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Anticancer Peptides Derived from the Venom of Scorpions Inhabiting Various Biotopes

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ABSTRACT

Despite advances in surgical techniques and adjuvant therapies, the relative prevalence rate of all cancers has risen sharply over the last three decades. Consequently, research into novel biological agents that can be used alone or in conjunction with existing FDA-approved medications is essential for effectively treating complex cancer disorders. Humans have utilized drugs derived from venom for hundreds of years; however, anticancer drugs derived from venom are still uncommon in the market. This scarcity is largely due to the poorly understood mechanisms of action for many venom-derived drugs, including peptides from scorpion venom. Scorpion venom contains a wealth of bioactive compounds, and several peptides isolated from it have demonstrated promising medicinal potential, thanks to advancements in peptide isolation, characterization, and biotechnological methods. As a result, scorpion peptides have emerged as a promising and potentially effective therapeutic resource for cancer treatment. Overall, this article highlights the anticancer mechanisms of certain venom peptides isolated from various scorpions inhabiting diverse biotopes.

Keywords: Apoptosis; Cytotoxicity; DBP; Ion channel blocker; NDBP.

INTRODUCTION

Cancer is one of the primary contributors to global mortality(Torre *et al.*, 2015). According to assessments by the World Health Organization and other international cancer bodies, cancer holds the second position in causing fatalities worldwide (Bray *et al.*, 2018). The most common cancers associated with mortality include breast, lung, colorectal, liver, and stomach cancers, which account for a significant proportion of cancer-related deaths (Sung *et al.*, 2021). In 2018, there were an estimated 18.1 million newly diagnosed cancer cases and approximately 9.6 million deaths attributable to cancer (Bray *et al.*, 2018). By 2020, these figures had risen to approximately 19.3 million new cases and around 10 million deaths due to cancer-related causes (Sung *et al.*, 2021). The increasing incidence and mortality rates underscore the urgent need for enhanced cancer prevention, early detection, and treatment strategies worldwide.

In Egypt, the cancer incidence rates from 2008 to 2011 were recorded at 113.1 per 100,000 individuals for both sexes. In comparison, the global age-standardized incidence rate during the same period was significantly higher, at 166.6 per 100,000 individuals for both sexes (Ibrahim and Mikhail, 2015). According to GLOBOCAN estimates for 2020, Egypt experienced 134,632 new cancer cases, accompanied by 89,042 cancer-related deaths. Furthermore, the five-year prevalence of cancer cases in the country was estimated to be 278,165 for both sexes (Ibrahim and Shash, 2022; GLOBOCAN, 2021). These figures underscore the significant burden of cancer in Egypt, highlighting the need for enhanced cancer prevention strategies, early detection programs, and improved treatment options to address this public health challenge effectively.

Conventional radioactive and chemotherapeutic treatments are highly cytotoxic to healthy tissues (Ferlay *et al.*, 2015), underscoring the urgent need for innovative cancer prevention and treatment strategies that incorporate natural compounds derived from animal venoms. The identification and extraction of cancer-specific peptides with growth-suppressing properties from various animal venoms represent a significant advancement in oncological research, offering the potential for more targeted and less harmful therapeutic options.

The venom's ability to specifically target proteins and their subtypes makes it a promising and highly selective therapeutic resource for treating cancer (Ma *et al.*, 2017). Over the last three decades, natural products, including plant and animal venom and secretions, have significantly influenced new therapeutic discovery and development (Newman and Cragg, 2016). Several venom-derived peptide medications have been introduced into the market and are currently utilized in managing diverse conditions such as heart disease, diabetes, hypertension, and chronic pain (Takacs and Nathan, 2014). Peptides, due to their distinctive pharmacological qualities of smaller size (about 10-80 residues), specificity, selectivity, and stability, are an excellent option and a potential spearhead in the future battle against cancer (Ma *et al.*, 2017). This study focuses on certain peptides isolated from scorpion venom and discusses their anticancer mechanisms.

Scorpions are among the most primitive terrestrial arachnids, with over 2500 species identified so far (Santibáñez-López *et al.*, 2022). Scorpions are easily distinguished by their lengthy bodies and segmented tails, which end with a telson that houses the venomous glands (Abdel-Rahman *et al.*, 2015). Scorpion venom represents a sophisticated and advanced weapon used

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for defense and hunting that may either kill or paralyze its target (Abdel-Rahman *et al.*, 2015) while acting as a deterrent to potential competitors (Ortiz *et al.*, 2015).

Understanding the biological significance of venoms and their potential utility in scientific studies and treatment requires employing OMIC technologies (proteomics and transcriptomics) to analyze their composition. Proteomic analysis has been widely used to assess the overall amount and structure of molecules in scorpion venom. Scorpion transcriptomics is a supplementary method for obtaining venom peptide sequences by building cDNA libraries from venom glands, including mRNA sequences for all venom components (Abdel-Rahman *et al.*, 2016).

This review article intends to outline the most notable anti-cancer peptides and explore their potential effectiveness and mechanisms against tumor cells, drawing from recent literature based on their chemical structure. Within venom, various toxin groups exist, and it appears that their mechanisms involve blocking ionic channels, compromising the integrity of cell membranes, and damaging internal cellular structures. These characteristics present promising avenues for investigating drugs and adjuncts in cancer therapy.

