

Scorpion venoms as a potential source of novel cancer therapeutic compounds

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Abstract

Scorpions and their venoms have been used in traditional medicine for thousands of years in China, India and Africa. The scorpion venom is a highly complex mixture of salts, nucleotides, biogenic amines, enzymes, mucoproteins, as well as peptides and proteins (e.g. neurotoxins). One of the recently observed biological properties of animal venoms and toxins is that they possess anticancer potential. An increasing number of studies have shown that scorpion venoms and toxins can decrease cancer growth, induce apoptosis and inhibit cancer progression and metastasis *in vitro* and *in vivo*. Several active molecules with anticancer activities, ranging from inhibition of proliferation and cell cycle arrest to induction of apoptosis and decreasing cell migration and invasion, have been isolated from scorpion venoms. These observations have shed light on the application of scorpion venoms and toxins as potential novel cancer therapeutics. This mini-review focuses on the anticancer potential of scorpion venoms and toxins and the possible mechanisms for their antitumor activities.

Keywords: Scorpion, venoms and toxins, anticancer potential, apoptosis

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Introduction

The scorpion, which is one of the oldest creatures known, has existed on earth for more than 400 million years. Scorpions are known to be widely distributed all over the world, and there are over 1500 species that have been reported thus far.¹ Scorpions have developed a negative reputation due to their stings and envenomation, usually resulting in pain, swelling, hypertension, cardiac arrhythmia and other systemic manifestations.² Scorpion envenomation is a public health hazard in tropical and subtropical regions. More than 1,200,000 scorpion stings are reported to occur yearly with the number of deaths possibly exceeding 3250 per year worldwide. There is therefore, the need for improvement in specific (antivenom) and systematic treatments.³

However, human beings have also derived benefits from the scorpion. In China, fried scorpions are popularly consumed as food, and scorpion or snake wines are used to strengthen the immune system.⁴ The scorpion and its venom have been applied in traditional medicine for thousands of years in China, India and Africa. For example, in China, the dried whole bodies of scorpions have been widely used as an antiepilepsy and analgesic agent since the Song Dynasty (A.D. 960–1279).^{5,6} The *Buthidae* family of

scorpions has been widely studied for medical applications. The scorpion venom is a highly complex mixture produced from the venom gland to immobilize/paralyze the prey or to defend against predators. The venom which is found in the telson contains salts, nucleotides, biogenic amines, enzymes such as phospholipase, hyaluronidase, L-amino acid oxidase, metalloproteinase, serine protease, mucoproteins, as well as small peptides which are known to interact with various ion channels in excitable cell membranes, making them good candidates for drug design in the pharmaceutical industry.^{7,8} A number of antimicrobial peptides have also been isolated and reported to be bioactive against bacteria, fungi, yeasts and viruses including Mucroporin-M1 which inhibits the amplification of hepatitis virus B and Kn2-7 which possesses anti-HIV-1 activity.^{9,10}

This mini-review explores the significance of scorpion venoms as anticancer agents and provides biological insights into their mechanism (s) of action.

Scorpion venoms as potential cancer therapeutics

According to the World Health Organization, cancer has replaced heart disease to become the leading cause of

mortality worldwide, leading to 7.6 million deaths (around 13% of all deaths) in 2008.¹¹ Cancers of the lung, stomach, liver, colon and breast are known to be the highest contributors to cancer mortality each year. Even though treatment for cancer improved considerably over the past decade resulting in increased patient survival and better quality of life, early screening and diagnosis still play a very important role in improving the patient's survival rate, since many cancers have a high chance of cure if detected early and treated adequately.¹² Surgical resection of the primary tumor and regional lymph nodes is the main and most effective way to treat most patients with solid tumors.¹³ Adjuvant and neo-adjuvant therapies (chemotherapy and radiotherapy) are known to benefit patients by increasing their survival remarkably. However, the side effects and risks of treatment resistance and toxicity are of major concern. Newly emerging targeted therapy opens a novel avenue for surgical oncologists and clinicians to better understand the molecular mechanism of cancer and provide alternative and effective approaches to combat cancer.¹⁴

One of the recently discovered biological properties of scorpion venom and toxin is that they possess anticancer potential. An increasing number of experimental and pre-clinical investigations have demonstrated that crude scorpion venom and some purified proteins and peptides can impair cancer proliferation, arrest cell cycle, induce cell apoptosis and inhibit cancer metastasis in *in vitro* or *in vivo* setting. The anticancer effect and efficacy of scorpion venoms have been tested in glioma, neuroblastoma, leukemia, lymphoma, breast, lung and prostate cancer.^{15,16}

