Received: 31 January 2020 | Revised: 1 March 2020 | Accepted: 5 March 2020

DOI: 10.1002/jat.3976

REVIEW ARTICLE

Journal of Applied Toxicology WILEY

Scorpion venoms and associated toxins as anticancer agents: update on their application and mechanism of action

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Abstract

Cancer remains one of the deadliest non-infectious diseases of the 21st century, causing millions of mortalities per year worldwide. Analyses of conventional treatments, such as radiotherapy and chemotherapy, have shown not only a lower therapeutic efficiency rate but also plethora of side-effects. Considering the desperate need to identify promising anticancer agents, researchers are in quest to design and develop new tumoricidal drugs from natural sources. Over the past few years, scorpion venoms have shown exemplary roles as pivotal anticancer agents. Scorpion venoms associated metabolites, particularly toxins demonstrated *in vitro* anticancer attributes against diversified cell lines by inhibiting the growth and progression of the cell cycle, inhibiting metastasis by blocking ion channels such as K^+ and Cl^-, and/or inducing apoptosis by intrinsic and extrinsic pathways. This review sheds light not only on *in vitro* anticancer properties of distinct scorpion venoms and their toxins, but also on their mechanism of action for designing and developing new therapeutic drugs in future.

KEYWORDS

anticancer agents, cancer, mechanism of action, scorpion venom, toxins

1 | INTRODUCTION

Cancer or malignancy is a group of diseases that represents the continuous proliferation of abnormal cells capable of invasion and destruction of other tissues (Aibar et al., 2009). The uncontrolled growth of abnormal cells has made this disease a global health concern for humankind. According to GLOBOCAN (2018), there were a prevalence of 43 841 302 new cases of breast, colorectal, prostate, pulmonary, thyroid, bladder, and stomach cancers worldwide in both males and females.

Consequently, chemotherapy, radiotherapy, and immunotherapy have been implemented for the treatment of cancer. Despite the fact that chemotherapy has the capacity of destroying cancer cells and effectively suppressing tumor growth in patients with cancer, a significant proportion of tumors do not respond to treatment or later develop resistance to these chemotherapeutics (Lai, Visser Grieve, & Yang, 2012). Radiotherapy plays an integral role in the treatment of >50% of cancer cases (Evans & Staffurth, 2018). Unfortunately, there are severe side-effects (fibrosis, atrophy, vascular damage, hormonal deficiencies, infertility, and secondary malignancies) of this therapy that can be permanent, particularly in slow proliferating tissues such as kidneys, heart, and the central nervous system (CNS) (Barnett et al., 2009). In contrast, immunotherapy for cancer has shown some positive aspects by generating a tumor-specific immune response, which is capable of eliminating cancer cells selectively. Although immunotherapy has shown high efficacy for a variety of malignancies (Wilcox, Ramakrishna, & Magge, 2018), it is imperative to expand its application in humans with reduced toxicity.

Considering the adverse impact of conventional cancer treatments on human health, it is of vital importance to identify novel and effective agents from un/less exploited natural sources. Over the past few years, scorpion venoms have received considerable attention amongst the scientific community, due to the tremendous *in vitro* anticancer potency of their bioactive constituents against varied cancer cell lines (Ding, Chua, Bay, & Gopalakrishnakone, 2014).

2 | SCORPION VENOMS: PROMISING ANTICANCER AGENTS

The scorpion is one of the oldest known arthropods of kingdom Animalia. It has existed on earth for >400 million years and is widely distributed around the world. Among 1700 species described to date (Simard & Watt, 1990; Stockmann & Ythier, 2010), only the Buthidae family, with 30 species of scorpions, is considered dangerous to humans. Recently 21 species and one sub-species of medically important scorpion have been identified in Mexico and the USA. The *Centruroides* genus is the most common and widespread in Mexico (González-Santillán & Possani, 2018). Scorpion stings represent an important risk factor for human health in several countries. Annually, >1.5 million scorpion stings are registered worldwide, with an estimate of ~3000 being fatal (Chippaux, 2012). Scorpion venoms have been used in traditional therapies since antiquity in different countries, particularly in India, China, Africa, Cuba, and Spain (Díaz-García et al., 2013; González & Vallejo, 2013; Khusro, Aarti, Barbabosa-Pliego, Rivas-Cáceres, & Cipriano-Salazar, 2018; Ortiz, Gurrola, Schwartz, & Possani, 2015).

The scorpion venom is a complex mixture of neurotoxins, cardiotoxins, hemolytic toxins, antimicrobial peptides, enzymes, lipids, nucleotides, mucopolysaccharides, and biogenic amines. Neurotoxins (low-molecular-weight proteins) are considered as the main components of the venom and are responsible for the toxicity because they block or modify the function of ion channels (Escalona et al., 2014). In general, ion channels are integral membrane proteins that allow particular ions to pass through the plasma membrane. The plasma membrane acts as a barrier that separates the inner constituents of cell from the outside. The ionic concentrations inside the cell can be maintained at levels considerably different from those in the extracellular fluid, which results in the generation of an electrochemical gradient between the cytoplasm and the external medium through the plasma membrane for each species of ion. It creates an aqueous pore that becomes accessible to the ions after a conformational change in the structure of the protein, thereby opening the ion channels (Barker et al., 2017; Denac, Mevissen, & Scholtysik, 2000). The kinetics of ion channels activated by voltage are modulated by the membrane potential, while the ligand-activated ion channels are activated by the binding of a specific ligand to the ion channel (Suppiramaniam, Bloemer, Reed, & Bhattacharya, 2018).

Channels-based ion transport across the cell membrane is involved in the regulation of cancer cell survival and motility. As a matter of fact, ion transport across the cell membrane plays a paramount role in fundamental tumor cell functions, such as cell volume regulation, migration, cell cycle progression, and cell proliferation (Turner & Sontheimer, 2014). The survival and metastasis of cancer cells rely on these functions. Several ion channels or transporters, eg, mitochondrial channels (Leanza et al., 2013), cell membrane water channels (Tie et al., 2012), Na^+/H^+ exchanger (Andersen, Moreira, & Pedersen, 2014), Na^+, K^+, Cl^- cotransporters (Maeno, Takahashi, & Okada, 2006), KCl cotransporters (Gagnon, 2012), Na^+, K^+-ATPase (Bortner, Gomez-Angelats, & Cidlowski, 2001), and multi-drug resistance (Hoffmann & Lambert, 2014); as well as several H^+ transporters such as vacuolar H^+-ATPases, H^+/Cl^- symporters, monocarboxylate transporters, and Na^+-dependent Cl^-/HCO_3^- exchangers (Harguindey, Arranz, Wahl, Orive, & Reshkin, 2009) are involved in cell proliferation, cell death, tumor growth, and migration. In addition, intracellular ion channels expressed in several sub-cellular compartments such as the nucleus, endoplasmic reticulum, Golgi apparatus, lysosome, and mitochondria play a crucial role in cancer development and/or progression. Most of the identified oncogenic intracellular channels are located in the outer or inner mitochondrial membrane (Lang & Stournaras, 2014).