Scorpion habitat

Scorpions, belonging to the order Scorpiones, are terrestrial predators commonly found in tropical and subtropical regions worldwide (Polis and Yamashita, 1990). Their remarkable adaptability and robustness have enabled their colonization of various climates across continents, except Antarctica and a few Pacific islands (Xia *et al.*, 2023, Lourenço, 2018a). However, human expansion and population growth have significantly reduced scorpion habitats in recent years. These creatures thrive in diverse terrestrial ecosystems like deserts, dry forests, savannas, tropical humid forests, mountainous regions, paramos, punas, caves, and intertidal zones (Ochoa and Rojas-Runjaic, 2019). Certain scorpion species inhabit high-altitude mountain areas, limited to specific genera and families. The harsh ecological conditions in these regions likely drive these scorpions to spend much of their time in burrows, under rocks, tree bark, logs, gaps, or rock clefts (Polis and Yamashita, 1990, Ochoa *et al.*, 2011, Lourenço, 2018b). Twenty-two existing scorpion families have been recognized, some of which may include extinct genera or species (Santibáñez-López *et al.*, 2022). Among these, the Buthidae family encompasses all scorpions recognized as hazardous to humans (Goyffon *et al.*, 1982) in contrast to the Scorpionidae family, fortunately, includes only a few species that pose a threat (Hodgson, 2012).

Structure of scorpion venom

Scorpion venom has a diverse spectrum of biological components that can be utilized for various therapeutic approaches (Ramírez-Carreto *et al.*, 2015). According to venomics research, the venom of different species of scorpions may include hundreds of other peptides ranging in size from 1 to 9 kDa (Newton *et al.*, 2007). It contains the following (Figure **(1)** non-protein-based components: (inorganic salts, mucopolysaccharides, nuclear products, lipids, and amino free acids,), protein-based compounds, primarily peptides and enzymes (Rodríguez de la Vega and Possani, 2005, Abdel-Rahman *et al.*, 2015, Rapôso, 2017). The main ingredients are peptides from scorpion venom, which have a variety of biological and therapeutic properties. Based on their chemical structure, peptides can be classified as either disulfide-bridged (DBPs), which include neurotoxins, or non-disulfide bridged (ND-BPs), which include peptides with anticancer, anti-inflammatory, immune-modulatory, hemolytic, antimicrobial, and bradykinin-potentiating properties (BPPs) (Figure (**1**; (Zeng *et al.*, 2005, Almaaytah and Albalas, 2014, Ramírez-Carreto *et al.*, 2015, Abdel-Rahman *et al.*, 2016, Rawson, 2019).

The DBPs have been studied more thoroughly due to their therapeutic significance and high specificity to the targeted ion channels (Ramírez-Carreto *et al.*, 2015). Most DBPs are neurotoxins with 23 to 76 amino acid residues (Abdel-Rahman *et al.*, 2015) and three to four disulfide bridges. They can control and interact with ion channels (Machado *et al.*, 2016, Rawson, 2019) (Na^+, Cl^+, K^+, and Ca^{+2}) (Figure (1) as well as particular kinds of cell receptors (e.g., ryanodine receptor) (Harrison *et al.*, 2014). Toxins that bind to sodium channels (NaScTXs) (Figure (**1**) have the greatest impact on mammals, even humans. They are divided into two types: α-toxins, which delay the inactivation of the voltage-gated Na^+ channels, and β-toxins, which cause the channels to open at higher negative potentials (Rodríguez de la Vega and Possani, 2005). In low dosages, α-toxins cause significant plasma membrane depolarization and decreased excita-bility. They cause paralysis and cardiac arrhythmia at larger dosages by extending the action potential of excitable cells (Bosmans and Tytgat, 2007). β-toxins cause myoclonic or spastic muscle reactions (Chipp-aux, 2012). Other known scorpion toxins, which act on potassium, chlorine, and calcium channels, can have synergistic effects, resulting in clinical indications (Ortiz *et al.*, 2015).

Toxins that bind to chloride channels (ClScTxs) (Figure (**1**) are called the scorpion neurotoxin CTX and, also known as chlorotoxin**,** have been used in clinical studies to prevent glioma cell migration and invasion. CTX seems to have anti-metastatic activity through two pathways: inhibiting chloride channels, which are expressed only in glioma cells, and reducing the enzymatic capacity of matrix metalloproteinase-2 (MMP-2), which is overexpressed in these tumor cells (Deshane *et al.*, 2003, Abdel-Rahman *et al.*, 2016).

Toxins that bind to calcium channels (CaScTxs) (Figure (**1**) are important in cell death processes. Ca^{2+} influx is a normal and induced apoptosis component mediated by mitochondrial, cytoplasmic, or ER mechanisms (Pinton *et al.*, 2008). Cell cycle arrest during the G1/S transition is promoted by inhibiting Ca^{2+} entry into cells, which is crucial for cell growth and division. When calcium channels are down-regulated, the cell-cycle arrest protein p21 is increased, and proliferation

is suppressed through a p53 tumor-suppressing transcription factor-dependent pathway (Lu *et al.*, 2008, Prevarskaya *et al.*, 2010, Antal and Martin-Caraballo, 2019, Duenas-Cuellar *et al.*, 2020). Therefore, tumor cells depolarize cell membranes to facilitate the entrance of calcium ions through calcium channels, allowing unrestricted tumor cell proliferation (Varghese *et al.*, 2019).

Toxins that bind to the potassium channels (KScTxs) (Figure (**1**) regulate the influx of potassium ions because tumor proliferation is related to its increase. The blockage of ATP-sensitive potassium channels by human breast carcinomas, for instance, causes a reversible arrest of cells in the G0/G1 phase of the cell cycle and blocks growth. α- β, γ, and κ KScTxs are involved in causing apoptosis (Duenas-Cuellar *et al.*, 2020). The NDBPs are gaining popularity, and over 40 scorpion NDBPs have yet to be discovered and functionally described (Ramírez-Carreto *et al.*, 2015). Proteins in the NDBP family have sizes ranging from 10 to 50 amino acids (Figure (**1**; Abdel-Rahman *et al.*, 2016) and have a wide range of sequences. They are primarily cationic and have much structural flexibility. The lipid head groups of biological membranes are negatively charged, making them an easy target for positively charged NDBPs. Adhesion to a membrane leads to the formation of an amphipathic helix and the insertion of hydrophobic residues into the membrane, where they may exert their biological function (Huang *et al.*, 2010). Since no molecular target exists, their biological targets are broad (Ortiz *et al.*, 2015).