Chinese red scorpion (*Buthus martensii* Karsch) venom

Buthus martensii Karsch (BmK) (Figure 1), also known as Chinese red scorpion, belongs to the *Buthidae* family and can be extensively found from north western China to Mongolia and Korea. The medical use of BmK scorpion dates back to the Song Dynasty of China (A.D. 960-1279). To date, this scorpion venom has been well described as having antiepileptic, analgesic, anti-rheumatic and anticancer potential.^{5,6,15,16} Among all the scorpions used in cancer

research, BmK is probably the first to have been reported to possess antitumor properties.¹⁶ BmK scorpion venom has been well studied in China, with several active molecules having been isolated and characterized, making this scorpion venom a good source for the development of anticancer agents.

In 1987, Zhang Futong, extracted a solution from the dried whole body of the BmK scorpion (Quan Xie in traditional Chinese medicine) and administered the extract subcutaneously to mice with reticulum cell sarcoma and MA-737 mammary carcinoma at a dose of 0.04 g/mouse every other day for five times.¹⁷ On the 8th day following administration, the inhibitory rate of growth was 55.5% in reticulum cell sarcoma and 30.4% in mammary carcinoma, respectively. There was a decrease in DNA content in the tumor tissues after BmK venom treatment. This seminal finding formed the basis for the escalating reports on the anticancer potential of BmK scorpion venom.

Several groups later described the anticancer effects of the crude scorpion venom of BmK *in vitro* or *in vivo*. However, scientific literatures on the BmK venom which are published in Chinese will not be included in this review. Wang and Ji observed that the crude venom extract from BmK induced apoptosis of malignant glioma U251-MG cells *in vitro* especially at a dose of 10 mg/mL but was not cytotoxic to BEL7404 hepatocellular carcinoma cells and C400 Chinese hamster ovary cells.¹⁸ For the *in vivo* study, BmK venom was assessed using severe combined immunodeficiency mice bearing U251-MG tumor xenografts. Both tumor volumes and weights were significantly reduced compared with the control group after 20 mg/kg BmK venom treatment for 21 days. The authors proposed ion channels as targets for BmK venom in glioma cells. Another study by Gao et al.¹⁹ found that BmK venom could also inhibit growth of human Jurkat and Raji lymphoma cells by arresting the cell cycle and inducing apoptosis as evidenced by Annexin-V and propidium iodide staining and flow cytometry assay. Treatment with the BmK venom has been demonstrated to inactivate the PI3K/Akt signal pathway by increasing phosphatase and tensin homolog (PTEN) expression in Raji cells, whereas, in Jurkat cells, a PTEN-negative cell line, up-regulation of p27 (a cell cycle inhibitor) may partially account for the anticancer effect.¹⁹

In light of several reports on the anticancer potential of BmK crude venom, researchers attempted to purify and isolate the anticancer agent in BmK venom with techniques such as size-exclusive gel filtration, ion exchange chromatography and high-performance liquid chromatography.²⁰ Polypeptide extract from the scorpion venom (PESV), a group of polypeptides comprising 50–60 amino acids extracted from crude venom of BmK, was reported to induce growth inhibition and apoptosis of DU 145 human prostate cancer cell.²¹ PESV treatment on DU 145 cells resulted in a significantly dose-dependent inhibition of proliferation with G1 phase arrest in cell cycle, accompanied by enhanced expression of p27 and a decrease in cyclin E. PESV treatment also induced a high apoptosis index, which was verified by the TdT-mediated dUTP-biotin nick-end labeling (TUNEL) assay and probably due to an



Figure 1 *Buthus martensii* Karsch (Chinese red scorpion). Specimen from Jiangsu Province, PR China. Arrow indicates telson, the venom-producing gland. (A color version of this figure is available in the online journal)

increase in pro-apoptotic protein Bax. A recent study reported that another partially purified component from BmK scorpion venom (SVCIII), obtained after gel filtration with a molecular weight of approximate 70–80 kDa, could inhibit cell proliferation of THP-1 and Jurkat human leukemia cells and caused cell cycle arrest at G1 phase.²² A decrease of cyclin D1 expression was observed in a dose-dependent manner after SVCIII treatment. The anti-proliferative effect has been attributed to the suppression of NF- κ B activation.

