditions, the pharmacological activities of scorpion venom biomolecules have received a great deal of interest. Hereafter, we shall discuss different pharmacological properties of scorpion venom peptides, which have been reported to be potentially valuable for developing novel and high-quality therapeutic agents (Fig. 1).

Anticancer peptides

Cancer is the most common cause of mortality and a profound impediment to extending life expectancy all over the world [65]. In 2019, the World Health Organization (WHO) reported cancer as the primary cause of mortality before the age of seventy in 112 of 183 nationalities [66, 67], and in other 23 nations, it was ranked as a third or fourth cause. By 2030, there will be an estimated 22 million new cases of cancer and

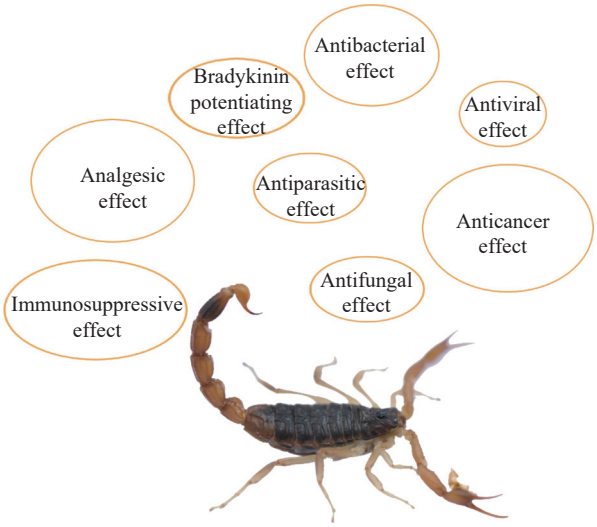

Fig. 1 Potential pharmacologcial activities of scorpion venom peptides discussed in this review

13 million cancer-related deaths around the world [68, 69]. In recent decades, great advances have been made in cancer dignosis and therapy. However, the conventional treatments available today, such as chemotherapy, surgery and radiotherapy, have some defects [6]. Poor tumor selectivity and, consequently, toxicity to non-tumor tissues, severely restricts the efficacy of existing chemotherapeutic agents. The search for highly efficient and selective anti-tumor agents, either derived from the nature or generated *de novo*, will attract increasing interest in the near future.

Anticancer peptides show strong effect against a broad spectrum of cancer cells. Several small molecules are penetrated and effectively absorbed within tissues. Several hypothesized mechanisms of action defining their cytostatic and cytotoxiceffectsoncancercellsentailcellsurfacebinding,leading to membranolysis or internalization to reach their intracellular target [70]. Many physiologically active peptides in scorpion venoms may have potential anti-cancer effects *in vitro* and *in vivo*, in which one has passed phase I and phase II clinical trials [6, 71].

Chlorotoxin (Cltx), a peptide identified from the species *Leiurus quinquestriatus*, is among the most active peptides discovered in scorpion venoms. Cltx is comprised of 36 amio acid residues with 4 disulfide bonds [72, 73]. It has been reported to inhibit chloride inflow in glioma cell membranes [74]. Cltx binds exclusively to glioma cells, with no or slight effect on normal cells. The peptide interacts with matrix metalloproteinase (MMP) II [75], and by binding of Cltx to MMP-2, the glioma cell membrane protein loses its gelatinase activity, MMP-2 expression decreases, chloride channels are inhibited, before internalization [75-77]. In addition, ClTx-modified liposomes have been reported to dramatically suppress the development of 4T1 cells, a breast cancer cell line that is metastatic and aggressive [78]. Interestingly, a peptide having 37 amino acids with 68 percent sequence similarity to charybdotoxin (ChTX), named iberiotoxin (IbTx), was

identified from the venom of *Mesobuthus tumulus* and proven to have outstanding selectivity and potency against BK channels [79]. The blockage of BK channels by IbTx in human 1321N1 astrocytoma cells eliminated tumor growth induced by these channels [80]. In addition, the blockage of BK channels by IbTx halted the progression of glioma cells into the S phase and promoted apoptosis [81]. Moreover, IbTx suppressed the development of hormone insensitive prostate cancer PC-3 cells, exhibiting functional overexpression and amplification of *KCNMA1* gene [82].

Furthermore, margatoxin (MgTX), a highly potent and selective K^+ channel peptidyl inhibitor, was isolated from the venom of *Centruroides margaritatus*. Based on peptide sequencing and compositional analysis, MgTX has a primary structure consisting of 39 amino acids. With the presence of MgTX, radiolabeled charybdotoxin was significantly inhibited from binding to voltage-activated channels in synaptic plasma membranes [83]. MgTX greatly inhibited the growth of A549 cells. In addition, specific inhibition of $K_V1.3$ enhanced the expression of $p21^{Waf1/Cip1}$ protein but lowered the expression of Cdk4 and cyclin D3. Moreover, MgTX decreased tumor size after exposure to cancerous tissue in a xenograft model in nude mice [84].

Gupta *et al.* identified an anticancer peptide named bengalin (72 kDa) from the venom of *Heterometrus bengalensis* Koch [85]. Bengalin suppressed the proliferation of K562 and U937 cells at IC_{50} values of 4.1 and 3.7 $mg \cdot mL^{-1}$, respectively, without effects on normal human lymphocytes. The suppressed proliferation of K562 and U937 cells by bengalin was a result of its apoptotic effect as demonstrated by the arrest of the cell cycle process primarily at the sub G_1 stage, an increase in DNA fragmentation, a rise in early apoptotic cells, a decline in telomerase activity as well as damaged nuclei [85]. D'Suze *et al*. isolated two novel antitumor peptides from the venom of *Tityus discrepans*, namely neopladine 1 and neopladine 2, and found that both the molecules were effective against SKBR3 human breast cacner cells [86]. Based on mass spectrometric analysis, neopladines 1 and 2 have a molecular weight of 29 918.5 and 30 388.88 Da, respectively. It was found that these peptides caused cell death in SKBR3 cell line, but no activity was reported after treatment on normal cells. Both neopladine 1 and neopladine 2 induced apoptosis in SKBR3 cells within 5 h of exposure; the results were more obvious for longer exposure times. The immunohistochemical analysis showed that neopladine bound to the surface of SKBR3 cells, causing the expression of BcL-2 and FasL [86].