Several NDBPs have multifunctional actions independent of the target cells, contrary to the mode of action of neurotoxins, which are directed at particular receptors (ion channels) to certain biological targets. There have been several reports of beneficial NDBP activity, including its antimicrobial, antiviral, antimalarial, cytolytic, anticancer, bradykinin-potentiating, and immunomodulatory effects (Figure (**1**, Almaaytah and Albalas, 2014). Most NDBPs identified in scorpion venom are α-helical AMPs with amphipathic properties (Machado *et al.*, 2016). This finding has elevated the NDBP to the ranks of extremely interesting and potential therapeutic medication possibilities (Ortiz *et al.*, 2015).

Scorpion Venom Anti-cancerous DBPs

Various peptides derived from scorpion species and their effects on cancer cell lines and tumor models are summarized in Table (1). Among these, Chlorotoxin (CTX) is a prominent drug-binding protein (DBP) identified for its anti-cancer properties. CTX is a 4 kDa neurotoxin derived from the venom of the *Leiurus quinquestriatus* scorpion. It specifically binds to chloride channels, which are crucial for various cellular processes (Possani *et al.*, 2000). Research has shown that CTX can identify and block Cl- channels in tumor cells, leading to a reduction in tumor cell proliferation and invasion. Additionally, CTX has been found to suppress the epithelial-mesenchymal transition (EMT) of glioma cells, a process that is often associated with increased metastatic potential. By inhibiting EMT, CTX not only curtails the migratory capabilities of glioma cells but also enhances their sensitivity to conventional therapies. This dual action makes CTX a promising candidate for targeted cancer therapy, particularly for aggressive tumors that exhibit high levels of metastasis. Further studies are necessary to elucidate the full range of CTX's mechanisms of action and its potential integration into cancer treatment protocols.

CTX exhibits two distinct effects on MMP-2 within cultured human glioma cells (D54-MG and CCF-STTG-1), specifically demonstrating anti-invasive properties through its selective interaction with MMP-2 isoforms (Figure 3). Significantly, CTX does not interact with other isoforms, such as MMP-1, -3, or -9, present in these glioma cells. Its modulation of MMP-2 involves both the inhibition of its enzymatic activity and a reduction in its surface expression (Deshane *et al.*, 2003). *In vivo* studies revealed that brain sections implanted with rat glioma (F98) showed hypervascularized angiogenic patches and irregular capillaries in the untreated group. Conversely, sections treated with CTX and its derivatives CA4 (5 and 10 µM) exhibited a significant reduction in the number and density of high-density vessels (Xu *et al.*, 2016). Meanwhile, current applications of CTX include the detection of brain tumors and the targeted delivery of therapeutic anti-tumor drugs. CTX comprises 36 amino acids (Mamelak and Jacoby, 2007) and exhibits a structural arrangement characterized by three small antiparallel β-sheets folded against an α-helix, stab-ilized by four disulfide linkages (Ma *et al.*, 2017). This robust structure enables CTX to effectively penetrate the blood-brain barrier (BBB), making it a valuable tool in treating malignancies of the central nervous system. Remarkably, CTX is primarily utilized in stu-dies focused on glioma malignancies (Ma *et al.*, 2017).

Numerous CTX-like peptides have been identified, such as BmKCTa isolated from the venom of *Buthus martenzii* (Fu *et al.*, 2005; Zeng *et al.*, 2000), GaTx1 and GaTx2 derived from the venom of *Leiurus quinquestriatus* (Thompson *et al.*, 2009; Fuller *et al.*, 2007), and AaCtx originating from the venom of *Androctonus australis.* These peptides share structural and functional simil-arities with CTX, suggesting a broader potential for venom-derived compounds in cancer therapy. Recent studies have demonstrated that CTX not only binds to specific receptors on tumor cells but also alters mem-brane dynamics, facilitating drug delivery and enhancing therapeutic efficacy. The exploration of these peptides continues to reveal their promise as innovative agents in oncological treatments, highly-ghting the need for further research into their mechanisms of action and potential clinical applications.

M-CTX-Fc is a monomeric form of chlorotoxin (CTX) created by attaching CTX to the amino terminus of the human IgG-Fc domain. This fusion protein demonstrated concentration-dependent inhibition of human pancreatic cancer (PANC-1) cell migration (Table 1; Figure 3) and significantly reduced the release of matrix metalloproteinase-2 (MMP-2) into the culture medium (El-Ghlban *et al.*, 2014).