The voltage-dependent anion channel mediates metabolic cross-talk between the mitochondria and the rest of the cell (Reddy, 2013), and plays key role in the regulation of mitochondria-mediated apoptosis. Indeed, a series of events occurring following permeability transition pore opening, including mitochondrial depolarization, generation of reactive oxygen species, release of mitochondrial Ca^{2+}, and swelling of mitochondria lead to breaches in the outer mitochondrial membrane that induce the release of intermembrane proteins and promote this channel as a promising oncological target (Lang & Stournaras, 2014). The mitochondrial calcium uniporter expression correlates with metastasis and invasiveness of breast cancer (Tang et al., 2015). Kv1.3 is a member of the Shaker family of the potassium channel (Gutman et al., 2005) and is the most expressed channel in the T lymphocytes. Kv1.3 displays an altered expression level in various cancers. The uncoupling protein family belongs to the mitochondrial anion-carrier proteins (Krauss, Zhang, & Lowell, 2005) and it is inner mitochondrial membrane protein that is ubiquitously expressed in various tumors such as breast, ovarian, bladder, esophagus, testicular, colorectal, kidney, pancreatic, lung, prostate, and leukemia (Leanza, Zoratti, Gulbins, & Szabo, 2014). The chloride intracellular channels (CLICs) are an emerging class of chloride-permeable channels involved in cancer growth. In particular, chloride intracellular channel 4 (CLIC4) is the most well-characterized member of a family of channel proteins that is highly conserved from *Caenorhabditis elegans* to humans. In general, alteration in the expression and sub-cellular localization of CLIC4 occur early in tumorigenesis. CLIC4 is emerging as a potential biomarker to monitor tumor progression and recurrence in multiple human cancers (Peruzzo, Biasutto, Szabò, & Leanza, 2016). The transient receptor potential (TRP) channel superfamily is one of the largest families of cation channels (Nilius & Owsianik, 2011). The TRP family comprises 28 members, divided into subfamilies, which are TRPC (canonical), TRPM (melastatin), TRPP (polycystin), TRPV (vanilloid), TRPML (mucolipin), and TRPA (ankyrin-like) (Nilius, 2007).

Among them, TRPM8 and TRPC1 are related to cancer development and progression. The calcium-permeable TRPM8 is located in the endoplasmic reticulum membrane and is over-expressed in several tumors (Zhang & Barritt, 2004).

Moreover, Ca^{2+} channels, K^+ channels, and Na^+ channels are of great importance for tumor growth and metastasis, and thus, these are considered as potential targets in the treatment of malignancy. Considering the importance of ion channels in the progression of cancer, Hernández-Plata (2012) demonstrated that the expression of ion channels, such as Na^+, in cancer cells is essential for the development of the metastatic phenotype. Hence, the adhesion, mobility, and invasiveness of cancer cells can be eliminated by blocking the activity of Na^+ channels. Stroka et al. (2014) revealed that ion channels played a critical role in the pathophysiology of cancer using several mechanisms. Ca^{2+}, Na^+, and K^+ channels are implicated in the proliferation of cancer cells by controlling and regulating several key signaling pathways of survival and membrane potential. They are also involved in the development of distinctive features of cancer, including insensitivity to the signals of anti-growth, evasion of apoptosis, unlimited replicative potential, and metastasis (Kale, Amin, & Pandey, 2015).

Scorpion venoms inhibit the growth of several kinds of cancer cell lines. However, only limited groups of toxins are responsible for anticancer characteristics via three different mechanisms: i) blocking a specific ion channel (Jäger et al., 2004), ii) inhibiting the invasion of cancer cells by binding to a specific site (different from an ion channel) in the plasma membrane (Deshane, Garner, & Sontheimer, 2002), and iii) activating intracellular pathways that induce apoptosis (Gupta, Gomes, Debnath, Saha, & Gomes, 2010).

Recent investigations have revealed pronounced activities of scorpion venoms against various cancer cell lines (Table 1). Al-Asmari, Islam, and Al-Zahrani (2016) demonstrated anticancer activity of *Androctonus crassicauda* against the HCT-8 cell line (human colorectal adenocarcinoma), which showed 98% cell death after 24 h at a concentration of 100 μg/mL. Akef, Kotb, Abo-Elmatty, and Salem (2017) reported anticancer characteristics of *Androctonus amoreuxi* against the PC-3 cell line (human prostate adenocarcinoma), exhibiting 93% cancer cells death within 24 h at a concentration of 5.58 μg/mL. *A. amoreuxi*, at a concentration of 0.61 μg/mL showed anticancer activity against the MCF-7 cell line (human breast adenocarcinoma) with 83.7% cancer cells death within 24 h (Salem, Shoukry, Teleb, Abdel-Daim, & Abdel-Rahman, 2016). *A. crassicauda*, at a concentration of 100 μg/mL had anticancer activity against the HCT-116 cell line (human colorectal carcinoma), which showed 80% of cancer cells death (Al-Asmari et al., 2016). In another study, *A. crassicauda* at 80 μg/mL, had an anticancer trait against the MDA-MB-231 cell line (human breast adenocarcinoma), with 24% of cancer cells death within 24 h (Salem et al., 2016). Díaz-García et al. (2013) reported anticancer attributes of *Rhopalurus junceus* (1 mg/mL) against the MDA-MB-468 cell line (human breast adenocarcinoma), which showed 64.5% of cancer cells death after 72 h. Al-Asmari et al. (2016) demonstrated tumoricidal property of *Androctonus bicolor* (100 μg/mL) in the MDA-MB-231 cell line, with 63% cancer cell death after 24 h. Similarly, *Leiurus quinquestriatus* showed 63% cancer cells death against the MDA-MB-231 after 24 h (Al-Asmari et al., 2016). Díaz-García et al. (2013) reported anticancer characteristic of *R. junceus* against the A549 cancer cell line (human lung carcinoma), with 61.5% of cancer cells death after 72 h. *Buthus martensii* Karsch was investigated for its tumoricidal attribute against the HeLa cancer cell line (uterine cervix adenocarcinoma), which exhibited 50% of cancer cells death at a dose of 34.5 μg/mL (Wang, Fu, Lu, & Cai, 2011).