In addition, Kampoet *et al.* investigated the effect of antitumor-analgesic peptide (BmK AGAP) from *Buthus martensii* Karsch on the epithelial-mesenchymal (EMT) and stemness transition of breast cancer cells. AGAP is a member of a class of long-chain peptides consisting of 66 amio acid residues with a molecular weight of 7142 Da [87, 88]. They discovered that recombinant-BmK AGAP (rBmK AGAP) reduced cell invasion, migration, epithelial-mesenchymal transition (EMT), and stemness after exposure to MDA-MB-231 cells and MCF-7 cells at various concentrations. In addition, rBmK AGAP elevated the levels of N-cadherin, Sox2, Oct4, and Snail and raised the amounts of E-cadherin. Moreover, *in vivo* and *in vitro* studies demonstrated that rBmK AGAP suppressed the migration, invasion, and EMT of breast cacner cells through downregulating PTX3 *via* the NF-B and Wnt/-catenin signaling pathways. A xenograft tumor model showed that rBmK AGAP inhibited EMT, tumour development, and stem-like characteristics [89]. Also, from the same species, an anticancer peptide (ANTP) was characterized, which showed that this peptide is rich in glycine but lack of threonine and histidine. According to 16.5% SDS-PAGE analysis, ANTP showed a relative molecular mass of 6280 Da. The pharmacological experiments revealed that ANTP has anticancer activity, as demonstrated in the Ehrlich ascites tumor model and a S-180 fibrosarcoma model in mice [87].

Moreover, gonearrestide (18 aa, 2192 Da), an anticancer peptide identified from *Androctonus mauritanicus*, was identified in an in-house constructed scorpion venom library. *Androctonus australis* (Egypt) (AAu) and *Androctonus mauritanicus* (AMa) yielded a total of 238 new peptides, of which 22 were chosen for further research based on a series of functional prediction assessments. Through a battery of *in vitro* biological functional screenings and bioinformatics analyses, gonearrestide was demonstrated as an effective antitumor molecule targeting a wide range of human cancer cells, with minimal or no cytotoxic effect on erythrocytes and epithelial cells. Further studies explained the specific anticancer mechanism of gonearrestide by examining its effects on HCT116 colorectal cancer cell line. To investigate the signaling pathways involved, the expression profiles of HCT116 cells grown with or without gonearrestide were obtained using NGS RNA sequencing. Through validation studies and *in vivo*, *ex vivo*, and *in vitro* experiments, it was demonstrated that this peptide inhibited the spread of primary colon cancer cells and solid tumors by halting the cell cycle in the G_1 phase [90].

Anti-bacterial peptides

In recent decades, a growing number of microbial pathogens have evolved resistance to conventional antibiotics. The widespread occurrence of previously undetected resistance patterns is attributable to the overuse of traditional antibiotics in clinical settings, as well as the enormous growth of worldwide transportation systems and movements [91]. The capacity of bacterial plasmids' mobile genetic components to propagate across a population boosts the resistance rate [92]. Even more concerning is the fact that the number of new antibiotics being developed has decreased over the same period of time.

Antimicrobial peptides (AMPs) are the protective strategy that straddles the evolutionary divide and continues to be an efficient method for combating invading pathogens. Due to their selectiveness for bacterial membranes and membrane-disrupting actions, microorganisms have no natural res-

istance, and recent research focus has shifted toward developing new antibiotics derived from these peptides [93]. A more significant percentage of the biologically defined scorpion venom NDBPs have antibacterial properties; hence they may be categorized as antimicrobial peptides (AMPs) [6, 38, 91]. It is unknown why they are present in scorpion venoms though it is speculated that they may have similar function in venomation or be the components of adverse antimicrobial response inside the venom gland of scorpions [94]. The two venom glands in the telson of scorpions possess a rather open connection with its surroundings, which might promote the invasion of saprophytic soil microbes. Therefore, scorpions are anticipated to have mechanisms for protecting themselves against the microbes prevalent within their surroundings [6].

Stigmurin, a peptide from the venom gland of *Tityus stigmurus* [95] was identified as a molecule consisting of 73 amino acid residues. This natural antibacterial peptide is effective against Methicillin-resistant *S. aureu*s MRSA and Gram-positive bacterial strains *Staphylococcus aureus*. Notably, stigmurin exhibited limited hemolytic activity (22%) at the maximum dose tested (139.5 μmol·L^{-1}) [96]. In 2015, Du *et al*. identified two new non-disulfide-bridged antimicrobial peptides, AaeAP1 and AaeAP2, in the venom of *Androctonus aeneas* [97]. The biosynthetic precursors of theses peptides encoded one copy of a putatively new nonadecapeptide with the primary structures FLFSLIPSVIAGLVSAIRN and FLFSLIPSAIAGLVSAIRN, respectively. The synthetic analogs of each natural peptide exhibited extensive antibacterial activity. AaeAP1 and AaeAP2 showed equal and more selective growth-inhibitory effects against Gram-positive bacteria *Staphylococcus aureus* (16 mg·L^{-1}), but neither was effective against *E. coli* at the highest dose tested (512 mg·L^{-1}) [97].

In a study published by Leentje *et al.*, a peptide identified as opistoporin1 was isolated from the venom of *Opistophtalmus carinatus* [98]. In their previous work, the team had identified parabutoporin from the venom of *Parabuthus schlechteri*, as a pore-forming peptide consisting of 45 amino acid residues without cysteine. A detailed investigation of the effect of synthetic opistoporin 1 and parabutoporin was conducted to evaluate the antibacterial potential of these molecules. A 50% growth inhibitory effect was achieved by both opistoporin 1 and parabutoporin at a dose of 2 μmol·L^{-1} on *Saccharomyces cerevisiae* [98]. Moreover, an antibacterial peptide, hadrurin (41 amino acid without cysteine), was discovered from *Hadrurus aztecus*. A highly positive correlation was observed between the three-dimensional folding of hadrurin and the two-*α*-helical segmented structure of an amphipatic molecule. At low micromolar concentrations, hadrurin showed antimicrobial activity against the growth of bacteria including *Enterococcus cloacae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella thyphi*, *Serratia marscences*, and *Klebsiella pneumonia*. Furthermore, it exhibited cytolytic function in human erythrocytes. The chemical synthesis of hadrurin and two of its analogs (all *D*-enantiomers and *C*-terminal amidated) was performed, and their capacity to reduce the diffusion potential of different liposome compositions was investigated in order to identify the possible molecular mechanism of actions. The results indicated that hadrurin does not bind to specific receptor molecules and that its effect is likely attribuable to membrane destabilizing effect [99].

