

REVIEW

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Harnessing the potency of scorpion venom-derived proteins: applications in cancer therapy

Jihad El-Qassas^{1,2}, Mahmoud Abd El-Atti¹ and Nagwa El-Badri^{2*}

Abstract

Despite breakthroughs in the development of cancer diagnosis and therapy, most current therapeutic approaches lack precise specificity and sensitivity, resulting in damage to healthy cells. Selective delivery of anti-cancer agents is thus an important goal of cancer therapy. Scorpion venom (SV) and/or body parts have been used since early civilizations for medicinal purposes, and in cultures, SV is still applied to the treatment of several diseases including cancer. SV contains numerous active micro and macromolecules with diverse pharmacological effects. These include potent anti-microbial, anti-viral, anti-inflammatory, and anti-cancer properties. This review focuses on the recent advances of SV-derived peptides as promising anti-cancer agents and their diagnostic and therapeutic potential applications in cancers such as glioma, breast cancer, prostate cancer, and colon cancer. Well-characterized SV-derived peptides are thus needed to serve as potent and selective adjuvant therapy for cancer, to significantly enhance the patients' survival and wellbeing.

Keywords SV-derived peptides, Anticancer agents, Cancer therapy, Drug development, Drug discovery, Peptide therapeutics

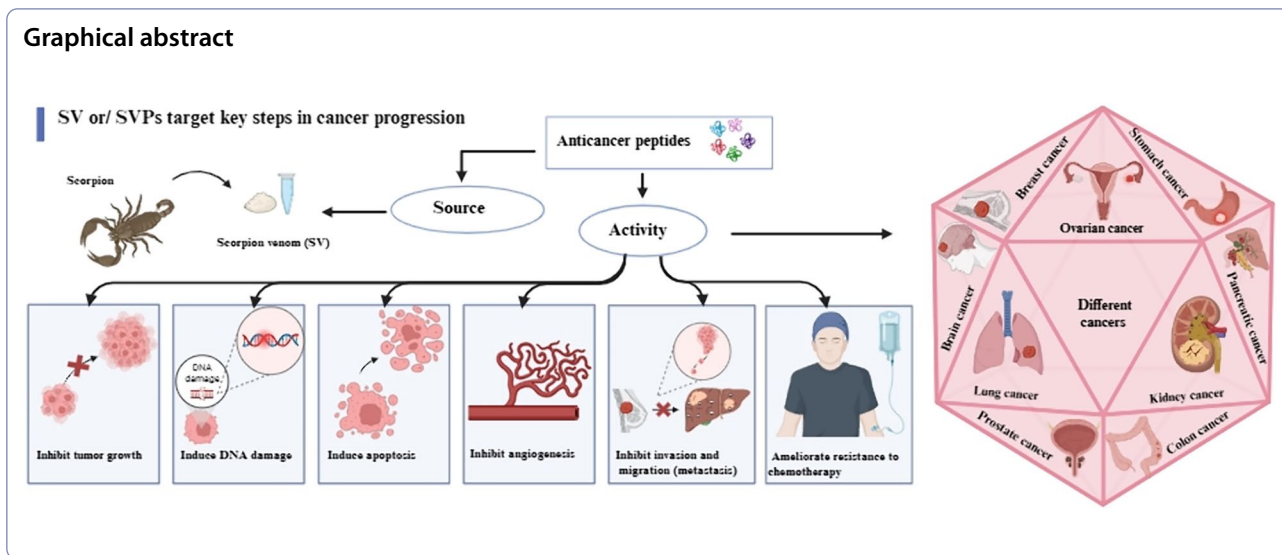
*Correspondence:

Nagwa El-Badri
nelbadri@zewailcity.edu.eg

Full list of author information is available at the end of the article



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Introduction

Scorpions are the most dangerous predators among the Arachnids class (Ruiming et al. 2010) as shown in Fig. 1a. Figure 1b shows that scorpions are easily recognized by their characteristic elongated body, which is divided into an anterior region (prosoma), middle region (mesosoma), and posterior region (metasoma). Scorpions possess a specialized venom apparatus composed of a pair of

venom glands connected by ducts to the aculeus at the tip of the telson on their posterior end, which produce venom for both offense and defense (Simone et al. 2021). Scorpions are terrestrial arthropods, that live mainly in deserts and can be adapted to a wide range of environmental terrains including caves, savannas, rain forests, and subtropical as well as tropical forests (Ruiming et al. 2010). They are classified phylogenetically into about 22

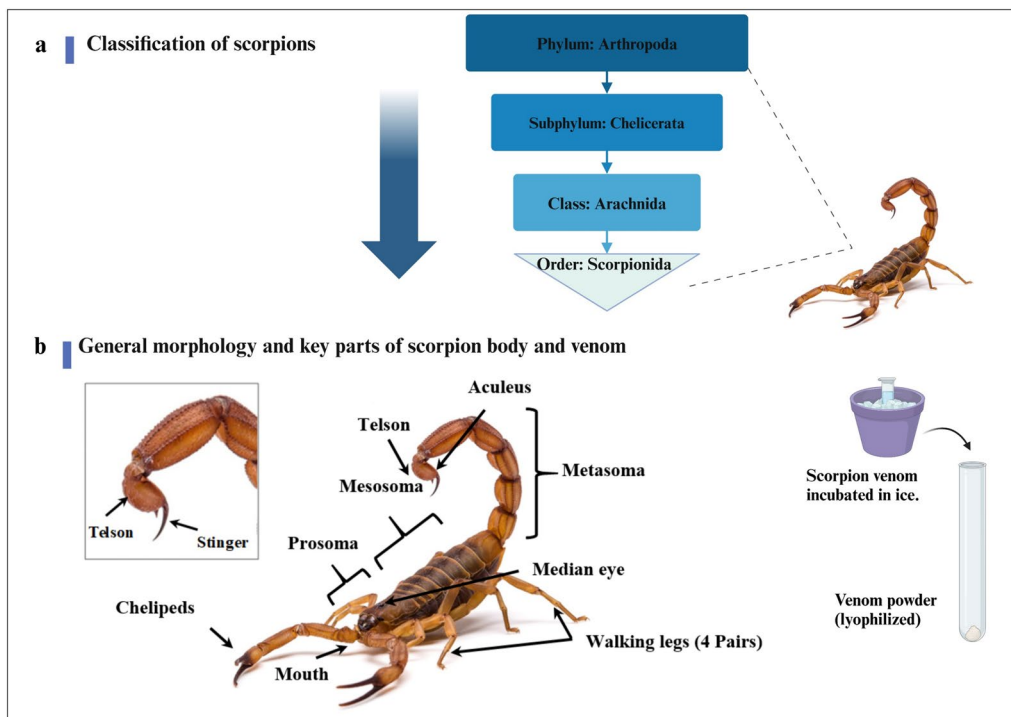


Fig. 1 a Classification of scorpions, b General morphology and key parts of scorpion body and venom

distinct families including over 2500 different species and subspecies. At least 25 species (fewer than 1%) are considered poisonous to humans (Ahmadi et al. 2020). The Buthidae family members contain many fatal scorpions (more than 70 genera and 770 species) represented by the following genera *Androctonus*, *Buthus*, *Leiurus*, *Mesobuthus*, and *Parabuthus* (Soleglad et al. 2003).

Pathological effects of scorpion venom

According to global public health data, about one million scorpion envenomings are recorded annually worldwide, resulting in approximately 3000 deaths (Ward

et al. 2018). The pathology of scorpion stings ranges from mild local inflammatory reactions (Cupo 2015) to moderate and severe envenoming causing heart failure, pulmonary edema, and pancreatitis, which may provoke lethal systemic responses, Fig. 2 (Pucca et al. 2016).

Despite the mortality associated with their stings, scorpions have been the target of much research interest due to their observed medicinal benefits and a wide range of pharmaceutical activities. Both crude SV and its derived proteins and peptides were used in applications ranging from cosmeceuticals and diagnostics to treatment of various ailments of the cardiovascular system, convulsions, cancer (Ahmadi et al. 2020; Srairi-Abid et al. 2019). Because of the lethality of scorpion toxins, the challenges associated with collecting the toxins, and the small amount of venom obtained from scorpions, marketing SV products for large-scale applications has been limited. Nevertheless, several toxin-based drugs have been approved and marketed over the last decade (Bordon et al. 2020). Of special importance is chlorotoxin (CTX) which showed remarkable target-specific activities in cancer patients (Wang et al. 2019).