3 | SCORPION VENOM ASSOCIATED TOXINS AS CYTOTOXIC AGENTS: PRODUCTION AND ANALYSIS

Guo et al. (2013) isolated various toxins from the venom of *Tityus serrulatus*. Using TsAP-S1 fraction, 98.5% (half-maximal inhibitory concentration [IC_{50}] value: 1.5 μM) of cell mortality was obtained against the NCI-H157 (human squamous cell carcinoma) and NCI-H838 (human lung adenocarcinoma) cell lines, 97.5% (IC_{50} value: 2.8 μM) against the U-251 cell line (human glioblastoma), 91.5% against the PC-3 cell line (IC_{50} value: 2.07 μM), and 89.5% against the MCF-7 cell line (IC_{50} value: 1.7 μM). TsAP-S2 was tested against the NCI-H838, U-251, NCI-H157, PC-3, and MCF-7 cell lines, revealing 98.5% (IC_{50} value: 1.6 μM), 97.5% (IC_{50} value: 2.04 μM), 91.5% (IC_{50}: 1.6 μM), and 89.5% (IC_{50} value: 1.8 μM) of cell mortality, respectively. TsAP-1 was assessed against the HCI-H838 and NCI-H157 cell lines exhibiting 58.8% (IC_{50} value: 5.2 μM) and 55.5% (IC_{50} value: 5.9 μM) of cell mortality, respectively. Likewise, the TsAP-2 fraction was tested against the NCI-H838, U-251, PC-3, MCF-7, and NCI-H157 cell lines, revealing 97% (IC_{50} value: 1.1 μM), 96.5% (IC_{50} value: 1.5 μM), 90.5% (IC_{50} value: 1.6 μM), 85.5% (IC_{50} value: 6.3 μM), and 80% (IC_{50} value: 4.1 μM) of cells death, respectively (Table 5).

Tong-ngam, Roytrakul, and Sritanaudomchai (2015) determined the anticancer attribute of *B. martensii* Karsch venom against an oral cancer cell line with a mortality rate of 95% within 24 h. Li, Hu, Zhang, and Wei (2006) revealed a tumoricidal property of a venom fraction against the HepG2 cell line (human hepatocellular carcinoma), with a mortality rate of 91.2% with an IC_{50} value of 200 mg. As per the investigation of Almaaytah, Tarazi, Mhaidat, Al-Balas, and Mukattash (2013), the toxin Mauriporin was isolated from the venom of *Androctonus mauritanicus* and exhibited tumoricidal characteristics against the PC-3 (adenocarcinoma of human prostate), as well as LNCaP and DU 145 cell lines (carcinoma of prostate) with high mortality rates (Table 5).

Gu, Liu, Ju, Li, and Cao (2012) reported the anticancer trait of recombinant analgesic-antitumor peptide (rAGAP) toxin (isolated from the *B. martensii* Karsch venom) against the SW-480 cell line (colorectal adenocarcinoma) and reported a mortality rate of 78.8% with an IC_{50} value of 8.4 μM. Fu, Jiao, Zheng, Liang, and Hu (2014) transfected the plasmid pEGFP-N1-BmK (4.0 μg of DNA), containing the BmK CT gene (isolated from *B. martensii* Karsch) into rat glioma C6 cells. Subsequently, the therapeutic agent LiCl (50 mM), which inhibits migration and invasion in glioma cells, was added as a co-treatment, obtaining 75% cytotoxicity within 24 h. Song et al. (2012) purified

TABLE 1 Crude scorpion venoms against various cancer cell lines

Cell line	Origin/source	Types of cancer	Scorpion species	Activity period, h	Viability reduction, %	Dose	References
HCT-8	Human	Adenocarcinoma-Ileocecal Colorectal	*A. crassicauda*	24	75/98	80/100 μg/ml	Al-Asmari et al. (2016)
PC-3	Human	Adenocarcinoma-Prostate	*A. amoreuxi*	24	93	5.58 μg/ml	Akef et al. (2017)
PC-3	Human	Adenocarcinoma-Prostate	*A. amoreuxi*	24	88	3.04 μg/ml	Akef et al. (2017)
MCF-7	Human	Adenocarcinoma-Breast	*A. amoreuxi*	24	83.7	0.61 μg/ml	Salem et al. (2016)
HCT-116	Human	Carcinoma-Colorectal	*A. crassicauda*	24	50/80	50/100 μg/ml	Al-Asmari et al. (2016))
MDA-MB-231	Human	Adenocarcinoma-Breast	*A. crassicauda*	24	67–72	40/80 μg/ml	Al-Asmari et al. (2016))
MDA-MB-468	Human	Adenocarcinoma-Breast	*R. junceus*	72	64.5	1 mg/ml	Díaz-García et al. (2013)
MDA-MB-231	Human	Adenocarcinoma-Breast	*A. bicolor*	24	50/63	50/100 μg/ml	Al-Asmari et al. (2016))
MDA-MB-231	Human	Adenocarcinoma-Breast	*L. quinquestriatus*	24	50/63	50/100 μg/ml	Al-Asmari et al. (2016))
A549	Human	Carcinoma-Lung	*R. junceus*	72	61.5	1 mg/ml	Díaz-García et al. (2013)
HeLa	Human	Adenocarcinoma-Cervix	*B. martensii* Karsch	48	50	34.5 μg/ml	Wang et al. (2011)
MDA-MB-231	Human	Adenocarcinoma-Breast	*R. junceus*	72	47.5	1 mg/ml	Díaz-García et al. (2013)
Hep-2	Human	Adenocarcinoma-Cervix	*R. junceus*	72	47.5	1 mg/ml	Díaz-García et al. (2013)
SH-SY5Y	Human	Neuroblastoma	*A. crassicauda*	24	46	200 μg/ml	Zargan et al. (2011)
MCF-7	Human	Adenocarcinoma-Breast	*A. crassicauda*	24	43.2	200 μg/ml	Zargan et al. (2011)
NCI-H292	Human	Carcinoma-Lung	*R. junceus*	72	41.5	1 mg/ml	Díaz-García et al. (2013)
HeLa	Human	Adenocarcinoma-Cervix	*R. junceus*	72	40	1 mg/ml	Díaz-García et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*B. martensii* Karsch	24	40	800 μg/ml	Li, Xin, et al. (2014)
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	48	36.5	41.5 μg/ml	Gupta et al. (2007)
HT-29	Human	Adenocarcinoma-Colorectal	*R. junceus*	72	35.5	1 mg/ml	Díaz-García et al. (2013)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	48	34.68	34.5 μg/ml	Li et al. (2015)
SiHa	Human	Adenocarcinoma-Cervix	*R. junceus*	72	31.5	1 mg/ml	Díaz-García et al. (2013)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	24	30.74	100 μg/ml	Li et al. (2015)
SMMC-7721	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	24	30	800 μg/ml	Li, Li, et al. (2014)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	48	28.54	50 μg/ml	Li et al. (2015)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	48	27.2	88.3 μg/ml	Gupta et al. (2007)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	24	24.63	50 μg/ml	Li et al. (2015)
U-937	Human	Histiocytic lymphoma	*R. junceus*	72	20	1 mg/ml	Díaz-García et al. (2013)
K-562	Human	Chronic myeloid leukemia	*R. junceus*	72	15.5	1 mg/ml	Díaz-García et al. (2013)
HeLa	Human	Adenocarcinoma-Cervix	*C. limpidus limpidus*	24	0.005	400 μg/ml	Contreras-Ortiz et al. (2013)