Vejovine (4.8 kDa, 47 amino acids), a long-chain antibacterial peptide, was also identified from the venom of *Vaejovis mexicanus* [100]. Vejovine shares 52% homology with hadrurin. In liquid broth antimicrobial experiments, both natural vejovine and synthesized analogs demonstrated selective effect against *E. coli*, but no effect was shown against *S. aureus*. When newly milked venom is stored, vejovine eventually degrades into a shortened derivative (Vm36), without the first 8 *N*-terminal residues as seen in vejovine. Vm36, unlike vejovine, exhibited no antibacterial effect, highlighting the significance of the modified region (*N*-terminal) and other AMPs with equivalent structures. Vejovine peptide assumed a secondary *α*-helical structure in 60% TFE when subjected to circular dichroism (CD) analysis but remained disordered in water. In contrast, Vm36 acquired an *α*-helix structure in an aqueous solution, suggesting that a greater versatility of vejovine plays a critical role in enhancing antibacterial effect. In eukaryotic cytotoxicity experiments, 50 μmol·L^{-1} of vejovine elicited 40% hemolysis in human erythrocytes [100].

IsCT and IsCT2 are short-chain AMPs identified from the African scorpion *Opisthacanthus madagascarieni* venom [101, 102]. These two molecules have 78% similarity (approximately 1.5 kDa and 13 amino acids for each). Interestingly, these molecules showed an extensive variety of profiles against most Gram-positive and Gram-negative bacteria (generally MICs 0.6−16 μmol·L^{-1}), with the exception of *Pseudomonas strains*, which were notably resistant (MICs frequently > 66 μmol·L^{-1}). Both IsCT and IsCT2 were slightly hemolytic [102], but IsCT (about 3 μmol·L^{-1}) was significantly more effective than mastoparan as determined experimentally [101]. A pore-forming mode of action [102] was hypothesized where both the peptides exhibited a membrane-disrupting mechanism. At lower peptide doses, there was a preference for phosphatidic acid (PA) over phosphatidylcholine (PC), which however was not observed with the increase of peptide concentrations. Almaaytah *et al*. also identified two antibacterial peptides (AamAP1 and AamAP2) from the venom of *Androctonus amoreuxi* [103]. Both the peptides include 18 amino acids and vary by only two residues, with leucine replaced by proline at position 2 and phenylalanine replaced by isoleucine at position 17. Predictions of the secondary structure indicated that AamAP2 displayed a significantly larger random coil area than AamAP1. Nonetheless, these structural distinctions were not accompanied by alterations in biological effects. Although neither of the two peptides was highly effective (MICs 20−150 μmol·L^{-1}), AamAP1 was more effective against Gram-negative bacteria than Gram-positive ones. In the same dosing range, both the peptides induced significant hemolysis of red blood cells in a similar manner [103]. Notably, by focusing on the venom of *Urodacus yaschenkoi*, an in-depth study using transcriptome

techniques and a combination of MS/MS was conducted in order to identify a variety of AMPs [104, 105]. Three α-helical peptides (UyCT1, UyCT3, and UyCT5) belonging to the family of short-chain toxins were found, which consist of amidated *C*-termini and 43%−77% sequence similarity to that of IsCT were identified. These three peptides were equally effective against Gram-positive and Gtram-negative bacteria and had a mild cytolytic effect.

Moreover, the cDNA collection of *Buthus martensii*'s venom gland led to the discovery of two AMPs, BmKb1 peptide (52-amino-acid) and BmKn2 peptide (47-amino-acid) [106]. Both the peptides have amidated *C*-terminals. BmKn2 is significantly more effective than BmKb1 (MICs for Gram-positive bacteria were generally 0.4−6 μmol·L^{-1} for BmKn2, compared with 9−45 μmol·L^{-1} for BmKb1; MICs for Gram-negative bacteria were generally 1−15 μmol·L^{-1} for BmKn2, compared with 10−50 μmol·L^{-1} for BmKb1) [106]. More scorpion-derived peptides with anti-bacterial effects are shown in Table 1.

Anti-fungal peptides

Fungal pathogens have been linked to infectious illnesses in humans and other animals for a long time. Approximately 1.5 million people die annually from fungi, affecting over a billion individuals [113]. Although most deaths caused by fungal diseases are preventable, they are often neglected by public health authorities. It's rather typical that severe fungal infections often occur in conjunction with another illness or condition, such as AIDS, corticosteroid therapy for asthma, organ transplantation, and cancer [113-115]. Additionally, the incidences of fungal infections are increasing at an alarming rate, posing a formidable challenge for the medical field. This rise is directly attributed to an expanding number of immunocompromised patients, particularly young chidren, due to changes in medical practice, such as the increased use of rigorous chemotherapeutics and immunosuppressive medicines [116]. Fungi can develop resistance to antifungal drugs through specific or generic mechanisms, such as using an efflux pump to effectively convey them out of the cell [6]. Therefore, it is crucial to discover new anti-fungal agents to overcome resistance mechanisms.