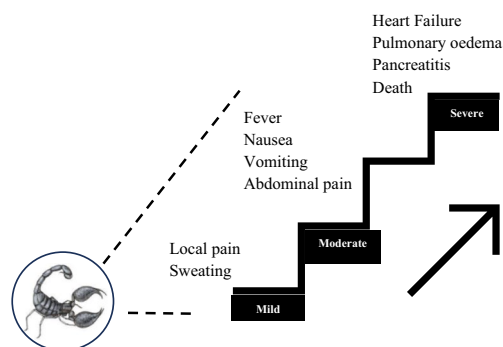


Fig. 2 Clinical signs and symptoms of mild, oderate, and severe scorpion stings

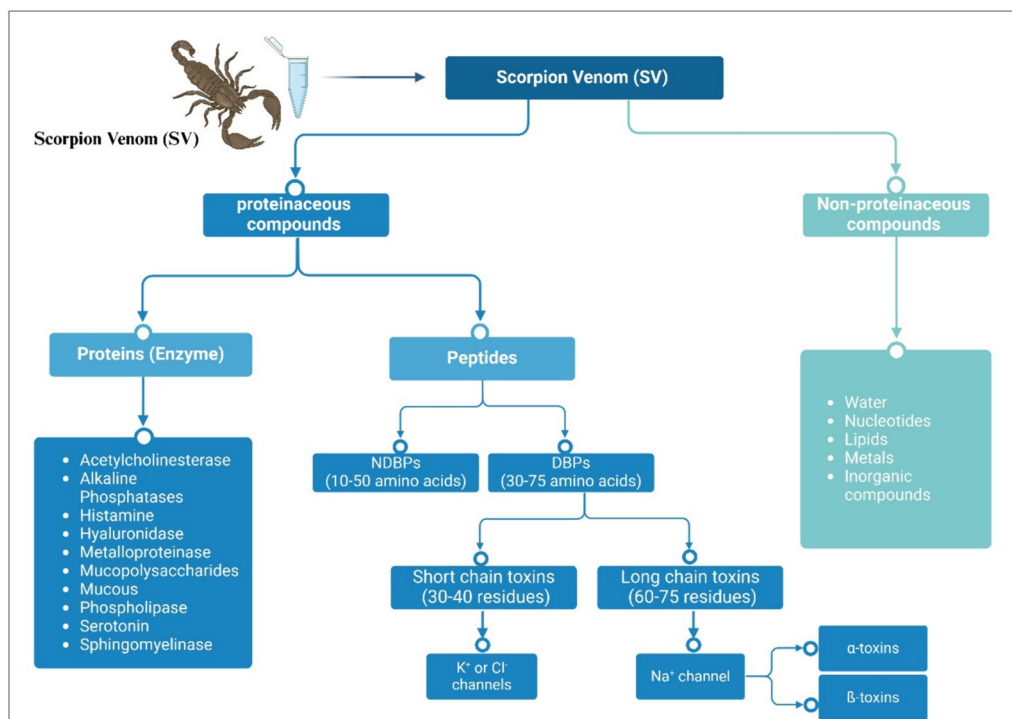


Fig. 3 Classification of SV according to structure and effect

Classification and biochemical profile of scorpion toxins

Scorpions employ their paralytic and lethal venom for defense and prey capture (Possani et al. 2000), although it has also been reported to be used during mating (Inceoglu et al. 2006). Scorpion toxins are classified based on the peptide length, receptor, or ion channel molecules to which the toxin specifically binds (Ca^{+2} , Na^+ , Cl^{-1} , and K^+). They can be also classified based on induced receptor response (activation/blocking) and the toxin's three-dimensional structure (DeBin et al. 1993; Dueñas-Cuellar et al. 2020; Mendes et al. 2023), Fig. 3. SV is composed of more than 500 different components including peptides that present promising sources for new pharmaceuticals, as shown in Figs. (2–6) and (2–7) (Uzair et al. 2018). Neurotoxic peptides in SV are responsible for the main pathological manifestations of envenoming. These include hyaluronidases, phospholipases, serotonin, histamine, sphingomyelinases (Cordeiro et al. 2015), acetylcholinesterase, alkaline phosphatases, proteolytic enzymes, enzyme inhibitors, mucopolysaccharides, low-molecular-weight peptides (3–10 kDa), mucoproteins, and oligopeptides. SV harbors potent neurotoxic peptides that specifically target ion channels in the nervous system that are crucial for nerve signaling, leading to paralysis (Mendes et al. 2023). Neurotoxins binding to ion channels on cell membranes cause various effects by blocking nerve impulses and modulating cell function leading to excessive stimulation or cell death (Mendes et al. 2023).

SV in traditional medicine

The long-established tradition of using scorpion bodies and their venoms to treat ailments was reported in diverse parts of China, India, and Africa and was especially popular in Spanish folk medicine (Goudet et al. 2002). In traditional Chinese medicine, whole scorpions of the *Buthus martensii karsch* (*Bmk*) species have been used as a painkiller and to treat chronic inflammatory arthritis, spasms, convulsions, and spondylitis “Scorpio-analgesia” (Chen et al. 2022). The dry scorpion body contains components such as Makatoxin-3 which was shown to have significant pain-relieving effects (Chen et al. 2022). The venom of *Mesobuthus martensii* species, which is abundant in Eastern Asia was effectively used to treat chronic pain, rheumatoid arthritis, epilepsy, and apoplexy (Ahmadi et al. 2020; Monge-Fuentes et al. 2015). Interestingly, SV itself can be a source of antivenom. For instance, in Sudan, scorpion stings are treated by processed or diluted SV, or by immersing the whole scorpion body in sesame oil and applying this infusion to the site of the sting (Cloudsley-Thompson 1993). Traditional medicine practices have explored SV for a

wider range of ailments, including cancer, infections, malaria, and immune disorders (Ling et al. 2019). Studies from traditional Chinese medicine showed that SV contained anti-cancer ingredients. For example, peptides purified from the Chinese scorpion *Buthus martensii karsch* (*Bmk*) (Jia et al. 2024; Shao et al. 2014), which has a history back to the Song Dynasty of China (960–1279 AD) and well known as having potential on epileptic (Zhou et al. 1989), analgesic (Shao et al. 2014), rheumatic and cancer. *Bmk* displayed dose-dependent effects on MCF-7 cells and anti-proliferative effects on a panel of cancer cell lines (Gao et al. 2010). *Bmk* prevented human lymphoma cells (Jurkat and Raji) growth and arrested the cell cycle at the G0/G1 phase triggering apoptosis (Heinen et al. 2011). Many of these studies however lack appropriate risk aversion, as improper preparation or use can lead to precarious outcomes and use can be dangerous and result in significant side effects. Deviation from recommended temperature or dosage protocols was also reported to cause unexpected adverse effects (Ahmadi et al. 2020). These include local reactions in the form of pain, swelling, redness, and itching, allergic reactions, and muscle tissue damage (muscle necrosis) caused by myotoxins in the SV (Ahmadi et al. 2020). Resurgent interest in SV and SVPs as remedies for cancer however is fuelled by the increasing spread of the disease and inadequate current therapy.

SV: a natural compound with biological properties and a range of applications in cancer research and drug discovery

Biological properties of SV and their derived peptides

Anti-microbial activity

SV and their peptides have been shown to exert a multitude of therapeutic effects, as shown in Fig. 4, because of their specific binding affinity to ion channels (Mendes et al. 2023; Quintero-Hernández et al. 2013) such as chloride (Lippens et al. 1995), potassium (Giangiacoimo et al. 2004), and sodium (Possani et al. 2000). A significant number of non-disulfide-bridged peptides (NDBPs) from SV have demonstrated anti-bacterial properties (Table 1). For example, BmTXKS-2, a peptide purified from *Buthus martensii* triggered an antibacterial activity against *N. gonorrhoeae* (Shao et al. 2014). Smp-24 (2578 Da) and Smp-43 (4654.3 Da), isolated from *Scorpio maurus palmatus*, demonstrated anti-bacterial activity that was specifically effective against Gram-positive bacteria, albeit of limited activity against *C. albicans* (Harrison et al. 2016). Among 11 scorpion venom-derived non-disulfide-bridged peptides, ToAP-1, ToAP-2, and ToAP-3 purified from *T. obscuru* showed effectiveness against human pathogens *Cryptococcus neoformans* and *Candida* spp. (Guilhelmelli et al. 2016). SV-derived peptides have shown

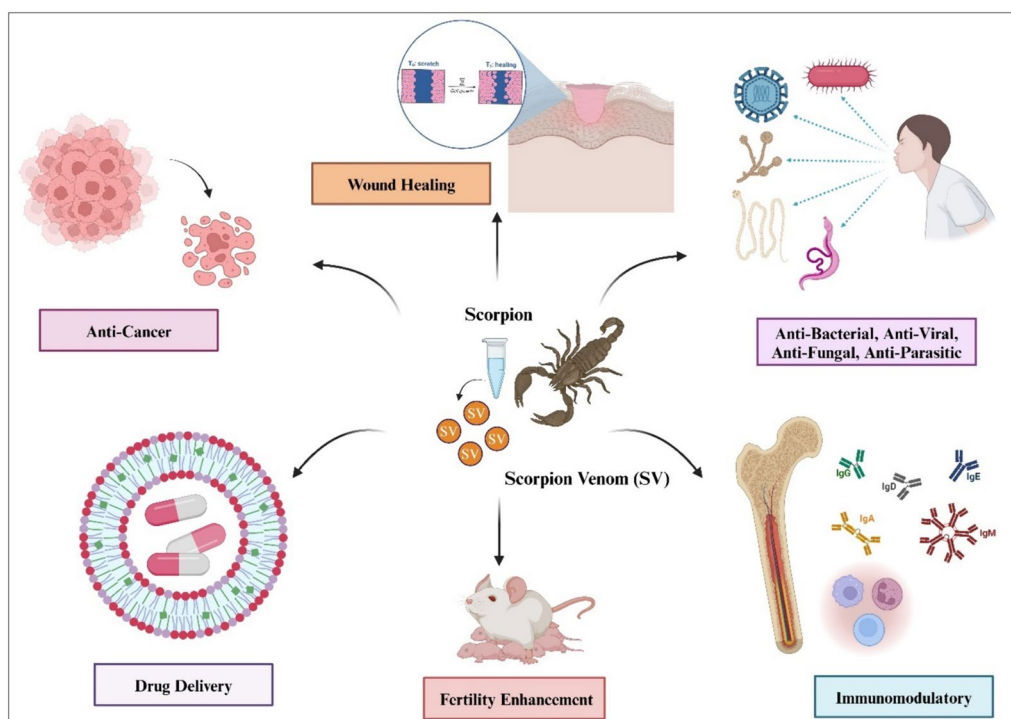


Fig. 4 Biological properties of scorpion venom

inhibitory effects on various bacteria (Symeonidou et al. 2018). SV peptides such as *A. Aeneas* and *T. stigmurus* were reported to inhibit the viral infection spread (Krawczyk et al. 2013; Thakur et al. 2012), while others displayed anti-fungal properties (Table 2).