TABLE 2 Scorpion venoms associated toxins against various cancer cell lines

Cell line	Origin/source	Types of cancer	Scorpion species	Activity period, h	Viability reduction, %	Toxins isolated	IC_{50} values	References
NCI-H157	Human	Carcinoma-Squamous	*T. serrulatus*	24	98.5	TsAP-S1	1.5 μM	Guo et al. (2013)
NCI-H838	Human	Adenocarcinoma-Lung	*T. serrulatus*	24	98.5	TsAP-S1	1.5 μM	Guo et al. (2013)
NCI-H838	Human	Adenocarcinoma-Lung	*T. serrulatus*	24	98.5	TsAP-S2	1.6 μM	Guo et al. (2013)
U-251	Human	Glioblastoma	*T. serrulatus*	24	97.5	TsAP-S1	2.8 μM	Guo et al. (2013)
U-251	Human	Glioblastoma	*T. serrulatus*	24	97.5	TsAP-S2	2.04 μM	Guo et al. (2013)
NCI-H838	Human	Adenocarcinoma-Lung	*T. serrulatus*	24	97	TsAP-2	1.1 μM	Guo et al. (2013)
U-251	Human	Glioblastoma	*T. serrulatus*	24	96.5	TsAP-2	1.5 μM	Guo et al. (2013)
HSC-4	Human	Carcinoma-Oral Squamous	*Mesobuthus martensii* Karsch	24	95	BmKn-2	29 μg/mL	Tong-ngam et al. (2015)
NCI-H157	Human	Carcinoma-Squamous	*T. serrulatus*	24	94.5	TsAP-S2	8.2 μM	Guo et al. (2013)
PC-3	Human	Adenocarcinoma-Prostate	*T. serrulatus*	24	91.5	TsAP-S1	2.07 μM	Guo et al. (2013)
PC-3	Human	Adenocarcinoma-Prostate	*T. serrulatus*	24	91.5	TsAP-S2	1.6 μM	Guo et al. (2013)
Hep G2	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	12	91.2	Fractión III	200 mg	Li et al. (2006)
PC-3	Human	Adenocarcinoma-Prostate	*T. serrulatus*	24	90.5	TsAP-2	1.3 μM	Guo et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*T. serrulatus*	24	89.5	TsAP-S1	1.7 μM	Guo et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*T. serrulatus*	24	89.5	TsAP-S2	1.8 μM	Guo et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*T. serrulatus*	24	85.5	TsAP-2	6.3 μM	Guo et al. (2013)
PC-3	Human	Adenocarcinoma-Prostate	*A. mauritanicus*	24	81.5	Mauriporin	50 μM	Almaaytah et al. (2013)
LNCaP	Human	Carcinoma-Prostate	*A. mauritanicus*	24	81.5	Mauriporin	50 μM	Almaaytah et al. (2013)
DU 145	Human	Carcinoma-Prostate	*A. mauritanicus*	24	81.5	Mauriporin	50 μM	Almaaytah et al. (2013)
NCI-H157	Human	Carcinoma-Squamous	*T. serrulatus*	24	80	TsAP-2	4.1 μM	Guo et al. (2013)
SW-480	Human	Adenocarcinoma-Colorectal	*B. martensii* Karsch	24	78.8	rAGAP	18.4 μM	Gu et al. (2012)
C6	Rat	Glioma	*B. martensii* Karsch	24	75	pEGFP-N1-*BmK* CT + LiCl	4.0 μg of DNA + 50 mM	Fu et al. (2014)
THP-1	Human	Acute monocytic leukemia	*B. martensii* Karsch	48	66.6	SVCIII	50 μg/mL	Song et al. (2012)
C6	Rat	Glioma	*B. martensii* Karsch	48	60.5	I-BmK CT	2.0 mg/mL	Zhao et al. (2010)
Jurkat	Human	Acute T- cell leukemia	*B. martensii* Karsch	48	58.7	SVCIII	50 μg/mL	Song et al. (2012)
NCI-H838	Human	Adenocarcinoma-Lung	*T. serrulatus*	24	58.5	TsAP-1	5.2 μm	Guo et al. (2013)
NCI-H157	Human	Carcinoma-Squamous	*T. serrulatus*	24	55.5	TsAP-1	5.9 μM	Guo et al. (2013)
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	24	54.7	Bengalin	3.7 μg/mL	Gupta et al. (2010)

(Continues)

TABLE 2 (Continued)