An anti-fungal peptide, ctriporin, from the venom of *Chaerilus tricostatus* was identified, which consists of 19 amino acid residues and an amidated *C*-terminus. At 20 mg·mL^{-1}, ctriporin proved efficient against *Candida albicans* [117]. In a study published by Leentje *et al*., an anti-fungal peptide identified as opistoporin1 was isolated from the venom of *Opistophtalmus carinatus* [98]. In previous studies, parabutoporin (45 amino acids without cysteine) was characterized from the venom of *Parabuthus schlechteri*. A detailed investigation of synthetic analogs or both the peptides was conducted to evaluate their antifungal potential. A 50% growth inhibitory effect was achieved by both opistoporin 1 and parabutoporin at a dose of 2 μmol·L^{-1} on *Saccharomyces cerevisiae* [98]. More scorpion-derived anti-fungal peptides are shown in Table 2.

Table 1 Representative scorpion-derived peptides with antibacterial effects

Peptide	Species	Anti-bacterial effect	Reference
StigA6	*T. stigmurus*	Gram-positive and -negative bacteria	[107]
StigA16	*T. stigmurus*	Gram-positive and -negative bacteria	[108]
Serrulin	*T. serrulatus* (hemolymph)	Gram-negative and -positive bacteria	[109]
N-LaIT2	*L. australasiae*	Gram-negative bacteria	[107]
LaIT2	*L. australasiae*	Gram-negative bacteria	[107]
Megicin-18	*M. gibbosus*	Gram-positive bacteria	[110]
Marcin-18	*M. martensii*	Gram-positive bacteria	[110]
Um2	*U. manicatus*	Gram-negative and -positive bacteria	[111]
UyCT1	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
UyCT3	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
UyCT5	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
Uy17	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
Uy192	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
Uy234	*U. yaschenkoi*	Gram-positive and -negative bacteria	[111]
Uy234	*U. yaschenkoi*	*Streptococcus* strains	[112]
Uy17	*U. yaschenkoi*	MDR bacteria	[112]
Uy192	*U. yaschenkoi*	MDR bacteria	[112]
Um3	*U. manicatus*	Gram-negative and -positive bacteria	[111]
Um4	*U. manicatus*	Gram-negative and -positive bacteria	[111]
Um5	*U. manicatus*	Gram-negative and -positive bacteria	[111]

Table 2 Representative scorpion-derived peptides with anti-fungi effects

Peptide	Species	Anti-fungal effect	Reference
Ts1	*T. serrulatus*	*A. nidulans*	[118]
StigA6	*T. stigmurus*	*C. albicans*, *C. glabrata* and *C. krusei*	[108]
StigA16	*T. stigmurus*	*C. albicans*, *C. glabrata* and *C. krusei*	[108]
Stigmurin	*T. stigmurus*	*C. glabrata*, *C. albicans*, and *C. krusei*	[96]
AaeAP1	*A. aeneas*	*C. albicans*	[97]
AaeAP2	*A. aeneas*	*C. albicans*	[97]
Hypotensin TistH	*T. stigmurus*	*C. albicans*, *C. tropicalis* and *Aspergillus flflavus*	[119]
Serrulin	*T. serrulatus* (hemolymph)	*A. niger* and *C. albicans*	[109]
ToAcP	*T. obscurus*	*Candida* species as well as *Cryptococcus neoforman*	[120]
ToAP2	*T. obscurus*	*Candida* species as well as *Cryptococcus neoforman*	[120]
ToAP4	*T. obscurus*	*Candida* species as well as *Cryptococcus neoforman*	[120]
ToAP3	*T. obscurus*	*Candida* species as well as *Cryptococcus neoforman*	[120]
ToAP1	*T. obscurus*	*Candida* species as well as *Cryptococcus neoforman*	[120]

Analgesic peptides

Pain accounts for a substantial physiological and financial burden in the general public [121, 122]. It is estimated that about 600 billion US dollars are directed towards pain management each year in the United States alone, exceeding the combined annual cost of cancer, heart disease, and diabetes [123]. The currently available analgesic drugs in the markets have low efficacy and numerous side effects [124]; thus, there is an urgent need to develop novel analgesic drugs with enhanced efficacy and limited side effects. Whole scorpions, scorpion tails, or the derivatives of scorpion venoms have indeed been proven to be effective in the treatment of various neurological conditions, including facial hemiplegia, paralysis apoplexy, and epilepsy, and be useful in soothing the nerves and relieving pain induced by rheumatism cerebral palsy, as well as meningitis [125, 126].

The scorpion *Buthus martensii* Karsch (BmK) has attracted much attention due to the abundance of bioactive peptides in its venom. Hundreds of distinct analgesic peptides derived from BmK have been discovered in recent decade [127]. In light of the critical functions of voltage-gatedsodium channel subtypes in pain conduction [128, 129], blockage of VGSCs by natural compounds may be essential in the treatment of persistent pain conditions [24, 130]. The neuropeptides of scorpion BmK are a great source of molecules modulating sodium channel. In *in vivo* investigations, the *β*/*β*-like scorpion peptides such as BmK AS and BmK IT2, which target VGSC receptor site 4, exhibit antinociceptive properties. BmK AS peptid is a distinct *β*-like scorpion peptide consisting of 66 amino acid residues [131] and can induce analgesic activity in the peripheral nervous system (PNS) on mechanical hyperalgesia, inflammation-induced pain, and heat-induced pain. Patch-clamp recordings demonstrated that BmK AS substantially decreased the excitability of small DRG neurons by reducing tetrodotoxin-sensitive (TTX-S) Na^+ currents of DRG neurons and the peak tetrodotoxin-resistant (TTX-R), and inducing a negative shift in voltage-dependent activation.

BmK IT2 peptide, composed of 61 amino acids including 4 disulfide bonds, potentially generates a high level of insect toxicity [132]. Pre- or post-administration of intrathecal BmK IT2 successfully inhibited pain behavior induced by formalin and spinal c-Fos expression, which suggested that this peptide might not only target insect Na_V but also bind to mammalian Na_V subtypes. Notably, suppression of total Na^+ currents by BmK IT2 was seen in small DRG neurons [133]. By analyzing Na_V isoforms in a system expressing *Xenopus oocytes*, it was determined that $Na_V1.2$, $Na_V1.3$ and $Na_V1.6$ were unresponsive to BmK IT2, implying that those additional isoforms, particularly $Na_V1.7$–1.9, may be implicated in the inhibitory effect of BmK IT2 in rat models [134]. These findings suggested that BmK IT2 has the potential to be developed as a new analgesic candidate for clinical applications.