Two anticancer peptides have been purified and characterized from BmK scorpion venom. Early in 2002, Liu and colleagues first isolated an analgesic-antitumor peptide (AGAP) from BmK scorpion venom with a series of purification steps.²³ This peptide had a relative molecular mass of 6280 Da and exerted antitumor effects in the mouse S-180 fibro sarcoma model and Ehrlich ascites tumor model. The AGAP gene was determined, cloned and expressed in the *Escherichia coli* system in 2003 by the same group (GeneBank No. AF464898) and the protein showed effective analgesic and antitumor activities.²⁴ Subsequently, BmK AGAP was classified as a voltage-gated sodium channel scorpion toxin and three transcription regulatory elements were elucidated in the BmK AGAP intron.²⁵ A recombinant fusion protein SUMO-AGAP which combined a small ubiquitin-related modifier to AGAP was proven to have antitumor activity.²⁶ Further study showed that SUMO-AGAP inhibited cell proliferation and migration of SHG-44 human malignant glioma cells by inducing cell cycle arrest and interfering with the p-Akt, NF- κ B, Bcl-2 and MAPK signaling pathways.²⁷

BmKCT, another purified anticancer peptide from BmK with 68% homology to chlorotoxin (a promising antiglioma toxin that will be discussed later), was cloned from a cDNA library made from the venom glands of the BmK scorpion.²⁸ BmKCT contains 59 amino acid residues and comprises a mature toxin of 35 residues with four disulfide bridges and a signal peptide of 24 residues. Subsequently, the recombinant peptide of BmKCT was shown to inhibit the growth of glioma cells (SGH-44) dose-dependently with IC₅₀ value of approximately 0.28 μ M while showing no toxicity to normal astrocytes under the same condition.²⁹ Whole-cell patch-clamp technique indicated that the chloride current in SHG-44 glioma cells was inhibited by BmKCT in a voltage-dependent manner (up to 55.86% inhibition at 0.14 μ M treatment) and histological analysis of tissues from BmKCT-treated mice showed that the brain was one of the targets of this toxin. Furthermore, *in vivo* evidence from Fan et al. using the glioma/SD rat model³⁰ demonstrated that BmKCT toxin inhibited glioma proliferation and tumor metastasis and ¹³¹I-labeled or Cy5.5-conjugated BmKCT selectively targeted the glioma *in situ*. All these observations provide evidence for the potential therapeutic application of BmKCT for glioma diagnosis and treatment.

Two scorpion enzymes, isolated by our research group from BmK scorpion venom, have also been reported to possess anticancer potential. One is the serine proteinase-like protein named BmK-CBP, which can dose-dependently bind with human breast cancer cells MCF-7.³¹ The other, BmHYA1, a homogeneous hyaluronidase from the BmK

scorpion, was shown to modulate the expression of CD44, a cell surface marker in the MDA-MB-231 breast cancer cell line.³²

Scorpion venom targeted ion channels

A novel and promising field of cancer research is targeting Na⁺, K⁺, Ca²⁺ and Cl[−] ion channels in cancer, given that altered or abnormal expression and activity of ion channels are related to cancer processes and pathology including cell volume and motility, cell proliferation and death, as well as cell adhesion, migration and invasion. Moreover, blocking ion channel activity can impair cancer growth and metastasis.^{33,34}

Functional expression of voltage-gated sodium channels has been reported to be associated with several strongly metastatic carcinomas, such as breast and prostate cancer, as evidenced by their over-expression in aggressive cancer-derived cell lines and biopsies as well as its role in controlling multiple steps of metastatic cascades.³⁵ Fraser and co-workers³⁶ observed that functional expression of Na_v1.5 was up-regulated in metastatic human breast cancer cells and tissues, and its activity could potentiate cellular behaviours linked to metastasis, such as directional motility, endocytosis and invasion. Also, a strong correlation was found between Na_v1.5 expression and lymph node metastasis in a clinical study. Similar findings were also observed for the involvement of Na_v1.7 in prostate cancer.^{37–39}