Immunosuppressive activity of SV-derived peptides

Immune cells, similar to cancer cells, express voltage-gated potassium channels (KV) designed to control various physiological functions and immunological responses (Petricevich 2004). In immune cells, charged ions inserted within the hydrophobic membrane pores through ion channels help in the regulation of negative membrane potential (V_m), which indirectly controls Ca^{+2} ion influx and immune cell signaling/activation (Feske et al. 2015). One specific example is the KV1.3 potassium channel in T Helper 17 (Th17) cells, known to be a critical regulator of autoimmune disorders by controlling calcium ion influx (Zhao et al. 2015). Neurotoxic substances in SV were reported to directly and indirectly modulate voltage-gated Na^+ , K^+ , and Ca^{+2} ion channels (Quintero-Hernández et al. 2013). SV and its peptides interact with potassium channels and preferentially trigger KV1.3 to modulate channel expression and plasma membrane activity (Zhao et al. 2015). Studies on SV-derived peptides with immunosuppression activity that target ion channels and their clinical importance (Al-Asmari et al.

2018b; Jacoby et al. 2010; Kampo et al. 2019; Song et al. 2012) are summarized in Table 3.

Anti-cancer activity of SV peptides

Cancer cells have been shown to use ion channels (Mikaelian et al. 2020) in their progression and metastasis, as shown in Fig. 5, via the modification in the cell volume and morphology (Capatina et al. 2022). For instance, in glioma, Cl^- and K^+ ions cause electrochemical efflux mediated by intracellular Ca^{+2} ion increase resulting in tumor shrinkage (McFerrin et al. 2006; Sontheimer 2008). In breast cancer, the Ca^{+2} channels's deactivation was reported to prevent tumor growth and proliferation (Aydar et al. 2009). Similarly, Cl^- channels were dysregulated in human colorectal cancer (Bustin et al. 2001), and modified in glioma to regulate the migration and invasion of cancer cells (Ullrich et al. 1996). Voltage-gated potassium channels-Kv and/or calcium-activated potassium channels-KCa and their subtypes were shown to be over-expressed or dysregulated in multiple cancers including glioblastoma (Griffin et al. 2020), breast (Northcott et al. 2012), colon, and prostate cancer (Comes et al. 2013) and lymphoma (Comes et al. 2015). Other studies showed that voltage-gated sodium channels (VGSCs) Nav1.5, Nav1.6, and Nav1.7 were also over-expressed in many cancers like breast cancer, colon cancer, cervical cancer, prostate cancer, and lung cancer. This overexpression

Table 1 SV-derived peptides with anti-bacterial activities

Peptide/venom	Sequence	Species	Dose	(Activity) anti-bacterial effect against	Reference
Serrulin	GFGGRGGFGGRRGGGGGI- GGGGGGYGGGKIKG	<i>T. serrulatus</i> (hemolymph)	(0.5–1) µM	Gram-positive bacteria (<i>Micrococcus luteus</i> A270)	(de Jesus Oliveira et al. 2019)
Scorpine or Panscorpine (KBX3_ PANIM)	GWINEEKIQKIDERMGNTVGG- MAKAIV HKMAKNEFQCMANMDML- GNCEKHCOQT SGEKGYCHTKCKCGT- PLSY	<i>Pandinus imperator</i> (Scorpionidae)	1 µM	Gram-positive and -negative bacteria	(Luna-Ramirez et al. 2017)
Stigmurin 1795.22 Da (0)	FFSLIPLVKGLISAFK	<i>T. stigmurus</i>	1 µg/mL	Gram-positive bacteria including <i>S. aureus</i> and Methicillin-resistant <i>S. aureus</i> (MRSA)	(de Melo et al. 2015)
Marcin-18 2135.63 Da	FFGHLFKLATKIIPSLFR	<i>M. martensii</i>	1.5 µM	<i>Staphylococcus aureus</i>	(Zerouti et al. 2021)
Megicin-18 2068.04 Da	FFGALFKLATKIIPSLFR	<i>M. gibbosus</i>	1.5 µM	<i>Staphylococcus aureus</i>	
Meucin-18 2107.13 Da (0)	FFGHLFKLATKIIPSLFQ	<i>M. eupeus</i>	1.5 µM	<i>Staphylococcus aureus</i>	
Um3	GFWGKLWEGVKSAL	<i>U. manicatus</i>	2 µM	Gram-positive and -negative bacteria	(Luna-Ramirez et al. 2017)
Um5	IFKAIWSGKSLF	<i>U. manicatus</i>	2 µM	Gram-positive and -negative bacteria	
StigA16 1949 Da	FFKLIPLVKGLISAFK	<i>T. stigmurus</i>	2.34 µM	Gram-positive bacteria (<i>S. aureus</i>)	(Luna-Ramirez et al. 2017)
StigA6 1908 Da	FFSLIPLVKGLISAFK	<i>T. stigmurus</i>	2.34 µM	Gram-positive bacteria (<i>S. aureus</i>)	
Meucin-49 5574.93 Da	MNKILLIVFVITMLIVDEVNSVDFGS- FIKRWRSKLAIKLRAGKELLRDYAN- RVLSPREEAAAPVPKRRR	<i>M. eupeus</i>	3.07 µM	Gram-positive bacteria (<i>S. aureus</i>)	(Zerouti et al. 2021)
Um2	ISQSDAILSAIWSGKSLF	<i>U. manicatus</i>	4 µM	Gram-positive and -negative bacteria	(Luna-Ramirez et al. 2017)
UyCT1	GFWGKLWEGVKNAL	<i>U. yaschenkoi</i>	4 µM	Gram-positive and -negative bacteria	
BmTXK52 (BmKb1) (BmKb2)	MEIKYLLTVFLVLLVSDHCQAFIFS- LIPSAISGLISAFK	<i>Buthus martensii</i>	4.3 µM	Gram-negative bacteria	(Shao et al. 2014)
LalIT2 6628.2 Da (3)	MEIKYLLTVFLVLLVSDHC- QAFLLSIPSAISGLISAFK	<i>L. australasiae</i>	7 µM	<i>E. coli</i>	(Luna-Ramirez et al. 2017)
Um4	AKKPFVORVKNAAASKAYNKLK- GLAMQSQYGGPISNMCEHDHCRRK- KMEGQCILLDCVCS				
UyCT3	FFSALLSGIKSLF	<i>U. manicatus</i>	8 µM	Gram-positive and -negative bacteria	(Luna-Ramirez et al. 2017)
Smp-43 4654.3 Da (0)	ILSAIWSGKSLF	<i>U. yaschenkoi</i>	8 µM	Gram-positive and -negative bacteria	
Ctriporin	GWWDWIKKTAGKIMWSEPVKALKSQAL- NAAKNFVAEKIGATPS	<i>Scorpio maurus palmatus</i>	5, 10 µg/mL	Highest activity against Gram-positive bacteria, limited activity against <i>C. albicans</i>	(Harrison et al. 2016)
UyCT5	MDSKYLFLVLFNVVIDLCOGFLWGLIP- GAVTSLIAISK	<i>Chaerilus tricostratus</i>	10 µg/mL	Gram-positive bacteria	(Almaaytah et al. 2014)
Uy17	IWSAIWSGKIGLL	<i>U. yaschenkoi</i>	15 µM	Gram-positive and -negative bacteria	(Luna-Ramirez et al. 2017)
Uy234	ILSAIWSGKIGLL-NH ₂ FPPELLSLIPSAISAIKRL-NH ₂	<i>U. yaschenkoi</i>	23.2 µM 29.6 ± 25 µM	<i>Staphylococcus aureus</i> <i>Staphylococcus aureus</i>	(Luna-Ramirez et al. 2017; Pedron et al. 2017)

Table 1 (continued)

Peptide/venom	Sequence	Species	Dose	(Activity) anti-bacterial effect against	Reference
AaeAP1 2016.18 Da (0)	FLFSLIPSVIAGLVS AIRNa	<i>A. aeneas</i>	32 mg/L	<i>Staphylococcus aureus</i>	(Du et al. 2015)
AaeAP2 1986.15 Da (0)	FLFSLIPSAIAGLVS AIRNa	<i>A. aeneas</i>			
Uy192	FLSTIWNIGIKGLL-NH ₂	<i>U. yaschenkoi</i>	42.4 μM	<i>Staphylococcus aureus</i>	
ToAP2 9486 Da	FFGTLFKLGSKLIPGVMKLFSKKKER	<i>T. obscurus</i>	50; 12.5; 200; > 400; 25 μM	<i>Mycobacterium massiliense</i>	
Cm38 2149 Da (2)	ARDGYVDEKGGCKFACFIN	<i>C. margaritatus</i>	64 μM	<i>Klebsiella pneumonia</i>	(Dueñas-Cuellar et al. 2015)
Smp-24 2578 Da (0)	IWSFLIKAATKLLPSLFGGGKKDS	<i>Scorpio maurus palmatus</i>	64 μM	Highest activity against Gram-positive bacteria, limited activity against <i>C. albicans</i>	(Harrison et al. 2016)