Cell line	Origin/source	Types of cancer	Scorpion species	Activity period, h	Viability reduction, %	Toxins isolated	IC_{50} values	References
HSC-4	Human	Carcinoma-Squamous Oral	*B. martensii* Karsch	24	50	BmKn2	17.26 μM	Arpornsuwan et al. (2014)
SW620	Human	Adenocarcinoma-Colorectal	*B. martensii* Karsch	24	50	BmKn2	40 μM	Arpornsuwan et al. (2014)
MCF-7	Human	Adenocarcinoma-Breast	*Vaejovis mexicanus smithi*	24	50	VmCT1	25 μM/L	Pedron et al. (2017)
C6	Rat	Glioma	*L. quinquestriatus*	24	50/40	CTX-GO + DOX	2.5/5.0 μg/mL	Wang et al. (2014)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	24	47.8	Bengalin	4.1 μg/mL	Gupta et al. (2010)
MCF-7	Human	Adenocarcinoma-Breast	*B. martensii* Karsch	24	45	LMWSVP	N/A	Li, Xin, et al. (2014)
F98	Rat	Malignant Glioma Not Differentiated	*B. martensii* Karsch	48	40	CTX-23	6 μM	Xu et al. (2016)
U-251	Human	Glioblastoma	*B. martensii* Karsch	48	40	CTX-23	6 μM	Xu et al. (2016)
F11	Mouse	Neuroblastoma	*Centruroides noxius* Hoffmann	48	40	Cn2	160 nM	Escalona et al. (2014)
F98	Rat	Malignant Glioma Not Differentiated	*B. martensii* Karsch	48	38.5	CA4	6 μM	Xu et al. (2016)
U-251	Human	Glioblastoma	*B. martensii* Karsch	48	35.5	CA4	6 μM	Xu et al. (2016)
SMMC-7721	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	24	34.5	LMWSVP	0.28, 0.7, 1.4, 2.8, and 5.6 μg/mL	Li, Li, et al. (2014)
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	24	33.3	Bengalin	3.7 μg/ml	Gupta et al. (2010)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	24	29.8	Bengalin	4.1 μg/ml	Gupta et al. (2010)
K-562	Human	Chronic myeloid leukemia	*B. martensii* Karsch	48	20	BmKKx2	6.7 nM	Ma et al. (2013)
SK-BR-3	Human	Adenocarcinoma-Breast	*Tityus discrepan*	5	6.3	Neopladine 1	33 μM	D'Suze et al. (2010)
SK-BR-3	Human	Adenocarcinoma-Breast	*T. discrepan*	5	5.6	rNeo2a	33 μM	Olvera et al. (2016)
SK-BR-3	Human	Adenocarcinoma-Breast	*T. discrepan*	5	4.1	Neopladine 2	33 μM	D'Suze et al. (2010)
PC-3	Human	Adenocarcinoma-Prostate	*T. serrulatus*	24	0	TsAP-1	N/A	Guo et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*T. serrulatus*	24	0	TsAP-1	N/A	Guo et al. (2013)
U-251	Human	Glioblastoma	*T. serrulatus*	24	0	TsAP-1	N/A	Guo et al. (2013)

DOX, doxorubicin; N/A, not available.

TABLE 3 Mechanisms of action of various scorpion venoms against distinct cancer cell lines

Cell line	Origin/source	Types of cancer	Scorpion species	Cell death	Mechanisms of action	References
PC-3	Human	Adenocarcinoma-Prostate	*A. amoreuxi*	Apoptosis	Negative regulation of Bcl-2	Akef et al. (2017)
MCF-7	Human	Adenocarcinoma-Breast	*A. amoreuxi*	Apoptosis	Expression of C-3	Salem et al. (2016)
A549	Human	Carcinoma-Lung	*R. junceus*	Necrosis	Expression of p53 and Bax	Díaz-García et al. (2013)
HeLa	Human	Adenocarcinoma-Cervix	*B. martensii* Karsch	Apoptosis	Positive regulation of p21	Wang et al. (2011)
Hep-2	Human	Adenocarcinoma-Cervix	*R. junceus*	Apoptosis	Overexpression of p53 and Bax	Díaz-García et al. (2013)
SH-SY5Y	Human	Neuroblastoma	*A. crassicauda*	Apoptosis	Cell arrest in S phase/ production of iNOS/ expression of C-3/DNA fragmentation	Zargan et al. (2011)
MCF-7	Human	Adenocarcinoma-Breast	*A. crassicauda*	Apoptosis	Cell arrest in S phase/production of iNOS/ expression of C-3/DNA fragmentation	Zargan et al. (2011)
NCI-H292	Human	Carcinoma-Lung	*R. junceus*	Necrosis	Expression of p53 and Bax	Díaz-García et al. (2013)
HeLa	Human	Adenocarcinoma-Cervix	*R. junceus*	Apoptosis	Over expression of p53, Bax, C-3, and C-9	Díaz-García et al. (2013)
MCF-7	Human	Adenocarcinoma-Breast	*B. martensii* Karsch	Apoptosis	Expression of C-3, inhibition of Bcl-2, and cell arrest in G1 and S phase	Li, Xin, et al. (2014)
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	Apoptosis	Cell arrest in Sub-G1 phase	Gupta et al. (2007)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	Apoptosis	Expression of C-3 and p21	Li et al. (2015)
SiHa	Human	Adenocarcinoma-Cervix	*R. junceus*	Apoptosis	Over expression of p53, Bax, C-3, and C-9	Díaz-García et al. (2013)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	Apoptosis	Expression of C-3 and p21	Li et al. (2015)
SMMC-7721	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	Apoptosis	Expression of C-3, inhibition of Bcl-2, and cell arrest in G1 and S phase	Li, Li, et al. (2014)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	Apoptosis	Expression of C-3 and p21	Li et al. (2015)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	Apoptosis	Cell arrest in Sub-G1 phase	Gupta et al. (2007)
KYSE-510	Human	Carcinoma-Esophageal Squamous	*H. liangi*	Apoptosis	Expression of C-3 and p21	Li et al. (2015)

iNOS, inducible nitric oxide synthase.

TABLE 4 Mechanisms of action of scorpion venoms associated toxins

Cell line	Origin/ source	Type of cancer	Scorpion species	Toxin isolated	Cell death	Mechanisms of action	References
HSC-4	Human	Carcinoma-Oral Squamous	*M. martensii* Karsch	BmKn-2	Apoptosis	Expression of C-3, C-9, and Bcl-2	Tong-ngam et al. (2015)
HepG2	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	Fracción III	Apoptosis	Negative regulation of Bcl-2 and activity of C-3	Li et al. (2006)
SW-480	Human	Adenocarcinoma-Colorectal	*B. martensii* Karsch	rAGAP	Apoptosis	Expression of p27/Bax and, cell arrest in G1 phase	Gu et al. (2012)
C6	Rat	Glioma	*B. martensii* Karsch	pEGFP-N1-BmK CT + LiCl	Apoptosis	Inhibition of MMP, GSK-3, and B-Catenin	Fu et al. (2014)
THP-1	Human	Acute monocytic leukemia	*B. martensii* Karsch	SVCIII	N/A	Cell arrest in G1 phase by inhibition of NF-kB	Song et al. (2012)
C6	Rat	Glioma	*B. martensii* Karsch	I-BmK CT	N/A	Cell arrest in S and G2/M phases	Zhao et al. (2010)
Jurkat	Human	Acute T-cell leukemia	*B. martensii* Karsch	SVCIII	N/A	Cell arrest in G1 phase by inhibition of NF-kB	Song et al. (2012)
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	Bengalin	Apoptosis	Cell arrest in Sub-G1 phase/activity of C-3/reduction of telomerase activity	Gupta et al. (2010)
C6	Rat	Glioma	*L. quinquestriatus*	CTX-GO + DOX	N/A	Blocking of Cl^- channels and MMP2- inhibition	Wang et al. (2014)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	Bengalin	Apoptosis	Cell arrest in Sub-G1 phase/activity of C-3/reduction of telomerase activity	Gupta et al. (2010)
F98	Rat	Malignant Glioma Not Differentiated	*B. martensii* Karsch	CTX-23	N/A	Blocking of Cl^- channels, inhibition of angiogenesis, and cell migration	Xu et al. (2016)
U-251	Human	Glioblastoma	*B. martensii* Karsch	CTX-23	N/A	Blocking of Cl^- channels, inhibition of angiogenesis, and cell migration	Xu et al. (2016)
F11	Mouse	Neuroblastoma	*C. noxius* Hoffmann	Cn2	Apoptosis	Blocking of Na channels and cell arrest in G0/G1phase	Escalona et al. (2014)
F98	Rat	Malignant Glioma Not Differentiated	*B. martensii* Karsch	CA4	N/A	Blocking of Cl^- channels, inhibition of angiogenesis, and cell migration	Xu et al. (2016)
U-251	Human	Glioblastoma	*B. martensii* Karsch	CA4	N/A	Blocking of Cl^- channels, inhibition of angiogenesis, and cell migration	Xu et al. (2016)
SMMC-7721	Human	Carcinoma-Hepatocellular	*B. martensii* Karsch	LMWSVP	Apoptosis	Expression of C-3 and inhibition of Bcl-2	Li, Li, et al. (2014)