Compared to Na⁺ channels, K⁺ channels are mainly implicated in cancer cell proliferation and survival. There is a tight relationship between K_v expression and cell proliferation and apoptosis, but the underlying mechanism is still not clear. Generally, by regulating the membrane potential, K_v channels can control the Ca²⁺ fluxes and cell volume, and therefore exert their role in cell cycle regulation and cell death.⁴⁰ A number of K_v channels have been detected to be abnormally expressed in many primary cancers. K_v1.3 has been analyzed in gliomas, colon, prostate and breast cancers.⁴¹ The aberrant expression of K_v1.3 was observed to promote cancer cell growth. The roles of K_v 1.5, K_v10.1 and K_{Ca}3.1 have been studied in gliomas, colon cancer and melanoma. K_v11.1, also known as hERG, is expressed in several cancers, including leukemia, neuroblastoma, stomach and colorectal cancers. The blockage of K_v11.1 with a channel inhibitor or siRNA interference can impair cell proliferation *in vitro* and reduce cell invasive-ness, making it a novel therapeutic target for cancer.⁴²

Among the peptides found in scorpion venoms, the most well-studied are the long-chain toxins with 60–70 amino acid residues cross-linked by four disulfide bridges, which interact with Na⁺ channels. Short-chain toxins with 30–40 amino acid residues are known to modulate K⁺ or Cl[−] (chloride ion) channels.⁴³ Compared to massive Na⁺ or K⁺ channel toxins, only few calcium channel-related toxins (with a variable number of amino acids) have been purified or cloned from scorpion venoms.⁴⁴

Chlorotoxin (CTX), a 36-amino acid small peptide, first purified from the *Leiurus quinquestriatus* scorpion venom in 1993, contains a single tyrosine residue that is available for

radioiodination, eight cysteine residues, and four disulfide bonds.⁴⁵ Originally, CTX was described as a Cl^- channel blocker that acts as a paralytic agent for small insects and other arthropods. CTX had been largely applied as a tool in the study of voltage-gated chloride channel until the seminal findings of Ullrich and co-workers in cancer research.^{46,47} They adapted the whole cell patch-clamp recording technique to identify and characterize the voltage-activated outwardly-rectifying Cl^- currents in human astrocytoma/glioblastoma cells. Cl^- currents were observed in all tumor cells of glial origin (primary cultures of six freshly resected brain tumors and seven established human astrocytoma cell lines), while interestingly they were absent in normal non-malignant glial cells or non-glial tumors such as melanoma, breast, rhabdomyosarcoma and neuroblastoma. Their study also demonstrated that CTX could block the Cl^- current and inhibit cell proliferation of astrocytoma cells.

The specifically expressed Cl^- channel in glioma and its high affinity and sensitivity to CTX led to the use of this peptide by Soroceanu and colleagues to target gliomas in 1989.⁴⁸ They showed that biotinylated and fluorescence-tagged CTX and CTX-conjugated molecules had specific staining for glioma cells *in vitro*, *in situ* and in patient biopsies. Another survey of over 200 tissue biopsies from patients with various malignancies also suggest that CTX bind to the surface of gliomas and other embryologically related tumors of neuroectodermal origin but not to normal brain.⁴⁹ Furthermore, CTX has been reported to significantly reduce the glioma cell migration dose-dependently and inhibited cell invasion into fetal brain aggregates at 5 μM concentration.⁵⁰

The receptor of CTX was initially believed to be related to the Cl^- channel from electrophysiological evidence (as described above). Further studies with a recombinant His-CTX revealed that the principal receptor is matrix metalloproteinase-2 (MMP-2), a proteinase that is present on the surface of glioma cells, and specifically over-expressed in gliomas and related cancers, but normally not expressed in brain.⁵¹ CTX could inhibit the enzymatic activity and reduce the expression of MMP-2, causing disruption of chloride channels and Cl^- currents. A synthetic CTX coupled with radioactive iodine isotope (¹³¹I-TM-601), produced by Transmolecular, Inc. (Cambridge, MA) has been approved by the US Food and Drug Administration for tumor imaging and diagnosis. Preclinical and Phase I clinical trials have been completed in recurrent glioma patients, with the conclusion that intracavitary dose of ¹³¹I-TM-601 is safe and minimally toxic, and that ¹³¹I-TM-601 binds malignant glioma with high specificity and for long duration.⁵² A Phase II trial using a higher dose of radioactivity and repeated local administrations is currently in progress. Because CTX binds tumor with high affinity and specificity and shows low toxicity, it represents a promising diagnostic agent for imaging and targeted therapies for gliomas and other cancers.