Table 2 SV-derived peptides with anti-fungal activities

Peptide/venom	Sequence	Species	Dose	Anti-fungal activities against	Reference
Ts-1 (8300 Da)	KEGYLMDHEGCKLS-CFIRPSGYCGRECGLK-KGSSGYCAWPACYCYGLPNWVKVWDRATNKC	<i>T. serrulatus</i>	(1.5, 3 and 6 µg/well, which correspond to 2.18, 4.36, and 8.72 µM, respectively)	Inhibited the fungal growth of <i>A. nidulans</i>	(Santussi et al. 2017)
StigA-16 (1949 Da)	FFKLIPKLVKGLISAFK	<i>T. stigmurus</i>	1.17–9.38 µM	Inhibited fungal growth of <i>C. albicans</i> , <i>C. glabrata</i> and <i>C. krusei</i>	(Parente et al. 2018)
ToAcP	EEDDLLGFSEEDLKAIEH-RAKNA-NH ₂	<i>T. obscurus</i>	12.5 µM	Reduced the viability of <i>Candida sp.</i> as well as <i>Cryptococcus neoforman</i>	(Guilhelmelli et al. 2016)
ToAP-2	FFGTLFKLGSKLIPGVMKLF-SKKKER	<i>T. obscurus</i>	12.5 µM	Reduced the viability of <i>Candida sp.</i> as well as <i>Cryptococcus neoforman</i>	(Guilhelmelli et al. 2016)
Serrulin (3564 Da)	GFGGGRGGFGGGRGGFGGGGI-GGGGFGGGYGGGKIKG	<i>T. serrulatus (hemolymph)</i>	12–24 µg/mL (3–6 µM) for <i>Aspergillus niger</i> , and 6–12 µg/mL (1.5–3 µM) for <i>Candida albicans</i>	Reduced the growth of <i>A. niger</i> and <i>C. albicans</i>	(de Jesus Oliveira et al. 2019)
ToAP-3	FIGMIPGLIGLISAIK-NH ₂	<i>T. obscurus</i>	25 µM for <i>Candida sp.</i> and 100 µM for <i>Cryptococcus neoforman</i>	Reduced the viability of <i>Candida sp.</i> as well as <i>Cryptococcus neoforman</i>	(Guilhelmelli et al. 2016)
AaeAP-1 (2016.18 Da)	FLFSLIPSVIAGLVSAIRNa	<i>A. aeneas</i>	32 mg/L	Decreased four-fold (16 > 4 mg/L) and eight-fold (32 > 4 mg/L), respectively against <i>C. albicans</i>	(Du et al. 2015)
AaeAP-2 (1986.15 Da)	FLFSLIPSAIAGLVSAIRNa	<i>A. aeneas</i>		Decreased four-fold (16 > 4 mg/L) and eight-fold (32 > 4 mg/L), respectively against <i>C. albicans</i>	(Du et al. 2015)
StigA-6 (1908 Da)	FFSLIPKLVKGLISAFK	<i>T. stigmurus</i>	1.17–37.5 µM	Inhibited fungal growth of <i>C. albicans</i> , <i>C. glabrata</i> and <i>C. krusei</i>	(Parente et al. 2018)
ToAP-1	FIGMIPGLIGLISAFK-NH ₂	<i>T. obscurus</i>	50 µM for <i>Candida sp.</i> and 25 µM for <i>Cryptococcus neoforman</i>	Reduced the viability of <i>Candida sp.</i> as well as <i>Cryptococcus neoforman</i>	(Guilhelmelli et al. 2016)
ToAP-4	FFSLIPSLIGGLVSAIK-NH ₂	<i>T. obscurus</i>	50 µM for <i>Candida sp.</i> and 25 µM for <i>Cryptococcus neoforman</i>	Reduced the viability of <i>Candida sp.</i> as well as <i>Cryptococcus neoforman</i>	(Guilhelmelli et al. 2016)
Hypotensin/or TistH (2700 Da)	ADMDFTGIAESIIKKIKET-NAKPPA	<i>T. stigmurus</i>	MIC 128 mg/mL	Showed growth inhibition against <i>C. albicans</i> , <i>C. tropicalis</i> and <i>Aspergillus flavus</i>	(Machado et al. 2016)
Stigmurin (1795.22 Da)	FFSLIPSLVKGLISAFK	<i>T. stigmurus</i>	> 150 µM	Inhibited fungal growth of <i>C. albicans</i> , <i>C. glabrata</i> and <i>C. krusei</i>	(de Melo et al. 2015)

displays as an important player in migration and invasion and has a distinct role in nerve signal transmission (Brisson et al. 2013), and presents a selective target for potent compounds with better-targeted drug delivery (Bordon et al. 2020; Uzair et al. 2018). Among these compounds, chlorotoxin (CTX) is a small venomous peptide (36 a.a.)

that was first isolated in 1993 from *Leiurus quinquestriatus* yellow scorpion (*L. quinquestriatus*). CTX is best known for its selective binding affinity to chloride channels on the surface of glioma cells (DeBin et al. 1993). It disrupts the cancer cell's ability to invade surrounding tissue by blocking the influx of chloride ions, which are

Table 3 SV-derived peptides with immunosuppressive activities

Peptide/venom	Sequence	Species	Dose	Immunosuppressive activities	Reference
Osk-1 (4.22 kDa)	GVINVKKISRQCLEPCKKAGMRFGKC-MNGKCHCTPK	<i>Orthochirus scrobiculosus</i>	Kv1.1: 0.6 nM Kv1.2: 5.4 nM K _{Ca} 3.1: 225 nM	Inhibits Kv1.3 more than Kv1.1, and Kv1.2 channels	(Gubič et al. 2021)
Margatoxin (MgTx)	TIINVKCTSPKQCLPPCKAQFGQSAGAKC-MNGKCKCYPH	<i>Centruroides margaritatus</i>	1 nM	Blocks Kv1.3 channels	(Feske et al. 2015)
St-20 (α-KTx)	TKCSGSPECVFCFRNGKCMNRSCKYLCS	<i>Scorpions tibetanushas</i>	(0, 1, 10, 100 nM)	Decreases CD69 expression and the release interleukin-2 IL-2, tumor necrosis factor (TNF-α), and IFN-γ in activated human T cells	(Padmanabhan and Prince 2006)
ImKTx-88	QIYTSKECNGSSESYHCEGITG-KRSGKCNKKCYCYR	<i>Isometrus masculatus</i> (Im)	100 nM, 1, and 10 μM	Specifically inhibits Kv1.3 channels	(Huang et al. 2017)
Bmk -AGAP	VRDGYADDKNCGRNAYCDECEKN-GAEGYQWAGYGNACWCYKLPDKLP-DKYPIRVPGKCNNG	<i>Buthus martensi Karsch</i> (Chinese scorpion)	0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 μM	Specially binds to Nav 1.5 channels	(Kampo et al. 2019)
Bmk fraction (SVCIII) (70–80 kDa)	CGPCFTTDANMARKRECCGGIGKCFG-PQCLCNRI		0, 1, 5, 10, 20, 30, 40 and 50 μg/ml	Inhibits NF-κB activation through inhibition of IκBα phosphorylation, degradation, and p65 nuclear translocation	(Song et al. 2012)
Ts-6	WCSTLIDLACGASRECYDPCFAFGRAH-GKGMNKCRCYT	<i>T. serrulatus</i>	50, 250, 1250 nM	Both inhibit the function and proliferation of several T-cell subgroups in vitro by blocking Kv2 channels	(Pucca et al. 2016)
Ts-15	GKFGKCPNICAKTCQTEKGGMGYCNK-TECVCSWE				