TABLE 4 (Continued)

Cell line	Origin/ source	Type of cancer	Scorpion species	Toxin isolated	Cell death	Mechanisms of action	References
U-937	Human	Histiocytic lymphoma	*H. bengalensis* Koch	Bengalin	Apoptosis	Cell arrest in Sub-G1 phase/activity of C-3/reduction of telomerase activity	Gupta et al. (2010)
K-562	Human	Chronic myeloid leukemia	*H. bengalensis* Koch	Bengalin	Apoptosis	Cell arrest in Sub-G1 phase/activity of C-3/reduction of telomerase activity	Gupta et al. (2010)
K-562	Human	Chronic myeloid leukemia	*B. martensii* Karsch	BmKKx2	Apoptosis	hERG potassium channel blocking	Ma et al. (2013)
SK-BR-3	Human	Adenocarcinoma-Breast	*Tityus discrepan*	Neopladine1	Apoptosis	Expression of FasL	D'Suze et al. (2010)
SK-BR-3	Human	Adenocarcinoma-Breast	*T. discrepan*	rNeo2a	Apoptosis/ Necrosis	Over expression of FasL	Olvera et al. (2016)
SK-BR-3	Human	Adenocarcinoma-Breast	*T. discrepan*	Neopladine 2	Apoptosis	Expression of FasL	D'Suze et al. (2010)

DOX, doxorubicin; N/A, not available.

SVIII toxin from *B. martensii* Karsch venom and investigated its anticancer potential against the THP-1 (acute monocytic leukemia) and Jurkat cell lines (acute T cell leukemia), obtaining 66.6% (IC_{50} value: 50 μg/mL) and 58.7% (IC_{50} value: 50 μg/mL) of cytotoxicity, respectively. Similarly, Zhao, Qiao, Zhang, and Shao (2010) utilized I-BmK CT fraction against the C6 cell line, and showed a mortality rate of 60.5% with an IC_{50} value of 2.0 mg/mL. Gupta et al. (2010) isolated Bangalin toxin from the venom of *Heterometrus bengalensis* Koch and evaluated its anticancer characteristics against the U-937 (human histiocytic lymphoma) and K-562 cell lines (human chronic myeloid leukemia), obtaining 54.7% (IC_{50} value: 3.7 μg/ml) and 47.8% (IC_{50} value: 4.1 μg/ml) of cells death, respectively within 24 h. BmKn2 isolated from *B. martensii* Karsch venom had anticancer activities against the HSC-4 and SW620 (human colorectal adenocarcinoma) cell lines too (Arpornsuwan et al., 2014). VmCT1, isolated from *Vaejovis mexicanus smithi* venom had a tumoricidal property against the MCF-7 cell line and showed a 50% rate of cells death with an IC_{50} value of 25 μM/L (Table 5).

4 | CYTOTOXICITY OF SCORPION VENOM: MECHANISM OF ACTION

Apoptosis plays a crucial role in tumoricidal properties of disparate scorpion venoms and their associated toxins. Apoptosis occurs via two mechanisms: the intrinsic and extrinsic pathways. The intrinsic pathway is related to the enhancement of the permeability of the mitochondrial membrane, thereby eliciting cytochrome c release due to the negative regulation of B cell leukemia/lymphoma 2 (Bcl2) that avoids its release and positive regulation of Bcl2-associated X (Bax), apoptosis regulator that promotes its release. Subsequently, the activation of caspase is executed, activating caspase 9 that cleaves procaspase-3 downstream and results in the activation of caspsa 3 that culminates in the cytotoxicity (Gupta et al., 2010). The extrinsic pathway is stimulated by the overexpression of Fas ligand (FasL) (D'Suze, Rosales, Salazar, & Sevcik, 2010), which binds to the Fas receptor (a protein of the cytotoxicity-inducing receptors family present on the surface of the cell membrane) (Fulda, 2015; Sánchez Torres & Diosdado Vargas, 2003). The caspase 3 and 7 consist of various substrates such as poly ADP-ribose polymerase (PARP), lamin, caspase-activated DNase inhibitor (iCAD), and the protein 8-related to XK (XKr8). Caspases cleaves these substrates by modulating distinctive events of apoptosis, particularly by nuclear condensation, DNA fragmentation, membrane blisters, and phosphatidylserine exposure (McArthur & Kile, 2018).