BmK IT-AP is a peptide made up of 72 amino acid residues derived from the venom of *Buthus martensi* Karsch. The peptide caused rapid excitatory contractility paralysis on house fly larvae. Besides, using a twisting test model, the peptide demonstrated apparent analgesic activity in mice. The effect of BmK IT-AP, which has beenthoroughly studied at the molecular level, is the first to be documented among recognized scorpion insect neurotoxins [135]. In addition, two peptides, BmNaL-3SS2 and BmKBTx, were characterized in a cDNA library isolated from the venom gland of *Buthus martensi* Karsch and exerted analgesic properties through inhibiting $Na_V1.7$ [136]. BmNaL-3SS2 comprises 64 amino acid residues connected by three disulfide bridges, while BmKITx is made up of 58 amino acid residues connected by four disulfide bridges. At a concentration of 1.0 $mg \cdot kg^{-1}$, both the peptides reduced writhing behaviors in mice. The analgesic effects of BmKBTx (1.0 $mg \cdot kg^{-1}$) and morphine (1.5 $mg \cdot kg^{-1}$) did not differ significantly, while the analgesic ac-

tion of BmNaL-3SS2 (1.0 mg·kg^{-1}) was stronger than that of morphine (1.5 mg·kg^{-1}). These findings indicated that both the peptides can be used to develop antinociceptive drugs which are more effective than morphine [136].

Moreover, in the venom of *Buthus martensi* Karsch, BmK-YA was identified, with a sequence similar to enkephalin. BmK-YA is capable of binding to opioid receptors (μ, δ, and also κ); its specificity for the δ opioid receptor is 6.8 times and 12 times greater than that of the μ and κ opioid receptors, respectively. A further distinction is that, unlike morphine, BmK-YA is a partial agonist of the μ receptor. Accordingly, the EC_{50} value of BmK-YA for the μ receptor is 72 times less effective than morphine, suggesting that the BmK-YA peptide may induce less adverse effects *via* this receptor. The results indicated that BmK-YA may be a preferred alternative to morphine [137].

TsNTxP, a derivative from the venom of *Tityus serrulatus*, was reported to exhibit antinociceptive effects in rodents by inhibiting glutamate release [138]. TsNTxP shares a similar structure to Na_V-targeted neurotoxins such as Ts7. This peptide shows no toxicity to animals. The analgesic activity of TsNTxP on acute and neuropathic pain in 184 adult male and female Swiss mice was investigated. The results indicated that TsNTxP possesses potent analgesic activity, possibly because of a massive decline in glutamate release. These findings, together with the absence of detrimental effects, implied that TsNTxP peptide is a potential future remedy for pain management.

Leptucin, an analgesic molecule consisting of 55 cysteine-rich amino acids, was isolated from the venom of *Hemiscorpius lepturus*. In a hot plate assay, it displayed 95 % percent analgesic effect at a concentration of 0.48 mg·kg^{-1} [139]. In addition, in the thermal tail-flick test, 0.32, 0.48, and 0.64 mg·kg^{-1} of leptucin exerted potent analgesic activity. At 8 and 16 μg, no cytotoxicity or hemolysis was observed. Due to its great *in vivo* efficacy and lack of detectable toxicity, this molecule may be a therapeutic lead candidate in preclinical acute pain studies [139].

Peptides with antinociceptive effects such as AmmVIII, LqqIT2, hetlaxin, and BotAF have been evidenced in *A. mauretanicus*, *L. quinquestriatus*, *H. laoticus*, and *B. occitanus tunetanus*, respectively [19]. More scorpion-derived peptides with analgesic effects are shown in Table 3.

Antiparasitic peptides

Several scorpion venom-derived peptides exhibit inhibitory activity on several parasites. Meucin-24 (24 amino acids) and meucin-25 (25 amino acids) are two antimalarial linear NDBPs generated from the cDNA of *Mesobuthus eupeus* venom gland. Both the compounds suppressed the growth of *P. berghei* and eradicated intra-erythrocytic *P. falciparum* parasites at micromolar doses without affecting mammalian cells, suggesting their potential suitability as antimalarial drug candidates [158]. Also, scorpine (75 amino acids, 3 disulfide bridges, and molecular weight 8350 Da) was identified from the venom of the scorpion *Pandinus imperator* and showed significant inhibitory effect on the gamete (ED_{50}

Table 3 Representative scorpion-derived peptides with analgesic effects

Peptide	Species	Activity	Reference
Hetlaxin	*H. laoticus*	Modulating pain-related $K_V1.3$ and $K_V1.1$	[140, 141]
TsNTxP	*T. serrulatus*	Modulating glutamate release	[138]
BotAF	*B. occitanus tunetanus*	Modulating peripheral and spinal mechanisms	[142]
AmmVIII	*A. mauretanicus*	Modulating $Na_V1.2$ and endogenous opioid system	[143]
LqqIT2	*L. quinquestriatus*	Modulating endogenous opioid system	[143]
BmK AS	*M. martensii*	Acting on RyR, TTX-S, TTX-R ($Na_V1.8$, 1.9), TTX-S ($Na_V1.3$); inhibiting the reduction of neural excitability	[144]
BmK IT2	*M. martensii*	Targeting pain related TTX-S and TTX-R	[144]
BmK AGAP-SYPU2	*M. martensii*	Acting on Na_V (suspected)	[145]
BmK AS1	*M. martensii*	Targeting RyR-1, TTX-S, pain-related TTX-R, and TTX-S Na_V	[146]
BmKBTx	*M. martensii*	Targeting $Na_V1.7$	[136]
AmmVIII	*A. mauretanicus*	Targeting endogenous opioid system and $Na_V1.2$	[143]
BmK AEP/BmKANEP	*M. martensii*	Targeting $Na_V1.1$, $Na_V1.3$, $Na_V1.6$ and $Na_V1.7$	[142, 147, 148]
BmK AGAP	*M. martensii*	Preventing peripheral and spinal MAPK expression; decreasing spinal c-Fos expression; $Na_V1.7$, $Na_V1.8$, $Na_V1.4$, and $Na_V1.5$; and Ca_V	[149-153]
BmK Ang M1	*M. martensii*	Acting on pain related Na^+ and K^+	[154, 155]
BmK(M)9	*M. martensii*	Acting on Na^+ Channel ($Na_V1.4$, $Na_V1.5$, and $Na_V1.7$)	[156, 157]
BmK-YA	*M. martensii*	Targeting μ, κ,and δ-opioid receptors	[137]
BmNaL-3SS2	*M. martensii*	Targeting $Na_V1.7$	[136]