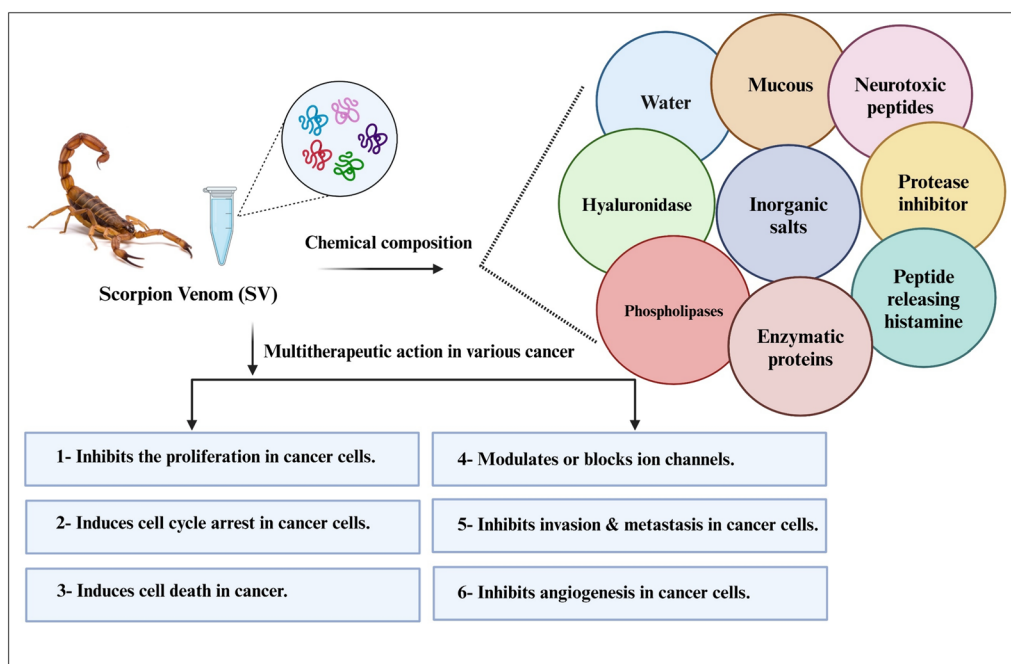


Fig. 5 Chemical profiles of SV representing the multi-therapeutical actions of SVs and their peptides in various cancers

essential for changes in cell shape and volume required for cell invasion (Deshane et al. 2003; McFerrin et al. 2006; Soroceanu et al. 1999). Notably, this effect appears to be specific to glioma cells and has not been observed in healthy cells (DeBin et al. 1993). Binding CTX to Cy5.5 fluorescence dye (CTX-Cy5.5 conjugated tumor-targeting peptide) enabled visualization of the tumor site (Veiseh et al. 2007) and facilitated precise surgery and targeted therapy without damaging healthy cells (Boltman et al. 2023). CTX conjugated with nanoparticles was shown to be effective in depositing drugs at specific tumor sites (Fu, Y. et al. 2012). CTX was conjugated with Iron oxide nanoparticles and targeting ligands, all connected via a polyethylene glycol (PEG) linker. This design facilitated preferential accumulation and enhanced cytotoxicity in glioblastoma and neuroblastoma cells (Boltman et al. 2023). CTX-conjugated with magnetic nano chains could target non-small-cell lung cancer A549 cells, leading to the release of free radicals and the production of reactive oxygen products (ROS). As a result, a significant increase in cancer cytotoxicity and a halt in tumor progression was observed when compared to CTX treatment alone (Zhao et al. 2011). SVPs products including CTX toxins (Wang et al. 2019) further their anticancer effect by altering molecular targets in cancer cells (Desales-Salazar et al. 2020), penetrating the cell membrane of the tumor cells (Veiseh et al. 2007), and attaching to other drug carriers for drug delivery (Chung et al. 2023), such

as nanoparticles (Chung et al. 2023), liposomes (Li et al. 2021), and oligonucleotides (Chen et al. 2020).

Tumors of the nervous system

Odontobuthus doriae's venom was reported to induce swelling and rupture of the neuroblastoma cell membrane and increase the release of cytosolic materials (Zargan et al. 2011b). SV-treated neuroblastoma cells exhibited an increase in lactate dehydrogenase (LDH), compromised cell viability, and up-regulation of caspase 3 leading to DNA damage, inhibited DNA synthesis, apoptosis, and necrosis. *Bmk*-peptide (*Bmk*-CTX) from *Buthus martensii Karsch*-*Bmk* upregulated tumor suppressor p53 protein in human glioblastoma U87-MG cells in vitro, as shown in Table 4 (Wu, S. et al. 2018), and in vivo study by xenografting U251-MG tumor in SCID mouse models Table 5. Notably, p53 protein was increased after *Bmk*-peptide treatment.

Glioblastoma or astrocytoma-IV is the most uncontrolled type of primary brain cancer (Minniti et al. 2021). Current therapies entail surgical resection, radiotherapy, and chemotherapy; however, the mortality rate remains high. The post-diagnostic survival of less than 15 months is due to neoplastic cells' migration to surrounding brain tissues (Tewarie et al. 2021), and chemotherapeutic resistance to drugs such as temozolomide (TMZ) (Jiapaer et al. 2018). CTX, purified from *Leiurus quinquestriatus* was found to specifically bind to glioma cells (Jacoby et al. 2010) sparing healthy cells (Lyons et al. 2002). It

Table 4 In vitro anti-cancer activities of SV and SVPs and their mechanisms of action on human cancer cells

Peptide/venom	Sequence	Dosage	Species origin	Activity	Cancer type	Cell line	Target	Reference
Crude venom	-	Dose dependant manner	<i>A. crassicauda</i>	Proliferation blocking	Human neuroblastoma Human breast cancer	SH-SY5Y MCF-7	Induces apoptosis through increasing nitric oxide production, caspase-3 activity, and depolarizing mitochondrial membrane and arrests S phase and arrests S phase (Probably) inducing cell lysis	(Zargan et al. 2011a, 2011b; Zargan et al. 2011a, b, c)
AcrAP-1 and AcrAP-2 (non-disulfide-bridged peptides) (NDBP), and their high cationic analogs (HC-AcrAP)	FLF KLIP KAI KGLI KAFK FLF KLIP KAI KGLL KAFK	IC ₅₀ (0.001–100 µM)	<i>A. crassicauda</i>	HC-AcrAP analogs proliferation blocking (IC50 2–3.6 µM)	Human lung adenocarcinoma. Human breast carcinoma. Human breast tumorigenic. Human prostate carcinoma	H460 MB435s MCF-7 PC-3		(Possani et al. 2000)
Bengalin 72 kDa	GPLTILHIND- VHAAFEQFNT	IC ₅₀ more than 3 (3.5–4) µg/mL	<i>Heterometrus bengalensis koch</i>	Proliferation blocking	Human leukemia	U937 and K562	Increases expression of Bax/Bcl-2 ratio, caspase 3 and 9, reduces mitochondrial membrane potential, heat shock proteins (HSP) 70 and 90	(Gupta et al. 2010; Heather et al. 2016)
Bmk (70-80 kDa)	CGPCFTTDAN- MARKRECCGGIG- KCFGPQCLCNRI	5. 10 µM	<i>B. martensii Karsch</i>	Proliferation blocking	Human leukemia	(THP-1) acute monocytic leukemia cell line	Inhibit the invasion ability of U87 glioma cell	(Song et al. 2012)
AaCTX	MCIPCFTTNPN- MAAKCNACCGSR- RGS-CRGPQCIC--	5. 200 µM	<i>Androctonus australis</i>	Inhibition the migration and invasion	Human glioma cells	U87	Inhibit U87 glioma cell migration	(Rjeibi et al. 2011)
Bmk-AGAP (66 amino acids)	VRDGYIADDKNCGR- NAYCDECEKN- GAESGYCQWAGYV- GNACWCYKLPDKLP- DKYPIRVPGKCNNGG	(IC ₅₀ = 40 µM for MCF-7 and 50 µM for MDA-MB-231 cells)	<i>B. martensii Karsch</i>	Proliferation blocking, sphere formation, colony formation epithelial-mesenchymal transition, migration, and invasion	Human breast cancer	MCF-7 and MDA-MB-231	Down-regulation of Oct4, SOX2, Nanog, N-cadherin, Snail, and PTX3 and up-regulation of E-cadherin at both gene and protein levels Interference of Na ⁺ toxin with P-AKT, NF-κB, Bcl-2, and MAPK signaling pathway	(Kampo et al. 2019)

Table 4 (continued)

Peptide/venom	Sequence	Dosage	Species origin	Activity	Cancer type	Cell line	Target	Reference
Crude venom		IC ₅₀ (20-100 µg/mL)	<i>A bicolor</i> <i>A crassicauda</i>	Prevents cell motility and colony mitosis	Human breast cancer Human colorectal cancer	MDA-MB-231 HCT-8 and HCT116	Two mechanisms that involved in migration and invasion of cancer cells are proposed a) a decrease in MMPs expression, and b) a reduction in FAK autophosphorylation levels	(Al-Asmari et al. 2016a, b) (Al-Asmari et al. 2016a, b)
Gonearestide (P13) (18 amino acids, 2192 Da)	W C Y K L P D R V S I K E K G R C N	IC ₅₀ (2-200 µM)	<i>A mauritanicus</i>	Proliferation blocking in dose-dependent	Human colon cancer	HCT116	Arrests cancer cell cycle in the G1 phase via modulating cell cycle checkpoint proteins (down-regulate CDK4, and upregulate cyclin D3, p21, p27)	(Li et al. 2018)
Bmk (50-60) amino acids 65 kDa	VRDAAYIAK- PENCVYECGTQDC- NKLCTENGAESGY- CQW	IC ₅₀ (10-200 µg/mL)	<i>B martensii</i> Karsch	Proliferation blocking	Human Prostate cancer	DUI45	Upregulation of Bax apoptotic gene expression, and down-regulated of Bcl-2 anti-apoptotic gene expression	(Zhang et al. 2009)
Bmk-CT	CGPCFTTDAN- MARKRECCGGIG- KCFGPQCLCNRI			Migration and invasion blocking	Human glioma	SGH-44	Inhibiting proliferation by G1/S arresting cancer cells cycle Blocking of Cl ⁻ ion channel, hence, selectively target glioma	(Kampo et al. 2019) (Himed et al. 2013; Jian 2014; Pedersen and Stock 2013)

Table 4 (continued)