Diverse species of scorpions' venoms affect the intrinsic pathway of apoptosis. *A. amoreuxi* regulated Bcl-2 adversely and induced the expression of caspase 3 (Li, Xiao, & Wang, 2015; Salem et al., 2016; Zargan et al., 2011), *Rhopalurus junceus* over-expressed Bax, caspase 3, and caspase 9 (Díaz-García et al., 2013). *B. martensii* Karsch expressed caspase 3 and regulated Bcl-2 negatively (Li et al., 2014). BmKn-2 expressed caspase 3 and 9, and inhibited Bcl-2 (Tong-ngam et al., 2015). Fraction III presented negative regulation of Bcl-2 and

TABLE 5 Toxins of scorpion venoms as cell growth inducers

Cell line	Origin/Source	Types of cancer	Scorpion species	Toxins isolated	Cell growth, %	References
PC-3	Human	Adenocarcinoma-Prostate	*A. crassicauda*	AcrAP1	35	Du et al. (2014)
NCI-H460	Human	Adenocarcinoma-Lung	*A. crassicauda*	AcrAP1	45	Du et al. (2014)
U-87	Human	Glioblastoma	*Scorpiops jendeki* Kovařík	pET-28a-Sj7170	75	Song et al. (2014)

caspase 3 activity (Li et al., 2006). rAGAP expressed Bax (Gu et al., 2012), Bengalin activated caspasa 3 (Gupta et al., 2010), and LMWSVP expressed caspase 3, as well as inhibited Bcl-2 (Li, Xin, et al., 2014) (Table 2 and 3). Neopladine 1 and 2 induced the expression of FasL (D'Suze et al., 2010), while rNeo2a over-expressed FasL (Olvera et al., 2016) (Table 2 and 3).

Another feature that was identified with the use of crude venom and toxins or isolated fractions is that they are capable of arresting the cell cycle at different phases (G0/G1, G2/M, G1/S). In the G2/M transition, the cyclin-dependent kinase 1(CDK1)/Cyclin B complex is the main regulator that leads to the progression of this phase. The presence of p21, a potent inhibitor of cyclin-dependent kinase is a key regulator that inhibits the activity of CDK1 and arrests the G2/M phase, which explains the inhibition of progression of cancer cells (Huang et al., 2011). *B. martensii* Karsh and *Heterometrus tangi* venom regulated p21 (Li et al., 2015; Wang et al., 2011). Tumor protein 53 (p53) was expressed in the presence of *R. junceus* venom too (Díaz-García et al., 2013). p53 is a protein that has the ability to induce cell cycle arrest (mainly through the activation of p21) (Labuschagne, Zani, & Vousden, 2018). During the G0/G1 transition of the cell cycle, the CDK2/Cyclin A complex is essential for its progression. The p27 protein has the potentiality to arrest cell cycle phases (Abbastabar et al., 2018; Gu et al., 2012) (Table 2).

In order to determine the capacity of the crude venom and isolated toxins to arrest the cell cycle, *A. crassicauda* induced cell cycle arrest in the S phase (Zargan et al., 2011). *B. martensii* arrested the cell cycle in the G1 and S phases (Li, Li, Zhao, Yuan, & Mao, 2014), while *H. bengalensis* arrested the cell cycle in the sub-G1 phase (Gupta et al., 2007). rAGAP and scorpion venom component III (SVCIII) induced cellular arrest in G1 phase (Gu et al., 2012; Song et al., 2012). On the other hand, Bengalin and Cn2 arrested the cell cycle in sub-G1 and G0/G1 phases, respectively (Escalona et al., 2014; Gupta et al., 2010) (Table 3).

Another mechanism that induces cytotoxicity involves ion channels activation by voltage. In glioma cells, the Cl^- channels present in the cell membrane are up-regulated after DNA damage, thereby promoting cell survival and giving the cells an improved capacity to transport Cl^-. The ion flux mediated by the channels can induce the osmotic flow of water through the nearby aquaporins at the edge of a migrating cell. The Na-K-Cl cotransporter 1 (NKCC1), located at the leading edge of the human glioma cell facilitates the accumulation of Cl^- and in turn provides an electrochemical driving force. The flow of Cl^- osmotically regulates the level of cytoplasmic water. It not only produces the modulation of morphological changes but also promotes metastasis (Brackenbury, 2016; Kale et al., 2015; Olsen, Schade, Lyons, Amaral, & Sontheimer, 2003; Soroceanu, Manning, & Sontheimer, 1999). Fu et al. (2014) purified rBmkCTa toxin from *B. martensii* Karsch. It has specific affinity for binding to C6 cells of rat glioma, thereby promoting the inhibition of chlorine channels and cell proliferation. It was also found that this fraction has the ability to bind and block matrix metalloproteinase-2 (MMP-2) from the extracellular matrix. The MMP-2 activation mechanism is modulated by various proteins that constitute a macromolecular complex for facilitating the migration and invasion of tumor cells (Cohen-Inbar & Zaaroor, 2016). On the other hand, the use of chlorotoxin conjugated graphene oxide (CTX-GO) fraction isolated from *L. quinquestriatus* venom was evaluated in rat glioma C6 cell line (Wang, Gu, Xiao, Ye, & Xu, 2014) (Table 3).

Potassium channels are considered crucial in cancer cells. The overexpression of these channels has been linked with the characteristics of the malignant transformation such as rapid growth, loss of inhibition by cell contact, and insensitivity to anti-growth signals (Kale et al., 2015; Pardo et al., 1999). The over expression of human ether-a-go-go-related gene (hERG) channels has been studied in neoplastic hematopoietic cells (Smith et al., 2002). BmKKx2 (isolated from *B. martensii* Karsch) showed the ability to block the hERG channels and induce cell cycle in the G1 phase. It was also shown that cell differentiation occurred after treatment with BmKKx2, often accompanied by apoptosis. Leukemic cells tend to be more sensitive to the inducers of apoptosis during the differentiation process. However, apoptotic cell death was not promoted in the prior studies (Hietakangas et al., 2003; Ma et al., 2013) (Table 3).

5 | CANCER CELLS GROWTH INDUCTION BY SCORPION VENOM

Some toxins isolated from scorpion venom induce growth in cancer cells. AcrAP1 (isolated from *A. crassicauda*) tends to increase the growth rate by 35–45% in the PC-3 and NCI-H460 cancer cell lines (Du et al., 2014). In a similar manner, pET-28a-Sj7170 (isolated from *Scorpiops jendeki*) induced growth by 75% in the U-87 (human glioblastoma) cell line compared to the control group. It increased the cell population in the S phase and promoted the expression of cyclin D1 (Song et al., 2014) (Table 4).

6 | EFFECT OF SCORPION TOXINS ON EXCITABLE TISSUE DISORDERS

Scorpion venoms-associated neurotoxins have the potential to modify distinct functional traits of ion channels in excitable tissues.