Apart from CTX, several other scorpion toxins associated with ion channels have been purified and investigated in cancer research. Iberitoxin (IbTX), a 37-amino acid neurotoxin from the Indian red scorpion *Mesobuthus tamulus*, has

been reported to block the large conductance Ca^{2+} activated K^+ (BK) channel and induce a slight depolarization in MCF-7 human breast cancer cells. Cells treated with IbTX (500 nM) were observed to accumulate in S phase of the cell cycle but did not alter the cell proliferation rate.⁵³ Another experiment showed that blockade of the BK channels by IbTX inhibited K^+ currents and growth of PC-3 prostate cancer cells.⁵⁴ Margatoxin (MgTX), which is isolated from the venom of *Centruroides margaritatus* scorpion, sharing a sequence homology and structural similarity with IbTX, has a high affinity and specificity against Kv1.3. Jang et al. found that MgTX can significantly inhibit the proliferation of A549 human lung adenocarcinoma cells by regulating the G1/S cell cycle progression. Western blot analysis showed increased expression of p21Waf1/Cip1 and decreased levels of Cdk4 after 1 nM MgTX treatment. The antiproliferative effect of MgTX was also verified in a nude mice xenograft model, as confirmed by a reduction of tumor volume after injecting MgTX into the tumor tissues.⁵⁵

Charybdotoxin (ChTX), another peptide isolated from *Leiurus quinquestriatus* scorpion venom, is structurally similar to IbTX and MgTX and acts as an inhibitor of Ca^{2+} -activated K^+ channel. Studies revealed that ChTX can inhibit the migration of NIH3T3 fibroblasts and human melanoma cells dose-dependently by up to 61%, possibly by depolarizing the cell membrane potential and reducing the electrochemical driving force for Ca^{2+} entry, which is important in the cell migration process.⁵⁶ However, in the same study, it was also observed that ChTX did not influence the disruption of the epithelial layer of renal cells by human melanoma cells, suggesting that K^+ channel activity was not involved in melanoma invasion.

Recent studies on the anticancer potential of scorpion venoms and toxins

Research on animal venoms and toxins has attracted greater interest because of advances in genomic and proteomic approaches such as the venomous systems genome project.⁵⁷ In addition, new emerging research regarding the relationship between ion channels and cancer progression and therapy has paved the way for novel clinical applications for scorpion venoms and toxins, given that scorpion venoms contain many disulfide-rich peptides and proteins which display high specificity, good permeability and stability against cancer cells.⁵⁸ In the last decade, more evidence has accumulated regarding the anticancer effect of scorpion venoms and toxins from different species and targeting assorted cancers.

In 2007, Gupta et al.⁵⁹ reported the antiproliferative and apoptogenic activities induced by *Heterometrus bengalensis* Koch (Indian black scorpion) against human leukemic U937 and K562 cell lines, characterized by cell cycle arrest, membrane blebbing, chromatin condensation and DNA degradation. The molecule of interest was subsequently purified and named Bengalin, a 72-kDa protein with an N-terminal sequence that shared no similarity with any protein in the scorpion toxin database. The IC₅₀ of Bengalin was determined as 3.7 $\mu\text{g}/\text{mL}$ and 4.1 $\mu\text{g}/\text{mL}$ for U937 and K562 human leukemic cells, respectively, without affecting

normal human lymphocytes. Bengalin induced apoptosis as confirmed by damaged nuclei, sub G1 peak, DNA fragmentation as well as decreased telomerase activity. Furthermore, Bengalin caused the loss of mitochondrial membrane potential, decreased the expression of heat shock protein (HSP) 70 and 90, activated caspase-3, 9 and induced cleavage of poly (ADP-ribose) polymerase.⁶⁰ These observations indicated activation of a mitochondrial death cascade, involving inhibition of HSPs by Bengalin.

Two peptides named neopladine 1 and neopladine 2, isolated from *Tityus discrepans* scorpion venom, were reported to be effective in inducing apoptosis and necrosis of SKBR3 breast cancer cells with negligible effect on non-malignant MA104 monkey kidney cells.⁶¹ Immunohistochemistry showed that neoplades bind to the surface of SKBR3 cell and triggered FasL and Bcl-2 expression. We have also found that the Indian red scorpion (*Mesobuthus tamulus*) venom decreased the cell viability of human breast cancer cells dose-dependently with minimal cytotoxic effect on normal breast epithelial cells *in vitro* (unpublished data).