Peptide/venom	Sequence	Dosage	Species origin	Activity	Cancer type	Cell line	Target	Reference
Iberitoxin (IbTX) (34 amino acids, 36.07 kDa)	GDCLPHLKRCK- ADNDCCGKKCKR- RGTNAEKRCR		<i>Buthus tumulus</i>	Prevents growth and proliferation	Human cervical cancer Human ovarian cancer Human breast cancer	HeLa A2780 MCF-7	Blocks calcium- activated potassium channels KCNMA1 (KCa1.1, BK) Found to be expressed in cervical cancer- hormone depend- ent block large conductance Ca ²⁺ activated K ⁺ (BK) channel	(Han et al. 2007; Ramírez et al. 2018)
Margatoxin (MgTX, 39 amino acids, 41.92 kDa)	TIINVKCTSPKQCLPP- CKAQFGQSAGAKC- MNGKCKCYPH	Dose dependant manner	<i>C. margaritatus</i>	Proliferation block- ing	Human lung adeno- carcinoma	A549	Blocks Kv1.3 and increases expression level of p21Waf1/Cip1 and decreases the expression level of Cdk4 and cyclin D3	(Jang et al. 2011)
Chlorotoxin (CTX/ or C1TX) (36 amino acids, MW4.02 kDa)	MCMPFTTDHQ- MARKDDCCGGK- GRGKCYGPOCLCR	IC ₅₀ more than 20 (20–100) µg/mL	<i>L. quinquestriatus</i>	Stops migration and invasion prevents cell motility, and colony mitosis	Human glioma Human breast cancer	D54-MG and CCF- STTG-1 MDA-MB-231	Specially binds to MMP-2 and mod- ulates active MMP-2 expression and enhance Cl- channel receptors uptake (ClC-3)	(Deshane et al. 2003; McFerrin et al. 2006)
crude venom	–		<i>L. quinquestriatus</i>		Human colorectal cancer	HCT-8 and HCT116	Two mechanisms proposed are a) a decrease in the expres- sion of MMPs, and b) a reduction in the phosphoryla- tion levels of FAK, which is involved in cell migration and invasion	(Al-Asmari et al. 2016a, b)
crude venom	–	IC ₅₀ (20–100) µg/ mL	<i>O. doriae</i>	Prevents prolif- eration and DNA synthesis	Human breast cancer Human neuroblas- toma	MCF-7 SH-SY5Y	Depolarizes mitochondria, activates Caspase-3, and depletes anti- oxidant activities	(Zargan et al. 2011a, b, c) Zargan et al. 2011a, b, c)

Table 4 (continued)

Peptide/venom	Sequence	Dosage	Species origin	Activity	Cancer type	Cell line	Target	Reference
crude venom	-	IC ₅₀ (100–1000) µg/mL	<i>R. junceus</i>	Proliferation blocking	Different human cancer cell lines	HeLa, SiHa, Hep-2, NCI-H292, A549, MDA-MB-231, MDA-MB-468, HT-29	Increased expression of P53, Bax, Caspase 3, 8, & 9 and reduced Bcl-2 in HeLa (apoptosis > necrosis) whereas reduced expression p53, did not affect Bax but reduced Bcl-2 in A549 (necrosis > apoptosis) reflecting concentration used > IC ₅₀ or < IC ₅₀	(Mikaelian et al. 2020)
Crude venom	-	IC ₅₀ (500–1000 µg/mL)	<i>A. bicolor</i> <i>A. crassicauda</i>	Proliferation blocking	Human breast cancer, Human colorectal cancer	MDA-MB-231 HCT	Induces apoptosis more than necrotic death, and arrests cells at G0/G1 phase upregulates p53, downregulates Bcl-XL	(Al-Asmari et al. 2016a, b; Al-Asmari et al. 2016a, b; Al-Asmari et al. 2018a, 2018b)
Neopladine-1 (29.918 kDa) and Neopladine-2 (30.388 kDa)	-	Dose dependant manner	<i>T. discrepans</i>	Both peptides induce apoptosis	Human breast carcinoma	SKBR3	Bind to SKBR3 cell surface and trigger FasL and Bcl-2 expression	(D'Suze et al. 2010)
TsAp-1 and TsAp-2 (17 amino acids) high cationic TsAP-1 and TsAP-2	ATGCAAATAAAACAT CTCATYACTCTCTTC TTTCTCGTCTTGATC GTTGC	Dose dependant manner	<i>T. serrulatus</i>	Highly proliferation inhibitors	Human squamous carcinoma lung adenocarcinoma, Human prostate adenocarcinoma Human breast carcinoma, Human glioblastoma	H157 H838 PC-3 MCF-7 U251-MG		(Guo et al. 2013)

Table 5 In vivo anti-cancer effect of SV and SVPs and their mechanisms of action

Peptide/venom	Sequence	Dosage	Duration	Species origin	Activity	Mechanism	Reference
Crude venom	-	0.22 mg/kg/day i.p. (20% LD dose)	13 days	<i>A amoreuxi</i>	Decreasing Ehrlich ascites carcinoma and solid Ehrlich tumor size, but mice-bearing intraperitoneal tumor survival increasing	Down-regulates Ki-67 and VEGF expression and up-regulates Caspase-3 expression	(Salem et al. 2016)
Bmk -AGAP 71.42kDa with 66 amino acids	VRDGYIADDKNCGRNAY- CDDECKNGAESGYC- QWAGVYGNACWCYKLP- DKLPDKVPIRVPGKNGG	(0.5 and 1 mg/kg) injected i.p	20 days at 48 h. intervals	<i>B martensii</i>	Reduced tumor growth of MDA-MB-231 cells in mice	Reduces gene and protein expression in ex vivo tumors of Oct4, SOX2, Nanog, N-cadherin, Snail, and PTX3, and increases the expression of E-cadherin	(Kampo et al. 2019)
Crude venom	-	17.5, 35, 52.5 µg	twice a week for 16 weeks	<i>L quinquestratus</i>	Decreased skin carcinogenesis incidence in mice	Downregulates expression of Ki-67, NF-κB, Cox-2, Bcl-2, VEGF, and pro-inflammatory cytokines (TNF-α and IL-6)	(Almaaytah et al., 2016)
TAM-601 (synthetic C1f) TAM-601	MCMPGFTTTHQ- MARKDDCCGGKGRGK- CYGPOCLCR	2, 10, or 100 mg/kg (i.v.)	3x/week for 2 weeks	<i>L quinquestratus</i>	Blocks angiogenesis in chick. Chorioallantoic membrane growing human tumors. Reduces micro-vessel count in mice using Matrigel plug assay	Inhibits VEGF, PDGF, and TNF-α action on vascularization and blocks MMP-2 activity	(Jacoby et al. 2010)
Gonearrestide 18 amino acids (P13) (2192 Da)	W C Y K L P D R V S I K E K G R C N	50 and 100 µM peritumoral injection	2 weeks	<i>A mauritanicus</i>	prevents tumor growth in HCT116 (colon cancer cell line) in dose-dependent	Cell cycle checkpoint proteins modulation (down-regulates CDK4, and up-regulates cyclin D3, p21, p27)	(Li, B. et al., 2018)

acted by preventing Cl^- ions inflow across glioma cell membranes by blocking small-conductance Cl^- channels (Soroceanu et al. 1998, 1999).

CITx was reported to target human D54-MG and CCF-STTG-1 glioma cells and prevent metastasis (Deshane et al. 2003; McFerrin et al. 2006). Invasion of glioma cells requires Cl^- ions inflow through the cell membrane (Soroceanu et al. 1999) and MMPs activation (Sawaya et al. 1996). CITx was found to selectively bind to glioma cell-MMP-2, but not to normal glial cells, forming a CITx-MMP-2 complex (Deshane et al. 2003). This results in MMP-2 deactivation and reduction in the gelatinase activity of the glioma cell membrane, leading to inhibition of glioma cell invasion into the surrounding brain tissues (Soroceanu et al. 1999). In vitro studies confirmed that CITx reduced glioma cell migration by MMP-2 deactivation and reduction in Cl^- ions expression, thus preventing glioma cells from shrinking and migration (Dardevet et al. 2015). CITx can also serve as a glioma-specific marker or “tumor paint” by conjugating with fluorescent dye to delineate the tumor boundaries and facilitate their surgical removal (Veiseh et al. 2007). Similarly, TM-601, a synthetic product of CITx, retarded the growth of U87-MG glioblastoma cells (Veiseh et al. 2007) and reduced angiogenesis in chick and mouse models through the suppression of both vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) signaling pathways (Jacoby et al. 2010). Iodine-131 radio-labelled CITx peptide (^{131}I -TM601, ^{131}I -CITx) was retained in patients with recurrent glioblastoma for up to 8 days after administration (Wu, X. S. et al. 2010). Experiments using ^{125}I - and (^{131}I)-labelled CTX injected into SCID mice bearing xenografted gliomas showed its specific affinity to glioma, and not normal, thus serving as glioma-specific markers (Soroceanu et al. 1998).

Bmk peptide, another SV-derived Cl^- channel inhibitor, was reported to inhibit human glioma SHG-44 cell growth and proliferation at 29 times lower concentration than that needed to inhibit normal astrocytes (Fu, Y. J. et al. 2007).