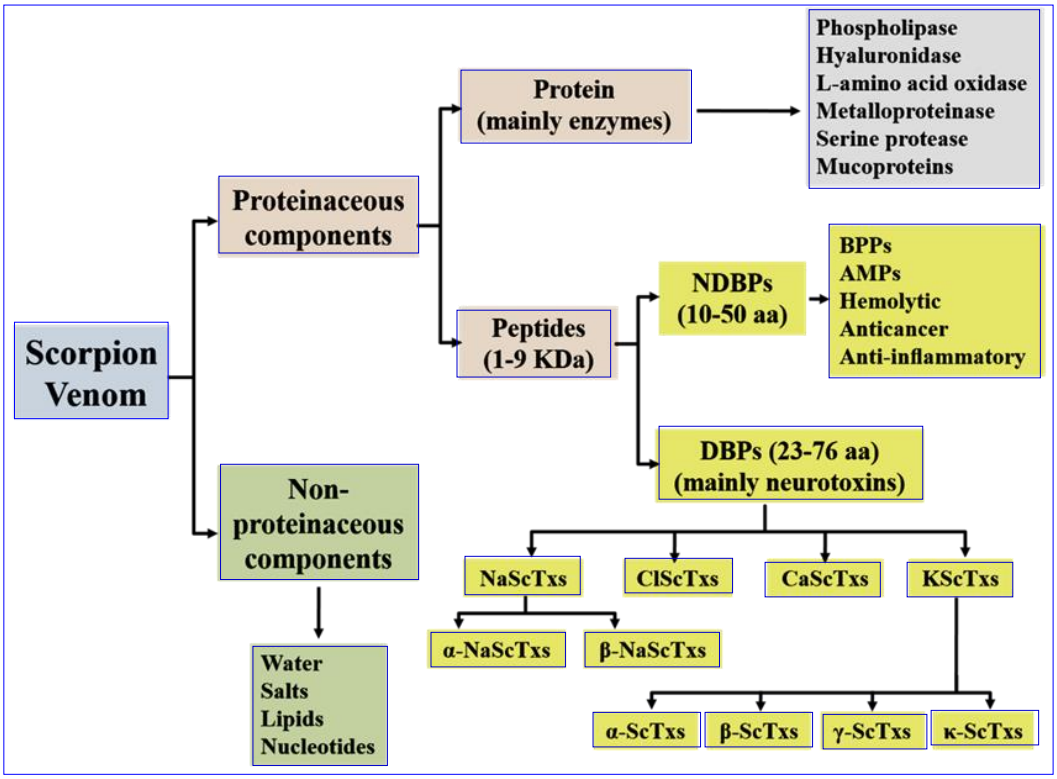

Figure (1). A chemical structure diagram of scorpion venom. Disulfide-bridged peptides (DBPs); non-disulfide-bridged peptides (NDBPs); antimicrobial peptides (AMPs); bradykinin-potentiating peptides (BPPs); sodium, chloride, calcium, and potassium ion channel toxins (NaScTxs, ClScTxs, CaScTxs, and KScTxs, respectively) (Abdel-Rahman *et al.*, 2016).

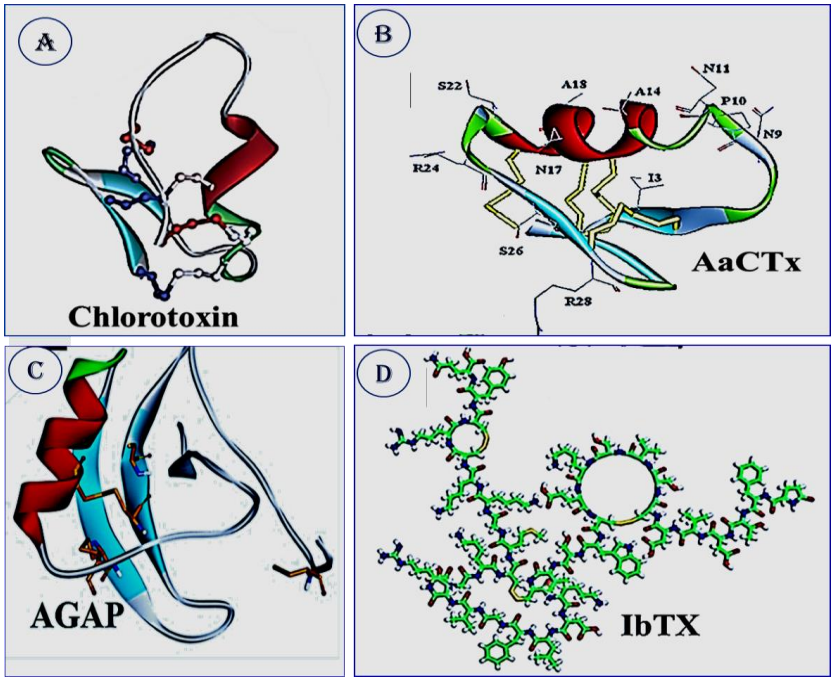

Figure (2): Structure of DBP Peptide toxins from different scorpions. **A:** 3D structure of the ion channel blocker chlorotoxin (Ma *et al.*, 2017). B, Homology model of AaCtx (Rjeibi *et al.*, 2011). C**,** AGAP structural model. The orange-colored residues form four disulfide bonds, while the α-helices and β-sheets are depicted in red and blue, respectively (Zhao *et al.*, 2023). D**,** Iberiotoxin structure using PyMOL Molecular Graphics System (Torres *et al.*, 2014).

Table (1): DBP Peptide toxins from different scorpions with anticancer activity, arrangement is based on the type of ion channels targeted by scorpion venom toxins.