10 mmol·L^{-1}) and ookinete (ED_{50} 0.7 mmol·L^{-1}) phases of *Plasmodium berghei* development [159]. It was later shown that the recombinantly expressed scorpine (RScp) in (*Anopheles gambie*) cells caused 98% lethality during the reproductive phase of (*Plasmodium berghei*) at 15 mmol·L^{-1} and a significant decline in parasitemia of *Plasmodium falciparum* at 5 mmol·L^{-1}. RScp also reduced the growth of the virus dengue-2 in C6/36 mosquito cells [160].

Pork tapeworm *(Taenia solium)*, which causes taeniasis and neurocysticercosis, poses a significant public health challenge, especially in developing countries. *T. crassiceps*, another member of the Taeniidae family of tapeworms, is an experimental model for evaluating and screening prospective antigens before testing in pigs [19, 161]. A naturally existing truncated form of a scorpine-like molecule from *Homanni-hadrurus gertschi* venom, Hge36, has been shown in *in vitro* experiments to limit the survival of *T. crassiceps* larval cysts at submicromolar doses, with trivial effect on human cells [162]. Accordingly, scorpion-derived molecules may be of therapeutic value for the treatment of human cysticercosis.

Leishmania parasites are vulnerable to ion-channel and antimicrobial inhibiting peptides. In light of the abundance of such molecules in scorpion venoms, the leishmanicidal effect of *Tityus discrepans* venom was examined, and the results showed that it inhibited the growth of promastigote forms of *L. chagasi*, *L. braziliensis*, and *L. mexicana*, *in vitro*, resulting in parasitic death [163].

The protozoan parasites *T. cruzi* and *T. brucei* cause Chagas illness (American trypanosomiasis) and sleeping sickness (African human trypanosomiasis), respectively. *In vitro* testing has shown that stigmurin and its analogs, namely StigA-6, -16, -25, and -31, possess potent antiparasitic effect over epimastigote variants of *T. cruzi*, typically present in the stomach of infected insect vectors [108, 164]. StigA16 and StigA6 shown to be active against the trypomastigote forms of *T. cruzi*. In general, the antiparasitic effect of these molecules is more significant at lower doses than benznidazole and nifurtimox, which are already marketed as remedies for the treatment of Chagas disease [108]. Hence, StigA16 and StigA6 may be used as therapeutic interventions for Chagas disease.

Bradykinin potentiating peptides

Bradykinin, a member of the kinin protein family, is an effective endothelial-dependent vasodilator molecule with hypotensive properties. The angiotensin-converting enzyme (ACE) degrades bradykinin, rendering it inactive [165]. The breakthrough of the first natural antagonist of this enzyme, bradykinin potentiating peptide (Bpp), enabled the development of blood pressure-controlling therapies.

Bradykinin potentiating scorpion venom peptides primarily lack disulfide bridges and are rich in proline residues at the *C*-terminus [166]. According to research [166], proline enrichment at the *C*-terminus of bradykinin enhances their bradykinin-potentiating action. Peptide T, isolated from the venom of the scorpion *Tityus serrulatus*, was the first scorpion component exhibiting a bradykinin potentiating effect. Peptide T increased the bradykinin contractile effect in the isolated guinea-pig ileum while inhibiting angiotensin-converting enzyme hydrolysis. This molecule also increased the depressor effect of bradykinin on arterial blood pressure in a rodent model [167]. Also, peptide K12, from the venom of *Buthus occitanus*, potentiated bradykinin activity in the rat uterus and isolated the guinea-pig ileum. Peptide K12 significantly increased the depressive effect of bradykinin on arterial blood pressure in rats. ACE was inhibited by peptide K12, although it was not proteolyzed by the enzyme [168]. Subsequently, Zeng *et al*. reported that the BmKbpp's *C*-terminal region (BmKbpp-C) is 72% equivalent to the peptide K-12 [169]. They discovered that BmKbpp and BmKbpp-C have bradykinin-potentiating activity, where BmKbpp-C is more potent than BmKbpp [169].

Verano-Braga et al. used a proteomic technique to explore a novel structural family of peptides from *Tityus serrulatus* [170]. *Tityus serrulatus* Hypotensins (TsHpt) are random-coiled linear peptides with a common bradykinin-potentiating peptide (BPP) amino acid signature. The first member of this family, TsHpt-I (2.7 kDa), was capable of inducing the hypotensive activities of bradykinin (BK) in normotensive rodents. By employing the *C*-terminus of this molecule to serve as a model and also as a template, a synthesized counterpart peptide TsHpt-I with BK-potentiating effect was created. TsHpt showed a significant hypotensive impact independent of BK (synthetic and native). The researchers also investigated their vasorelaxation effect using the male Wistar aortic rings and found that both the peptides were effective, though they could not avert the ACE action [170].

Antiviral peptides

Viruses can rapidly mutate to deceive and infect host cells, aided by virus-encoded peptides that evade host-cell immune defense [171]. Although many compounds have already been found as the inhibitors of viral infections, it is essential to identify more effective therapeutic agents with little or no side effects. In addition, the number of effective viral vaccines currently available is limited, compared with a wide range of diseases caused by viruses. The emergence of measles viruses, influenza A, and SARS-CoV over the past few years has caused serious concern about the circumstances under which infectious viral diseases may emerge or reemerge. Currently, there are no effective antiviral therapies that act by targeting RNA viruses such as SARS-CoV influenza H5N1 viruses, and measles. Therefore, the develoment of novel antiviral agents is needed close the vaccination gap and silence outbreaks.