Symptoms such as pain, fever, sweating, and hypertension are observed due to the massive release of neurotransmitters and repetitive neuronal depolarizations (Quintero-Hernandez, Jimenez-Vargas, Gurrola, Valdivia, & Possani, 2013). In addition, cardiac failure, pulmonary edema, and shock occur in severe cases (Aboumaad et al., 2014). The liver and kidney are also targeted by scorpion venoms. The major lesions in hepatotoxicity/nephron-toxicity being reported are edema, necrosis, hemorrhage, and inflammatory cell infiltration (Adi-Bessalem & Laraba-Djebari, 2013; Al-Harbi & Al-Hasawi, 2014). Cardiac abnormalities (sinus tachycardia, sinus bradycardia, sinoatrial, atrioventricular block, ventricular ectopic beats, and idioventricular rhythm) have been recorded after the application of scorpion venoms (e.g. *L. quinquestriatus quinquestriatus*, *Mesobuthus tumulus*, *T. serrulatus*) on experimental animals (Teixeira et al., 2001).

Scorpion venoms are also known to cause varied inflammatory disorders through complex mechanisms in various tissues. Lamraoui, Adi-Bessalem, and Laraba-Djebari (2015) examined the involvement of phospholipase A2 (PLA2) and cyclo-oxygenase (COX)-derived metabolites in hepatic and renal inflammation responses *in vivo*. Mice were envenomed with *Androctonus australis* hector scorpion venom in the absence or presence of inhibitors that can interfere with lipid inflammatory mediator synthesis, i.e., dexamethasone (PLA2 inhibitor), indomethacin (non-selective COX-1/COX-2 inhibitor), or celecoxib (selective COX-2 inhibitor). Findings showed that the venom alone induced an inflammatory response in tissues, marked by increased microvascular permeability and inflammatory cell infiltration, increases in levels of nitric oxide and lipid peroxidation, and decreases in antioxidant defense. Pre-treatment of mice with dexamethasone led to significant decrease in the inflammatory disorders in the hepatic parenchyma. Celecoxib pre-treatment showed more effectiveness against renal inflammation. Indomethacin pre-treatment slightly reduced the inflammatory disorders in the tissues. Results suggested that the induced inflammation response in the liver was mediated mainly by PLA2 activation, while the renal inflammatory process was mediated by prostaglandin formation by COX-2.

A previous study investigated the cardiotoxicity and mode of action of *A. bicolor* venom on isolated toad hearts. Direct application of scorpion venom into isolated toad hearts induced a remarkable bradycardia concomitant with a protraction in the conduction time (P–R interval). Also, a significant increase in the R-wave amplitude (ventricular contraction) was recorded after venom perfusion. Various cardiac disorders were recorded such as sinus arrhythmias, ectopic beats, and different degrees of heart blockage. The findings indicated that the venom of *A. bicolour* directly influenced the cardiac electrical activity of toads through β-adrenergic receptors (Abdel-Rahman, Ayed, Abdel-Mottaleb, Omran, & Nabil, 2015).

Paneque Peres et al. (2009) reported that the Brazilian scorpion *T. serrulatus* caused increased lung, kidney, liver, and heart inflammation, characterized by an increased density of mononuclear cells after injection in rats. They concluded that the venom leads to acute lung injury, characterized by distorted lung mechanisms and increased pulmonary inflammation. *T. serrulatus* venom also affected hemodynamics probably by a direct vasoconstrictor action, leading to increased renal flow in mice (Severino, Pereira, Knysak, Candido, & Kwasniewski, 2009).

Studies have reported that blood glucose levels increased after envenomation, thereby resulting in hyperglycemia in animal models. This might be due to a massive release of catecholamines, increased glucagon and cortisol levels, changes in thyroid hormone levels, and changes in insulin secretion (Adi-Bessalem, Hammoudi-Triki, & Laraba-Djebari, 2008; Petricevich & Peña, 2002). The elevation of circulatory catecholamines and angiotensin resulted in intense vasoconstriction and cardiac stimulation, increased myocardial oxygen requirement, and altered myocardial perfusion and metabolism, with hyperglycemia and an increase in circulating free fatty acids (Murthy, 2000).

Nencioni, Neto, de Freitas, and Dorce (2018) summarized in detail the major findings on the impact of Brazilian scorpion venoms on the central nervous system (CNS). Most of the studies have been performed with *Tityus* spp. The authors concluded that although the central effects rarely appear in patients, they can be fatal, requiring special attention in the treatment of envenoming cases. Additionally, these scorpion toxins may be pivotal tools for CNS studies.

7 | FINAL OBSERVATIONS

Although the purpose of exploitation of purified toxins was to increase the rate of cancer cell mortality with high efficacy and affinity, they have shown a lower cytotoxicity rate as compared to the crude venoms of scorpions. It is also important to note that there is the possibility of observing no effect of scorpion venom fractions against cancer cell lines. TsAP-1 isolated from *Tityus discrepans* showed a lack of anticancer activities against the PC-3, MCF-7, and U-251 cell lines (Guo et al., 2013). Crude venoms of different scorpion species have been reported to exhibit low cytotoxicity rates against certain cancer cell lines. *R. junceus* showed 31.5%, 20%, and 25.5% cytotoxicity against the SiHa, U-937, and K562 cancer cells, respectively (Díaz-García et al., 2013). On the other hand, the crude venom of *Centruroides limpidus limpidus* showed a lack of anticancer activity against the HeLa cell line (Contreras-Ortiz et al., 2013) (Table 5).

8 | CONCLUSIONS AND FUTURE PERSPECTIVES

In recent years, cancer has become one of the main public health problems, keeping the world population in a constant state of alert. Based on recent statistics, chemotherapy and radiotherapy are no longer effective and produce resistance in cancer cells. Scorpion venoms have shown exemplary cytotoxic activities against various cancer cell lines through the induction of apoptosis. In addition, venoms have revealed a unique potential to block ion channels in cancer cells, which lead to the inhibition of distinct characteristics. Venoms and their toxins are known to induce cell cycle arrest at early stages in the

G1, G2, and S phases, thereby avoiding the uncontrolled proliferation of cancer cells.

Despite a plethora of *in vitro* reports revealing the anticancer attributes of scorpion venoms against diversified cell lines, the usefulness of these toxins as promising tumoricidal agents is limited. Further, in depth *in vivo* research is essential to explore the anticancer attributes of scorpion venoms against a wide array of cancer cell lines using appropriate model organisms, which can undoubtedly set a robust foundation and open a new door for the scientific communities towards cancer treatment in future. Most importantly, scorpion toxin-associated anticancer drugs can be designed and commercialized only after obtaining zero toxicity in normal human cells during clinical trial phases.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

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How to cite this article: Desales-Salazar E, Khusro A, Cipriano-Salazar M, Barbabosa-Pliego A, Rivas-Caceres RR. Scorpion venoms and associated toxins as anticancer agents: update on their application and mechanism of action. *J Appl Toxicol*. 2020;1–15. https://doi.org/10.1002/jat.3976