Peptide	Scorpion species	amino acid number /disulfide bridges	Effective on	Blocked channel	• *In vitro* cancer cell lines ○ *In vivo* tumor models	References
Chlorotoxin (CTX)	*Leiurus quinquestriatus*	36/4	↓Invasion ↓migration	Cl^-	• Human glioma (D54-MG and CCF-STTG-1) • Brain sections implanted with rat glioma (F98)	(Deshane *et al*., 2003) (Xu *et al*., 2016)
M-CTX-Fc		36/4	↓migration		• Human pancreatic cancer (PANC-1)	(El-Ghlban *et al.*, 2014)
AaCtx	*Androctonus australis*	34/4	↓Invasion ↓migration		• Human glioma (U87)	(Rjeibi *et al.*, 2011, Akef, 2017)
BmKCT		35/4	↓Proliferation		• Human glioma (SHG-44)	(Fu *et al*., 2007, Cheng *et al*., 2014)
Analgesic-Antitumor Peptide (AGAP)	*Buthus martensii*	66/4	↓Proliferation ↓Angiogenesis ↑Apoptosis	Na^+	• Human colon cancer (SW480) • Human glioma (SHG-44)	(Gu *et al.*, 2013) (Zhao *et al.*, 2011)
rAGAP		66/4	↓Proliferation ↓migration		• Human glioma (SHG-44)	(Zhao *et al.*, 2011)
BmK AGAP-SYPU2		65/4	↑Survival ↓Tumor weight		○ Ehrlich ascites tumor ○ Mouse S-180 fibrosarcoma	(Shao *et al.*, 2014)
TiTx gamma	*Tityus serrulatus*	64/4	↓Proliferation		• Mouse neuroblastoma (NIE115)	(Barhanin *et al.*, 1983)
Cn2	*Centruroides noxius*	68/4	↓Proliferation ↓Migration ↓Metabolism ↑Apoptosis ↑G0/G1 cell cycle arrest		• Mouse neuroblastoma (F11)	(Escalona *et al.*, 2014)
Iberiotoxin (IbTX)	*Buthus tamulus*	34/3	↓Proliferation ↑G1 cell cycle arrest	KCa^{2+}	• Human glioma (U87-MG) • Human ovarian cancer (A2780) • Human cervical cancer (HeLa)	(Han *et al.*, 2007, Ru *et al.*, 2014, Ramírez *et al.*, 2018)
Tamapin	*Mesobuthus tamulus*	31/3	↓Proliferation ↑Apoptosis		• Human breast adenocarcinoma (MDA-MB-231) • Human Leukaemic T cell lymphoblast (Jurkat E6-1)	(Ramírez-Cordero *et al.*, 2014)
Margatoxin (MgTX)	*Centruroides margaritatus*	39/3	↓Proliferation ↓Tumor growth		• Lung cancer (A549) ○ A549 xenograft mice model	(Jang *et al.*, 2011)
KAaH1 and **KAaH2**	*Androctonus australis*	58/3	↓migration	K^+	• Human glioma (U87) • Breast cancer (MDA-MB-231) • Colon adenocarcinoma (LS174)	(Aissaoui *et al.*, 2018)
Charybdotoxin	*Leiurus quinquestriatus*	37/3	↓migration		• Human melanoma (A7)	(Schwab *et al.*, 1999)

⩛, Downward reaction; ⩚upward reaction.

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MMP-2, secreted as a proenzyme, is crucial for tumor cell invasion and requires activation to exert its catalytic effects. In contrast, AaCtx is a 34-residue peptide (Figure 3), isolated from the venom of *Androctonus australis*, characterized by four disulfide bonds (Rjeibi *et al.*, 2011). AaCtx has been shown to reduce glioma cell invasion in a dose-dependent manner (Ma *et al.*, 2017). While, AaCtx effectively prevents U87 human glioma cells from spreading and invasively migrating, it does not affect their attachment to various extracellular matrix proteins. The mechanism by which AaCtx inhibits migration and invasion likely involves direct blockade of chloride channels rather than integrin inhibition, similar to the action of chlorotoxin. However, it has been observed that AaCtx is less effective than chlorotoxin (CTX) in inhibiting migration and invasion. This reduced efficacy may be attributed to the structural differences between the two peptides, specifically the absence of negatively charged amino acids in the N-terminal loop and/or α-helix of AaCtx (Rjeibi *et al.*, 2011; Akef, 2017). These structural features are thought to play a crucial role in the mechanism by which CTX exerts its inhibitory effects on tumor cell behavior.

BmKCT is a chlorotoxin-like peptide extracted from the venom of the scorpion *Buthus martensii* (Majc *et al.*, 2022; Fu *et al.*, 2005). It consists of 35 amino acids and features four disulfide bonds (Table 1). Studies have demonstrated that BmKCT suppresses the proliferation of human glioma (SHG-44) cells in a dose-dependent manner. Similar to chlorotoxin (CTX), BmKCT selectively binds to the MMP-2 receptor, which inhibits the function of glioma-specific chloride channels (Figure 3; Fu *et al.*, 2007; Cheng *et al.*, 2014). This mechanism suggests that BmKCT may offer therapeutic potential in glioma treatment by targeting specific cellular pathways involved in tumor growth. Research indicates that BmKCT has a promising opportunity to become a leading therapeutic agent akin to CTX in the near future (Ma *et al.*, 2017). The unique structural and functional properties of BmKCT underscore its potential in drug development, particularly for conditions associated with gliomas. Further investigations into its pharmacological effects and mechanisms of action are warranted to fully elucidate its therapeutic applications.

AGAP, also known as Antitumor Peptide (ANTP), is sourced from the venom of the Chinese scorpion *Buthus martensii* venom (Liu *et al.*, 2002). AGAP is a long-chain scorpion toxin that recognizes sodium channels, having 66 amino-acid residues and four disulfide bridges (Table 1; Ma *et al.*, 2010). AGAP suppresses proliferation by causing G1 cell cycle arrest in human SW480 colon cancer cells (Gu *et al.*, 2013). AGAP also inhibits SHG-44 glioma cell growth. In addition, AGAP disrupted the development and migration of SHG-44 cells and lowered the levels of VEGF and MMP-9 proteins. This was done by decreasing the activity of NF-kB and BCL-2 (Figure (**4**), which was controlled by p-AKT, p-p38, and p-c-Jun (Zhao *et al.*, 2011, Ma *et al.*, 2017).

Recombinant AGAP (rAGAP), a protein made up of SUMO linked to a hexa-histidine tag by *Escherichia coli*, was used as an anticancer and analgesic (Gu *et al.*, 2013). rAGAP not only decreases SHG-44 cell migration (Figure (**4**) during wound healing, but it also inhibits the growth of glioma cells SHG-44 and rat glioma cell C6 (Table 1). The downregulation of p-AKT protein expression by rAGAP is responsible for the G1 cell cycle arrest and suppression of CDK2, CDK6, and p-RB. RAGAP also inhibits the activation of VEGF and MMP-9, whereas the synthesis of NF-B, BCL-2, p-p38, p-c-Jun, and p-Erk1/2 is greatly reduced. Cell cycle arrest and interference with p-AKT, NF-kappaB, BCL-2, and MAPK signaling pathways are implicated as mechanisms by which rAGAP suppresses SHG-44 cell proliferation and migration (Zhao *et al.*, 2011).