Novel antiviral agents that are generated from natural products, particularly those originating from scorpion venoms, have promising potential. For example, Ji *et al*. identified an antiviral peptide (Smp76) from *Scorpio maurus* palmatus. The recombinant Smp76 (rSmp76) was discovered to dose-dependently inhibit ZIKV and DENV infections in primary mouse macrophages and cultured cell lines. The anti-

viral activity of rSmp76 was not attributable to direct inactivation of viral particles but the suppression of the infected cells, a similar effect from interferon (IFN)-*β*. Smp76 is thus a promising novel antiviral drug with a distinct mechanism involving type-I IFN responses [172]. Mucroporin-M1, an antiviral peptide derivative of mucroporin (an AMP isolated from *Lychas mucronatus*), is effective against influenza, measles, and SARS-CoV viruses. The inhibitory model involved direct interaction with the virus envelope, leading to a reduction in viral pathogenicity [173]. A subsequent study found that Mucroporin-M1 suppressed HBV replication by activating the mitogen-activated protein kinase (MAPK) pathway, and consequently down-regulated HNF4 expression both *in vitro* and *in vivo* [174]. Additionally, the recombinant peptide, Ev37, from *Euscorpiops validus* was found to inhibit plenty of of viral infections, including Zika virus (ZIKV), hepatitis C virus (HCV), dengue virus type 2 (DENV-2), and herpes simplex virus type 1 (HSV-1) infections at noncytotoxic concentrations. rEv37 induced the alkalization of acidic organelles, inhibiting the low pH-dependent fusion of viral membranes with endosomal membranes, which restricted late viral entry by blocking the release of viral genomes from the endosomal membrane to the cytoplasm. As a broad-spectrum antiviral agent, EV37 is unique in that it exhibits a specialized molecular mechanism of action against viruses that undergo low pH-dependent fusion activation at the time of host cell entry. This makes it an excellent candidate for the development of antiviral agents [175].

A natural antiviral peptide (HP1090) from the scorpion *Heterometrus petersii* is effective against hepatitis C virus (HCV). HP1090 at 5 μmol·L^{-1} inhibited HCV replication *in vitro*. Additionally, Hp1090 at approximately 13 μmol·L^{-1} significantly suppressed HCV RNA amplification in Huh7.5.1 cell line with stronger effect than that of IFN-*α*. Moreover, HP1090 inhibited the initiation of HCV through direct interaction with a viral protein, leading to a swift degradation of their phospholipid membranes. Hp1090 may be a potential anti-HCV lead compound exhibiting virucidal properties and used as a therapeutic agent against HCV [176].

Ctry2459, a peptide derived from scorpion venoms, has been shown to reduce hepatitis C virus (HCV) infection by neutralizing infectious viral molecules. Conversely, Ctry2459 cannot inhibit existing HCV infection due to inadequate cellular absorption and endosome limitation. Using Ctry2459 as a molecular template, Ctry2459-H2 and Ctry2459-H3 were created, with improved cellular absorption and better intracellular dissemination. In addition, both the modified peptides and Ctry2459 (wild-type peptide) displayed virucidal activity against HCV. Compared with wild-type peptides, both the modified molecules effectively inhibited HCV infection at the cellular level, exhibiting reduced cytotoxicity and hemolytic properties [177].

Immunosuppressive peptides

Generally, autoimmune disorders are associated with tissue damage induced by autoantigen-specific T cells [178]. The voltage-gated potassium channels (K_V) have garnered considerable attention as they are expressed in nearly all body tissues. It should be noted that these channels control various physiological functions, including immunological response [179]. The K_V1.3 is a well-known biological indicator and promising pharmaceutical target for the treatment of autoimmune disorders [180]. Therefore, based on the interactions between potassium channels and scorpion toxins, tremendous efforts have been made to identify scorpion peptides that preferentially function on the K_V1.3. ImKTx88 (from the venom of *Isometrus masculatus*) was evaluated for its ability to avert blood-brain barrier breakdown and consequent subversion of auto-reactive lymphocytes in an EAE mouse model. By specifically inhibiting K_V1.3 channels, this molecule was able to reduce the disease severity and stabilize the barrier, resulting in altered expression of adhesion molecules, receptors, and interleukins. ImKTx88 is a possible therapy recommendation for multiple sclerosis [181, 182]. In addition, OsK1 from the scorpion venom of *Orthochirus scrobiculosus* is a promising immunosuppressive scorpion toxin, particularly its mutated version which is more selective to K_V1.3 channels than K_V1.1 and K_V1.2 channels. The toxin has been evaluated on human K_V1.5 (hK_V1.5) channels and MEL cell line stably expressing mouse K_V1.3 (mK_V1.3), K_V3.1 (mK_V3.1), and *in vitro* on L929 and *in vivo* on C57/BL6 mice. These findings indicated that the molecule and its analogs have potent inhibitory effect on K_V1.3 channels. OsK1 is regarded as an important peptide candidate for the development of immunosuppressive medicines [183]. More immunosuppressive peptides from several scorpion toxins that target K_V1.3 channels and their profound clinical implications can be found in a recently published review [178] .

Other molecular targets, including K_V3.1 and K_V2.1, are crucial for the activation and functioning of T-cells [19, 184]. By blocking K_V2, both Ts6 and Ts15 from *T. serrulatus* were reported to *in vitro* suppress the function and proliferation of various T-cell subgroups. It was also established that Ts15 reduced the delayed-type hypersensitivity (DTH) feedback *in vivo*, demonstrating Ts15 as a potential remedy for autoimmune illnesses [185]. Also, the immunosuppression effects of St20, a disulfide-bridged *α*-KTx from the venom of *Scorpiops tibetanushas*, have been described. This molecule inhibited the expression of the cell surface marker CD69 and the release of IL-2, tumor necrosis factor (TNF)-*α*, and IFN-*γ* in activated human T cells. Using a model of autoimmune disorder, this study revealed that treatment with St20 ameliorated DTH [186]. Therefore, the effect of novel immunosuppressive therapeutic agents obtained from scorpion venom toxins can be enhanced in terms of function and structure, enabling their potential application in clinical settings.