Another research finding showed that scorpion venom from *Odontobuthus doriae* inhibited cell growth and induced apoptosis in SH-SY5Y human neuroblastoma cells and MCF-7 breast cancer cells.^{62,63} Moreover, *Odontobuthus doriae* venom increased intracellular oxidative stress as evidenced by an increase in reactive nitrogen intermediates and depression of glutathione and catalases in MCF-7 cells, which may contribute to the induction of apoptosis. The cytotoxicity of another scorpion venom *Androctonus crassicauda* was also screened using MCF-7 and SH-SY5Y cell lines.⁶⁴ Similarly, *Androctonus crassicauda* venom caused the suppression of cell growth by S-phase cell cycle arrest and induced apoptosis by increasing nitric oxide production, thereby, activating caspase-3 and depolarizing mitochondrial membrane. The above findings suggest that the *Odontobuthus doriae* and *Androctonus crassicauda* scorpion venoms may be potential sources for isolating effective anticancer molecules.

Cytotoxic proteins such as Bengalin and Neopladine 1 and 2 with molecular weight more than 10 kDa are able to

inhibit cell viability and induce apoptosis or necrosis in cancer cells while showing negligible cytotoxicity to normal cells. Hence, such proteins are promising for developing as anticancer drugs.

Besides cancer therapy, scorpion venoms have also been applied in diagnostic imaging of tumor, mainly based on the conjugates of CTX and its homological peptides (e.g. BmKCT) to delineate the tumor margins. Researchers have combined CTX with other radioactive or fluorescence molecules, such as ¹³¹I, Cy5.5, and iron oxide nanoparticles coated with polyethylene glycol, and synthesized various probes that can be detected by γ -camera, single photon emission computed tomography or magnetic resonance imaging.^{52,65,66} Due to the binding specificity of CTX and the use of nanovectors, the CTX-conjugated probes can cross the blood-brain barrier and work as imaging agents in tumors of the central nervous system. In addition, the CTX-conjugated nanoparticles are now being developed as a carrier of DNA in gene therapy in glioma.⁶⁷

Conclusion

In summary, the anticancer effects of scorpion venoms and toxins have been reported for several scorpion species and in different cancer types, in both *in vitro* and *in vivo* settings. Scorpion venoms with anticancer properties and possible mechanisms of action are summarized in Table 1. It can be clearly seen that the anticancer effects are achieved mainly via targeting ion channels on cell membrane, or exerting antiproliferative or apoptotic activities by cell cycle arrest or induction of caspase-dependent apoptosis pathways.

Currently, only a few scorpion species have been investigated for anticancer effects. As many of the studies have been carried out in the *in vitro* setting, testing the antitumor potential of scorpion venoms/toxins in animal models is important for preclinical research work and drug design. Although purification and characterization of the active components which exert anticancer effects from crude venoms still remain a challenge, there is potential for the use of scorpion venoms as novel cancer therapeutics.

Table 1 Summary of the important molecules with anticancer potential and possible mechanisms

Molecules	Scorpion species	Tested cancer models	Possible mechanisms	References
BmK AGAP	<i>Buthus martensii</i> Karsch	Mouse fibro sarcoma, Rhrlich ascites tumor, SHG-44 glioma cells	Voltage gated sodium channel toxin, interfering p-AKT, NF- κ B, Bcl-2 and MAPK signaling pathway	23–27
BmKCT	<i>Buthus martensii</i> Karsch	SHG-44 glioma cells, glioma/SD rat	Inhibit chloride current and selectively target glioma	28–30
Chlorotoxin	<i>Leiurus quinquestriatus</i>	Glioma cells, animal models and clinical trials	Inhibit chloride current, bind to matrix metalloproteinase-2 (MMP-2)	48–52
Iberiotoxin	<i>Mesobuthus tamulus</i>	MCF-7 breast cancer cells	Block large conductance Ca ²⁺ activated K ⁺ (BK) channel	53, 54
Magatoxin	<i>Centruroides margaritatus</i>	A549 human lung adenocarcinoma cells and xenograft model	Inhibit Kv 1.3, increase expression of p21Waf1/Cip1 and decrease Cdk4	55
Charybdotoxin	<i>Leiurus quinquestriatus</i>	NIH3T3 fibroblasts and human melanoma cells	Inhibit cell migration does-dependently	56
Bengalin	<i>Heterometrus bengalensis</i> Koch	human leukemic U937 and K562 cells	Induce caspase apoptosis pathway by loss of mitochondrial membrane potential and decreased HSP 70 and 90	59, 60
Neopladine 1 and 2	<i>Tityus discrepans</i>	SKBR3 breast cancer cell line	Trigger FasL and Bcl-2 expression	61

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