BmK AGAP-SYPU2, an analgesic and anticancer peptide, is derived and purified from the venom of *Buthus martensii* scorpions. It comprises 65 amino acid residues forming four disulfide bridges (Table 1). Additionally, in vivo, it demonstrated anti-tumor effects by extending survival in the mouse Ehrlich ascites tumor model by 36.05% and decreasing tumor weight in the mouse S180 fibrosarcoma model by 46.3% (Shao *et al.*, 2014).

TiTx gamma, purified from *Tityus serrulatus* Brazilian yellow scorpion venom. TiTx gamma comprises 64 amino acids (Table 1; Marcotte *et al.*, 1997). TiTx gamma altered the functioning of sodium channels within NIE115 mouse neuroblastoma cells (Figure (**4**) (Barhanin *et al.*, 1983).

Cn2, a peptide composed of 68 amino acids and interconnected by four disulfide bonds, is extracted from the venom of the *Centruroides noxius* Hoffmann Mexican scorpion (Table 1; Calderon-Aranda *et al.*, 1999). By acting as a sodium channel blocker, Cn2 possesses the potential to arrest the cell cycle at the G0/G1 phase in F11 mouse neuroblastoma cells. Upon conducting proteomic analysis, the impact of Cn2 on protein abundance was evident, particularly concerning apoptosis, cell proliferation, and the rearrangement of the cytoskeleton. This toxin notably decreased the levels of proteins associated with shielding apoptosis (such as 14-3-3 zeta, nucleophosmin, HSP90), thereby inducing apoptosis akin to anticancer drugs. Simultaneously, alterations observed in mitochondrial proteins (including peroxiredoxin three and Tu translation elongation factor) suggested an apoptosis-mediated mitochondrial pathway. Furthermore, changes in the ubiquitin-activating enzyme E1 hinted at potential implications in cancer therapeutic strategies (Escalona *et al.*, 2014).

Cn2's modulation of sodium channels resulted in a reduced presence of cytoskeleton proteins (like fascin, NF-M, α-spectrin), which play crucial roles in axonal functions and signaling, potentially impacting cell migration and the reorganization of the cytoskeleton. Moreover, the toxin-affected processes related to RNA splicing and translation indicate their involvement in signaling cascades regulated by sodium channels.

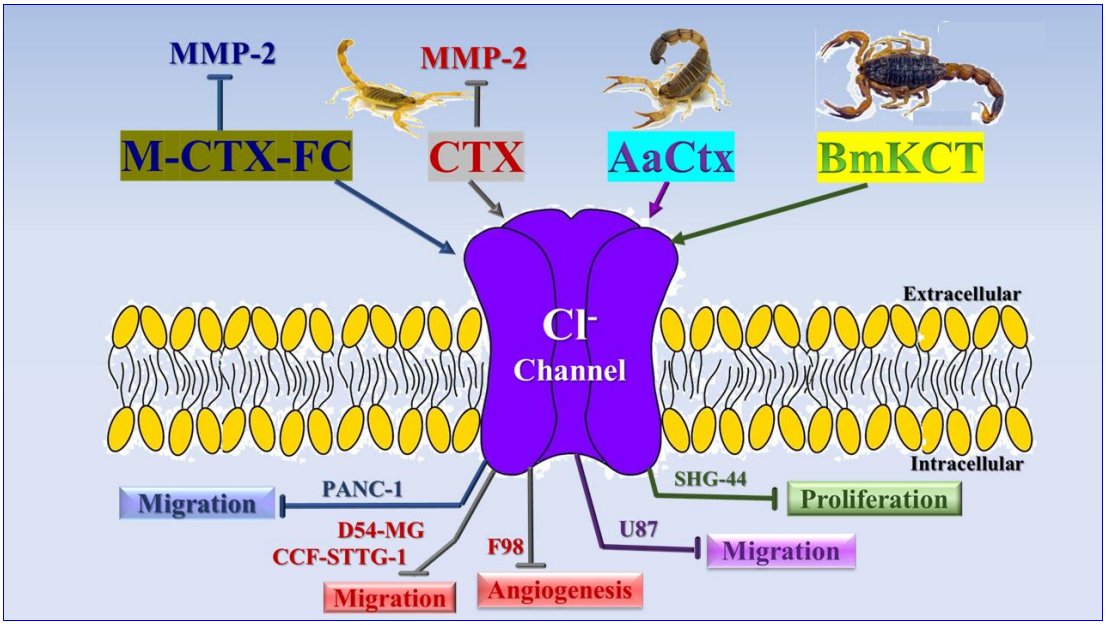

Figure (3): This image illustrates the role of scorpion venom-derived toxins in modulating chloride (Cl^-) ion channels and their effects on various cancer cell lines. The diagram highlights how different scorpion toxins target chloride channels to regulate cancer cell migration, proliferation, and angiogenesis. Specifically, it depicts the biological effects of scorpion neurotoxins on chloride ion channels in various cancer cells. Chlorotoxin (CTX) is a Cl^--channel blocker that is isolated from *Leiurus quinquestriatus* scorpion venom. CTX acts as an anti-invasive compound against Human glioma (D54-MG and CCF-STTG-1) cells while interacting and reducing MMP-2 expression. In addition, CTX inhibited hypervascularization of brain sections implanted with rat glioma (F98). M-CTX-FC restricts the invasion and migration of pancreatic cancer cells (PANC-1) in humans. by blocking Cl^- channel and reducing the release of MMP-2. AaCtx from *Androctonus australis* scorpion venom acts as an anti-metastatic agent on U87 human glioma cells not because it blocks integrins but because it directly blocks Cl^- channels. BmKCT from Buthus martensii scorpion suppresses the proliferation of human glioma (SHG-44) cells by blocking Cl^- channel.