Overview and Future Perspectives of Scorpion Venom Components in Drug Discovery

Evolution and natural selection have endowed animal venoms, including those from scorpions, with a wide range of

pharmacological properties. Due to their biological relevance, numerous venom components have been utilized to design new therapeutic agents [187, 188]. Several biologically active molecules from venomous organisms have been reported, but there is a significant gap between basic research and clinical interventions, which basically entails drug model validation and their use in clinical trials. Before clinical trials, drug candidates must undergo comprehensive *in vitro* and *in vivo* tests to confirm their biochemical and pharmacological effects, toxicity on reproduction, carcinogenicity, and safety [188, 189]. Among the established drugs derived from venom toxins are atracurium, captopril, eptifibatide, and ziconotide [190].

Chlorotoxin (CTx) is the only scorpion-derived peptide to have reached clinical trials [188]. CTx is a peptide from *Leiurus quinquestriatus* with 36 amino acids presenting 4070 Da and 4 disulfide bonds. The synthesized CTx has also developed and characterized [191]. CTx can bind to diverse targets, such as chloride channels, membrane type-2, MMP-2, and annexin A2 [191]. Nevertheless, the development of molecular fluorescence probes, including tumor paint, seems to have been a significant step in CTx discovery (CTx conjugated with Cy5.5 or CTx/Cy5.5). In animal studies, this bioconjugate can potentially perceive cancer foci and metastasis from sarcoma medulloblastoma, cancerous glioblastoma, and intestinal and prostate malignancies. Accurately identifying this fluorescence biochemical beacon (CTx/Cy5.5) enhances surgery resection accuracy and patient prognosis [76]. CTx/800CW (an infrared dye conjugate) has also been generated, through its progress in the clinical stage has proved difficult because the blood−brain barrier seems to have been compromised even in the early phases of the medulloblastoma malignancy [192].

A CTx indocyanine green conjugate, tozuleristide (BLZ-100), has been reported to bind to cancer cells without damaging normal tissues [193]. The Stage I trials of BLZ-100 in 17 surgical patients for glioma was concluded in 2016 (NCT02234297). In addition, 131-I-TM-601, a recombinant form of chlorotoxin (TM-601) radiolabeled with 131 iodine [194, 195] has been tested against several types of tumors (non-small cell lung cancer, pancreatic cancer, breast cancer, melanoma, prostate adenocarcinoma, glioma primary, colorectal cancer, and solid tumors). In 2009, Stage I, which included patients diagnosed with refractory or recurrent cerebral-metastatic and/or somatic solid tumors was concluded (NCT00379132). Many patent applications primarily related to intellectual property and pertain to CTx isoforms, bioconjugates, and application methods can be identified with a comprehensive list of records (including US20080260639A1, US20160096869A1, US20030021810A1, WO20006115633-A2, and WO2011142858A2).

Although CTx is the only scorpion peptide that has advanced to clinical phases, other scorpion toxins have shown promising clinical potential. SVAP, for example, has passed the preclinical stage as a possible antithrombotic peptide. SVAP, from the venom of *Mesobuthus martensii*, exhibited through *in vitro* investigations, its ability to stunt platelet aggregation in rabbits. SVAP (intravenous injection at 0.32 and 0.64 $mg \cdot kg^{-1}$) showed its ability to prolong the occlusion period of carotid artery thrombosis in rodent models. Therefore, SVAP is expected as a potential treatment choice for cardio-cerebral vascular diseases [196].

In recent years, cell-penetrating peptide (CPP)-based studies have opened up unprecedented possibilities for the application of vectors in a variety of fields, including basic research, technology, therapeutics, and medical imaging [188]. CPPs are cationic or amphipathic molecules with a short length of 9−35 residues with the potential of rapidly integrating across the membranes of the cells. Consequently, conjugated drugs can translocate across plasma membranes and are regarded as a safe and effective technique of drug delivery [197]. CPP-Ts, the first Ca^{2+} channel toxin produced by *T. serrulatus* venom, was reported to have potential for specific nuclear delivery and selective internalization, making it an effective intranuclear delivery system for the treatment of tumor cells [198]. In addition, reports have shown that maurocalcine, a toxin from the scorpion *Maurus palmatus*, acts on ryanodine receptors [188]. This toxin can penetrate the cells and thus may serve as a vector to aid in penetrating cargo molecules that are cell-impermeable. To develop better cell-penetrating peptides (CPPs), the modified analogs of maurocalcine have been synthesized and optimized [199]. Moreover, King *et al*. found that a cell-penetrating toxin known as WaTx, from *U. manicatus*, decreased TRPA1 ion channel permeation and could potentially be employed to get a better understanding of chronic pain mechanisms [200].

Generally, industrial development of toxin-related pharmaceuticals obtained from the nature is incredibly challenging and tedious, with minimal yield [201]. To circumvent such problems, the alternatives available seem to be the biochemical synthesis of molecules and the generation of biopharmaceuticals through heterologous expression using biotechnology. Although the purification and characterization of venom components are typically complicated and time-consuming, the remarkable specificity of scorpion peptides to their receptors makes them potential candidates for establishing better medicinal therapeutics. By deciphering the relationship between scorpion venom peptides and their receptors, newly designed drugs with minimal adverse effects will be developed. Even though a number of scorpion species have already been thoroughly investigated, there are still a lot of unexplored species, particularly within the family of non-Buthidae members. It is expected that alternative production and delivery technologies for biopharmaceuticals will be created in the near future. Thus, more progess is expected in the fields of scorpion venom research and drug discovery.

Conclusion

Scorpion venoms contain a wide range of bioactive peptides. Many scorpion venoms-derived peptides have potential therapeutic effect against cancer, bacterial infections, viral in-

fections, fungal infections, and pain, among others. Researchers can thus design new medicinal drugs based on the mechanism of action of scorpion venom peptides and their structure-function relationship investigations. In this regard, the application of scorpion venom-derived peptides as lead molecules and candidate drugs for the treatment of various diseases has a wide scope for application.

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