In an in vivo study, *Bmk* was bound to MMP-2 and inhibited the glioma C6 cells migration and invasion in rats via MMP-2 blockage (Fu, Y. J. et al. 2011; Fu, Y. J. et al. 2007). *Bmk*-AGAP is a long-chain neurotoxin with 7142 Da and 66 a.a. that is specific to the Na^+ channel. It was shown to suppress glioma cell growth by apoptosis induction. Iberitoxin-IbTx peptide (37 a.a.) purified from *Mesobuthus tumulus* with about 68% sequence similarity to charybdotoxin-ChTX, was reported to selectively bind to BK channel (Ortiz et al. 2015). IbTx inhibited cell growth of human 1321N1 astrocytoma cells (Ouaïd-Ahidouch et al. 2004), and caused S phase halt and

apoptosis induction in glioma cells (Griffin et al. 2020). Notably, IbTx inhibited the growth of HeLa cell and human ovarian cancer (A2780) cell lines (Mikaelian et al. 2020), and in hormone-dependent cancers like breast, prostate, ovarian, and cervix cancers, IbTx peptide inhibited cancer development and growth via inhibition of calcium-activated potassium channels (KCNMA1) (Oeggerli et al. 2012; Ramírez et al. 2018). Another peptide, AaCtx is the first CTX-like peptide isolated from *Androctonus australis* scorpion venom. Its amino acid sequence shares 70% similarity with CTX, from which it differs by 12 amino acids. Due to its very low concentration in venom (0.05%), AaCtx was chemically synthesized. Both native and synthetic AaCtx were active on invasion and migration of human glioma cells. However, their activity was found to be lower than that of CTX. The molecular model of AaCtx shows that most of amino acids differing between AaCtx and CTX are localized on the N-terminal loop and the α -helix. Based on known compounds that block Cl^- channels, it is suggested that the absence of negative charged amino acids on AaCtx structure may be responsible for its weak activity on glioma cells migration and invasion. This finding serves as a starting point for structure–function relationship studies leading to design high specific anti-glioma drugs (Rjeibi et al. 2011).

Hematologic malignancies

In various hematopoietic malignancies including leukemia, lymphoma, and multiple myeloma, SV and their peptides were shown to modulate the NF- κ B signaling pathway that is accountable for cancer cell growth and proliferation, and immune cell development and function, as shown in Table 4. (Escárcega et al. 2007). Activation of the NF- κ B signaling pathway by SV showed selective binding to human leukemia Jurkat cell line and THP-1 cells inducing apoptosis (Hayden et al. 2006). SV-derived SVCIII peptides (70–80 kDa) showed promise as an anti-cancer agent by selectively inhibiting the growth and proliferation of human leukemia (THP-1 cells) and lymphoma (Jurkat cells) cells, while having no effect on healthy peripheral blood lymphocytes. The peptide decreased cyclin D1 protein expression levels and led to G1-phase cell cycle arrest. This was associated with the deactivation of NF- κ B signaling pathways through I κ B α phosphorylation, degradation blocking, and p65 nuclear translocation (Song et al. 2012). In another study, Bengalin peptide purified from the Indian scorpion *Heterometrus bengalensis* Koch (Hbk) exerted cytotoxicity to K562 chronic myelogenous leukemia cells at IC_{50} values of 4.1 mg/mL. It is also human-inhibited U937 histiocytic lymphoma cells at 3.7 mg/mL without affecting healthy lymphocytes, (Gupta et al. 2010). Bengalin-mediated apoptosis was achieved by the intrinsic mitochondrial

death pathway, sub-G1 phase cell cycle arrest, silencing of telomerase activity, and DNA damage (Gupta et al. 2010).

Breast cancer

Breast cancer (BC) is one of the most pervasive cancers, accounting for nearly 1 in 8 newly diagnosed cases worldwide (Arnold et al. 2022). Hyaluronidase-BmHYA1 purified from Chinese red scorpion *B. martensi* was shown to specifically inhibit hyaluronan activity in BC cells, without observed toxic side effects (Feng et al. 2008). CITx peptide from *L. quinquestriatus* scorpion prevented the growth of 4T1 cell line, obtained from the most metastatic and aggressive BCs (Qin et al. 2014), as shown in Table 4.R

Two novel peptides isolated from *Tityus discrepans* (Neopladine-1 and Neopladine-2) displayed effectiveness against SKBR3 BC cell line. Both peptides were shown to selectively bind to SKBR3 cell membrane, causing upregulation in Bcl-2 and FasL expression in cancer cells after less than 5 h. of exposure (Ding et al. 2014). Similarly, peptides from *Odontobuthus doriae* venom induced DNA damage and apoptosis in MCF-7 BC cells (Zargan et al. 2011a, b, c). Another study reported the anti-cancer cytotoxic effect of SV-derived ICD-85 on both BC cell lines (MDA-MB-231 and MCF-7), as well as HELA HL-60 cancer cells, but not on normal human fibroblast MRC-5 cell line (Kheirandish Zarandi et al. 2019). Recombinant *Bmk*-AGAP was also shown to be effective against cancer cells by selectively binding to voltage-gated Na⁺ channels (Kampo et al. 2019).

rBmK AGAP peptide was reported to inhibit breast cancer cell stemness, epithelial-mesenchymal transition (EMT), migration, and invasion both in vitro and in vivo, as shown in Tables 4 and 5. This inhibition was mediated by down-regulating PTX3 through NF- κ B and Wnt/ β -catenin signaling pathways, which may be due to selective binding to one of the voltage-gated- Na⁺-channel subunits, Nav 1.5 (Kampo et al. 2019), which is over-expressed in BC and has a role in its progression (Brackenbury 2012). Selective binding of r*Bmk*-AGAP peptide to Nav 1.5 caused its upregulation and led to an increase in the pentraxin 3 (PTX3) mediator expression. This led to the deactivation of tumor necrosis factor (TNF)- α and modulation of the NF- κ B pathway resulting in the preventing of BC progression (Kampo et al. 2019). Intraperitoneal administration of 0.5 or 1 mg/kg of r*Bmk*-AGAP into mice bearing xenograft of MCF-7 or MDA-MB-231 cells led to EMT and inhibition of stem-like features in both cell lines. This was achieved via down-regulation of PTX3, N-cadherin, Snail-1, Oct4, Sox2, β -catenin, pGSK3- β , Nav 1.5, and p65/NF- κ B, and upregulation of E-cadherin and GSK3- β expression (Kampo et al. 2019).

Compared to controls both tumor volume and weight were significantly reduced in treated mice (Kampo et al. 2019). Another anti-cancer peptide (ANTP, 6280 Da), purified from *Buthus martensi karsch* (*Bmk*) scorpion showed cytotoxicity against cancer cells in mouse tumor model with Ehrlich ascites, and in S-180 fibrosarcoma mouse model (Liu et al. 2002).

Similarly, CTX was shown to inhibit breast cancer by downregulating ER α expression levels, which suggests that CTX might disrupt a key pathway involved in breast cancer progression by interfering with the ER α signalling pathway (Wang et al. 2019). CTX directly binds to ER α and affects several globular α -helical folded structures (H1-H12) in the specific secondary of ER α , potentially leading to altered biological functions of ER α (Wang et al. 2019). Vasodilator-stimulated phosphoprotein (VASP) which regulates cell movement (Carmona et al. 2016) was reported to be the target gene of the ER α signalling pathway in the same study (Padilla-Rodriguez et al. 2018). Furthermore, CTX acts as a direct modulator of ER α function, potentially impacting its role in breast cancer progression with no effect on normal cells (Wang et al. 2019).

Lung adenocarcinoma

Lung cancer is classified into small-cell lung cancer (SCLC) and non-small-cell lung carcinoma (NSCLC), both of which are among the most cancer-leading deaths worldwide with a low five-year survival rate (Lee et al. 2018). SV enzymes: acetylcholinesterase, alkaline phosphatase, phospholipase A2, and proteolytic enzymes with gelatinolytic and cytotoxic effects were reported to cause necrosis, hemolysis, and gangrene in lung cancerous cell lines (Almeida et al. 2002). Treatment with proteases from *Mesobuthus gibbosus* A caused remarkable toxicity in human lung adenocarcinoma A549 cell lines (Pessini et al. 2001). From *Centruroides margaritatus* species, Margatoxin (MgTX) is a highly selective K⁺ channel peptidyl inhibitor with 39 amino acids (Helms et al. 1997). MgTX showed significant inhibition of lung adenocarcinoma cell (A549 cell) growth, Table 4, and halted tumor growth in nude mice, Table 5 (Jang et al. 2011). In addition, MgTx peptide was tested to confirm its inhibitory effect and the results showed that MgTx could induce up-regulation of p21Waf1/Cip1 protein expression and downregulation of Cdk4 and cyclin D3 expression levels, both via inhibition of KV1.3 ion channels (Shahzadi et al. 2021).

Cervical cancer

Cervical cancer is classified as the fourth most common cancer type after BC in women worldwide (Jacobs et al. 2018). In 2016, a study found that the anti-microbial

peptide (AMP), TistH purified from *Tityus serrulatus* SV (TsV) showed a cytotoxic effect on SiHa primary uterine cell line Table 4, without any toxic effect on normal 3T3 embryonic mouse fibroblast cell line (Machado et al. 2016). Another study showed that treatment with crude venom of *Tityus serrulatus* scorpion (TsV) decreased HeLa cell viability in a dose-dependent manner, and increased caspase-mediated apoptosis of both SiHa and HeLa human cervical carcinoma lines, (Bernardes-Oliveira et al. 2019). An *in vitro* study demonstrated the anti-proliferative effect of LMWSVP, a low molecular weight peptide purified from *Bmk* crude venom, on SMMC7721 human hepatoma cells in a dose-dependent manner. LMWSVP also increased the expression of caspase-3 and decreased that of the anti-apoptotic protein Bcl-2 (Li et al. 2014).