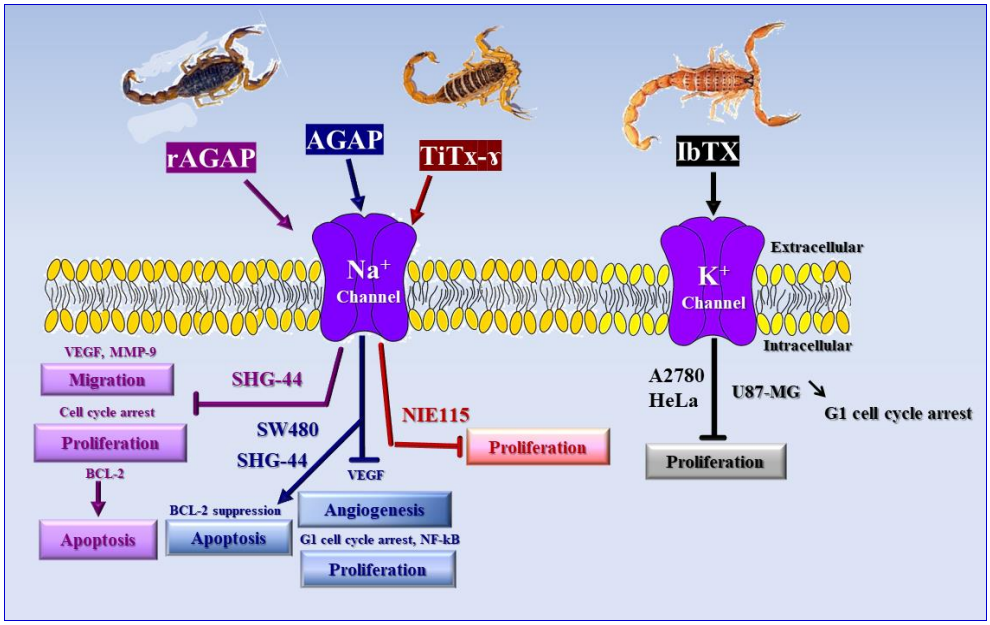

Figure (4). The diagram illustrates the modulatory effects of scorpion venom-derived toxins on ion channels and their potential roles in cancer therapy, focusing on proliferation, apoptosis, and angiogenesis. Analgesic-Antitumor Peptide (AGAP), isolated from *Buthus martensii* scorpion venom, demonstrates anticancer activity by blocking sodium (Na^+) channels. AGAP inhibits the proliferation of human colon cancer (SW480) and glioma (SHG-44) cells by inducing G1 cell cycle arrest and suppressing NF-kB signaling. AGAP also reduces vascularization and invasion by downregulating VEGF and MMP-9 and promotes apoptosis through the inhibition of the anti-apoptotic protein BCL-2. Its recombinant form, rAGAP, exhibits similar effects, including reduced glioma cell migration and enhanced apoptosis. TiTx-γ, derived from *Tityus serrulatus* scorpion venom, targets Na^+ channels and inhibits the growth of mouse neuroblastoma (NIE115) cells. By blocking sodium channel activity, TiTx-γ effectively impairs cellular proliferation. Iberiotoxin (IbTX), extracted from *Buthus tamulus* venom, acts on potassium (K^+) channels, suppressing the proliferation of human glioma (U87-MG) cells by inducing G1 cell cycle arrest. It also inhibits the growth of human cervical cancer (HeLa) and ovarian cancer (A2780) cell lines.

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Additionally, exposure to Cn2 influenced enzymes associated with energy metabolism, augmenting glycolytic pathways and facilitating the removal of ROS enzymes. This suggests stress-induced modifycations in proteins linked to energy processes. Overall, the research revealed the multifaceted influence of Cn2 toxin on cellular pathways that extend beyond sodium channels, indicating its relevance in apoptosis, reorganization of the cytoskeleton, RNA processing, energy metabolism, and responses related to antioxidants (Escalona *et al.*, 2014).

Iberiotoxin (IbTX), a 37 amino acid specific calcium-activated K^+ channel blocker (BKCa), as illustrated in Figure (**4**), with 3 disulfide bonds (Table 1; Garcia, 1997), obtained after being extracted from the *Buthus tamulus*, an Eastern Indian red scorpion. IbTX significantly inhibited the development of cultured human glioma (U87-MG) cells (Ru *et al.*, 2014). Furthermore, in a dose-dependent manner, it blocked the calcium-activated potassium channel KCNMA1 (subunit α-1 from subfamily M), leading to G1 phase arrest and the suppression of development and proliferation in human cervical cancer (HeLa) and human ovarian cancer (A2780) cell lines. (Han *et al.*, 2007, Ramírez *et al.*, 2018).

Tamapin is a 31 amino acid peptide with three disulfide bonds. It is isolated from the Indian red scorpion *Mesobuthus tamulus* venom (Table 1; Pedarzani *et al.*, 2002). It acts an anticancer efficacy on human Leukaemic T cell lymphoblast (Jurkat E6-1) and human breast adenocarcinoma (MDA-MB-231) by blocking calcium-activated potassium channels (KCa^{2+}) selectively. In Jurkat T cells, expressing these channels exhibited significant toxicity even at lower concentrations (0.1 nM) within 6 hours. Longer exposure to low concentrations did not decrease viability but showed a time-dependent effect. Cell death was induced in both cell lines by the recombinant Tamapin, resulting in apoptosis. Remarkably, this toxin exhibited low toxicity on cultures of human peripheral blood lymphocytes, suggesting its potential as an antiproliferative agent without adverse effects on typical T lymphocytes (Ramírez-Cordero *et al.*, 2014).