Melanoma (skin cancer)

Venom from the medically important scorpion *Leiurus quinquestriatus* demonstrated promising anti-cancer effects in mice. Treatment with this venom significantly inhibited the growth and number of tumors induced by DMBA and croton oil on mouse skin. Furthermore, the venom reduced the expression of pro-inflammatory cytokines and downregulated key molecular markers associated with tumor development, including Ki-67, nuclear factor kappa-B (NF- κ B), cyclooxygenase-2 (COX-2), B-cell lymphoma-2 (Bcl-2), and vascular endothelial growth factor (VEGF) as revealed by immunohistochemistry analysis (Al Asmari and Khan 2016). A study demonstrated that CTX specifically binds to gliomas and a variety of peripheral tumors of neuroectodermal origin (PNET), including melanoma. bCltx is a synthetic molecule that is biotinylated at the N-terminus which was found to specifically bind to exhibit high binding affinity, targeting 50% to 100% of the cells within melanoma tissues (Lyons et al. 2002). Similarly, a study demonstrated that TM-601 molecules, a synthetic peptide also have an anti-cancer effect against SK-Mel melanoma, as shown in Table 4 (Romo Vaquero et al. 2012).

Other cancers

Prostate cancer (PC) is the leading cancer in men worldwide (Rizzo et al. 2022). PESV is 60 amino acid polypeptide derived from *Buthus martensi Karsch* (*Bmk*) scorpion (Li et al. 2019). PESV showed cytotoxic activity on hormone-refractory, androgen-independent PC cell lines (Zhang et al. 2009). In mice, PEVS also inhibited neovascularization and tumor growth in S180-sarcoma and H22-hepatocellular carcinoma, as shown in Table 5 (Zhang et al. 2009).

In gastric cancer, *Bmk* venom was shown to decrease the viability and inhibit the proliferation of NUGC-3

human gastric cancer cells significantly at a dose of 5 mg/mL, Table 4. Treatment of NUGC-3 cells with 5 mg/ml *Bmk* venom for 24 h showed a 6% increase in the sub-G1 cell cycle phase, a 9% increase in the G1 phase, and an 11% decrease in the G2/M phase, and increased cell apoptosis (Jian 2014). In oesophageal cancer, a study demonstrated the cytotoxicity of *Heterometrus liangi* scorpion venom against human oesophageal cancer cell lines KYSE-510 cell lines led to inducing cell death through apoptosis pathway, as shown in Table 4.

Pancreatic cancer is known for local invasion, early metastasis, and a strong desmoplastic reaction. An *in vitro* study demonstrated that CTX at a concentration of 300 nM significantly inhibited the cell migration of PANC-1 pancreatic cancer cells. The monomeric form of chlorotoxin (M-CTX-Fc) was generated by joining the CTX peptide to the amino terminus of the human IgG-Fc domain without a hinge domain. This form inhibited the migration ability of PANC-1 cells when compared with the control, suggesting that M-CTX-Fc may be effective for targeting pancreatic cancer (El-Ghlban 2014).

In colorectal cancer, a battery of *in vitro* biological functional studies and bioinformatics analyses demonstrated that Goneyarrestide peptide, purified from *Androctonus mauritanicus* (Ama) exerted a potent anti-tumor effect (Liscano et al. 2020). Goneyarrestide is 18 amino acids long, and 2192 Da. It was also found to target a broad spectrum of cancer cells such as human colon cancer cell line HCT116, with no reported cytotoxicity on erythrocytes and surrounding epithelial cells (Li, B. et al., 2018). Goneyarrestide halted tumor growth and cancer cell proliferation by modulating cell cycle checkpoint proteins. It triggered cancer cell cycle arrest in the G1-phase through inhibition of cyclin-dependent kinases 4 (CDK4) and up-regulating the expression of cell cycle regulators/inhibitors—cyclin D3, p27, and p21. *In vivo*, xenograft mouse model treatment with Goneyarrestide significantly halted the growth of xenografted human tumors in a mouse model and reduced the tumor volume in a dose-dependent manner, in Table 5 (Li, B. et al., 2018).

SVPs targets in mammalian cells are related to key biological functions, many of which are related to cancer development and progress. In addition, studies now suggested that new molecules from SVs could neglectable cytotoxic effects by the isolation of each peptide by owns via unwinding the peptide bonds to facilitate their targets. Despite these successful discoveries, there is a gap between the number of peptides with interesting pharmacological properties obtained from SV. Basic research on scorpion venom faces two main limitations: the limited quantity obtained from different species and

the inherent complexity of the venom itself, which makes isolating specific toxins a challenge.

Conclusion and future directions

SVs are a rich bio-source of molecules with a wide range of biological and pharmaceutical applications. SVPs were found to be especially valuable for cancer therapy. As researchers identify and characterize an increasing number of peptides from different scorpion species, a wide range of toxic properties to cancer properties are discovered and applied to various types of malignancies, while sparing normal cells. The latter is a highly desirable character is modern approaches to cancer therapy, and to avoid the determinantal side effects of current cytotoxic therapies. Despite their high selectivity, the safety profile for new SV derived drugs requires extensive research. Only a few scorpion species have been extensively studied, but thousands remain unexplored, especially of the promising *Leiurus quinquestriatus* scorpion. Novel isolation techniques aim to deliver new molecules from SVs with neglectable cytotoxic effects by chemical manipulation of the target peptide Expanding the pool of SV sources still present a challenge since only a small volume of venom is collected from scorpions. Apply novel techniques in drug synthesis could pave the way to a larger scale of manufacturing anti-cancer peptides with the high SV characteristic selectivity and specificity to cancer cells.

Abbreviations

a.a.	Amino Acids
A549	Human lung adenocarcinoma
Aa	<i>Androctonus aeneas</i> Scorpion
Ama	<i>Androctonus mauritanicus</i> Scorpion
BC	Breast Cancer
Bcl-2	B-cell lymphoma 2
Bcl-xL	Basal cell lymphoma-extra large
BmHYA1	Purified hyaluronidase from Chinese red scorpion <i>Buthus martensii</i>
BmK	<i>Buthus martensii karsch</i>
BmK AGAP	Neurotoxin specific to Na ⁺ -channels
C6	Rat glioma cells
CDK4	Cyclin dependent kinase 4
ChTx	Charybdotoxin
CTX or ClTx	Chlorotoxin/ or chloride-bound toxins (Cl ⁻ channel scorpion toxins)
DNA	Deoxyribonucleic acid
EMT	Epithelial-mesenchymal transition
ERα	Estrogen receptor alpha
FAK	Focal adhesion kinase
H22	Hepatocellular carcinoma in mice
HCT116	Colorectal cancer cell line (human colon-cancer cell line)
HeLa	Immortalized cell line derived from cervical cancer cells
Hb	<i>Heterometrus bengalensis Koch</i>
HI	<i>Heterometrus liangi</i>
I.p.	Interperitoneally
IbTx	Iberitoxin
IC ₅₀	Half maximal inhibitory concentration,
ICD-85	Venom derived peptides
IL-2	Interleukin 2
IL-6	Interleukin 6

Im	<i>Isometrus masculatus</i>
Jurkat cells	Human T lymphoma
K562	Chronic myelogenous leukemia
KCa	Calcium-activated potassium channels
KCNMA 1	Calcium-activated potassium channel
KDa	Kilodalton
KTx	Potassium-bound toxins (K ⁺ channel scorpion toxins)
KV	Kilovolt
Kv	Voltage-gated potassium channel
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated proteins
MCF-7	Michigan cancer foundation-7 (breast cancer cells)
MDA-MB-231	Triple-negative breast cancer cells (epithelial human breast cancer cell line)
MgTx	Margatoxin
Mg/L	Milligram per liter
MIC	Minimal inhibitory concentration
MMP-2	Matrix metalloproteinase 2
MRC-5	Normal fibroblasts
NDBPs	Non-disulfide bridges peptides
NF-κβ	Nuclear factor-κβ
nM	Nanometer
NSCLC	Non-small-cell lung cancer
Osk-1	<i>Orthochirus scrobiculosus</i> selective to K ⁺
PANC-1	Pancreatic cancer cells
PC	Prostate cancer
PESV	Polypeptides Isolated from <i>Buthus martensii kirsch</i> scorpion
PTX3	Pentraxin-3
ROS	Reactive oxygen species
S180	Sarcoma
SCLC	Small-cell lung cancer
SHG-44	Human glioma cells
SK-Mel	Melanoma
Smp	<i>Scorpio maurus palmatus</i>
SV	Scorpion Venom
SVCIII	Scorpion venom fraction III (Bmk fraction)
SVPs	Scorpion venom-derived peptides
SVs	Scorpion venoms
THP-1	Human acute monocytic leukemia cell line
TM601	Synthetic product of CTX
TMZ	Temozolomide
TNF-α	Tumor necrosis factor
TsV	<i>Tityus serrulatus</i> venom
U87-MG	Glioblastoma cell line
U937	Human leukemia cell (histiocytic lymphoma)
VGSCs	Voltage-gated sodium channels
Vm	Negative membrane potential
μm	Micrometre

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Author details

¹Department of Zoology, Faculty of Science, Zagazig University, Zagazig 44519, Egypt. ²Center of Excellence for Stem Cells and Regenerative Medicine, Zewail City of Science and Technology, 6th of October City, Giza 12578, Egypt.

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