Margatoxin (MgTX) peptide is a KTx peptide (39 aa) with 3 sulfide bridges that is isolated from *Centruroides margaritatus* scorpion venom (Table 1). It significantly impeded A549 cell proliferation by explicitly blocking the Kv1.3 channel. Additionally, MgTX suppressed the growth of tumors induced by A549 cells in xenograft mice (Jang *et al.*, 2011). Meanwhile, KAaH1 and KAaH2, are two homologous blockers of Kv1.1 and Kv1.3 channels derived from the scorpion *Androctonus australis* (Table 1), exhibited antimigration properties in U87 (glioblastoma), MDA-MB-231 (breast cancer), and LS174 (colon adenocarcinoma) cells (Aissaoui *et al.*, 2018).

Charybdotoxin is a 37 amino acid peptide with three disulfide bonds. It is isolated from *Leiurus quinquestriatus* scorpion venom as recorded by Lambert *et al.*, (1990). It specifically blocks potassium channels, this lead to the reduction of A7 human melanoma cell lines in a dose-dependent fashion (Schwab *et al.*, 1999).

Scorpion venom anti-cancerous NDBPs

The scorpion anti-cancerous NDBPs is illustrated in table (2) in which Smp43 is a newly discovered and consist of 43 amino acids. This Smp43 is isolated from the Egyptian scorpion, *Scorpio maurus palmatus* (Abdel-Rahman *et al.*, 2013, Harrison *et al.*, 2016a). It is a cationic α-helical antimicrobial non-disulfide bridge peptide with amphipathic properties (Abdel-Rahman *et al.*, 2016, Chai *et al.*, 2021). There is no hemolytic effect on sheep red blood cells, and it is effective against gram-positive and effective against gram-positive and gram-negative bacteria and fungi. (Harrison *et al.*, 2016a).

Smp43 showed potent anticancer activities (Figure 5A; Table 2) toward KG1-a (myeloid leukemia) and CCRF-CEM (lymphoid leukemia) cell lines through cytotoxic activity, lactate dehydrogenase release, membrane disruption, and pore formation. The caspase-1 gene, responsible for pyroptotic cell death mechanisms, was up-regulated in both cell lines (Elrayess *et al.*, 2019). In addition, Smp43 exhibited decreased viability of HepG2 (hepatoma), Huh7 (hepatocyte cancer), and human primary HCC (hepatocellular cancer) cell lines through mitochondrial membrane disruption through induction of autophagy, necrosis, apoptosis, and cell cycle arrest while exhibiting minimal toxicity to normal human fetal hepatocyte cell line (LO2) cells. Smp43 also revealed effective tumor size reduction in the HepG2 xenograft mice model (Chai *et al.*, 2021).

Smp43 has been confirmed to induce apoptosis against MDA-MB-231 (human breast adenocarcinoma) and MCF-7 (breast cancer) cell lines and inhibit their proliferation, migration/invasion (Teleb *et al.*, 2022). Smp24 is an amphipathic cationic α-helical AMP (Figure 5B). It has the ability to inhibit microbes by disrupting membranes (Harrison *et al.*, 2016a, Harrison *et al.*, 2016b). This peptide was revealed to have a potent anticancer property (Table 2) due to its cytotoxic effect (Harrison *et al.*, 2016a) against human liver (HepG2) cancer cell lines compared to its minor effect against normal liver cells (LO2) (Nguyen *et al.*, 2022). In addition, it is more cytotoxic to leukemia cell lines (KG1-a and CCRF-CEM) than normal cell lines (CD34+, HACAT, and HRECs) (Elrayess *et al.*, 2020). Smp24 demonstrated antitumor effectiveness and reduced acute toxicity in the A549 lung cancer cell lines and lung cancer xenograft mouse model with reduced tumor volume and weight (Guo *et al.*, 2022).

Bengalin is another peptide toxin; it is a 72 kDa peptide composed of 20 amino acids, derived from the venom of the Indian black scorpion Heterometrus bengalensis (Gupta et al., 2010; Akef, 2017). It has been shown to inhibit the proliferation of human U937 leukemic cells. (Table 2; (Das Gupta *et al.*, 2013). Its mechanism of action relies on the interaction with signaling cascades, e.g., MAPK and PI3K pathways. Increased ERK 1/2 expression and decreased AKT activity led to apoptosis when bengalin was added to U937 cells. Apoptosis is triggered by bengalin-mediated caspase-3 activation. The effect of bengalin

Table (2): NDBP peptide toxins, isolated from different scorpion species, showed anticancer activity both *In Vitro* and *In Vivo* cancer cell line.

Peptide type	Scorpion species	Residues (number)	Effect on	• ***In vitro* cancer cell lines** ○ ***In vivo* tumor models**	References
Smp43	*Scorpio maurus palmatus*	43	↓Proliferation ↑Apoptosis,Pyropoptosis ↓Proliferation ↑intrinsic apoptosis ↑autophagy,↑necrosis ↓Proliferation ↓Migration, Invasion ↓Tumor size	• KG1-a (myeloid leukemia) • CCRF-CEM (lymphoid leukemia) • HepG2 (hepatoma) • Huh7 (hepatocyte cancer) • Human primary HCC (hepatocellular cancer) • MCF-7 (breast cancer) • MDA-MB-231 (human breast) ○ HepG2 xenograft mice model adenocarcinoma)	(Abdel-Rahman *et al.*, 2013, Elrayess *et al.*, 2019, Chai *et al.*, 2021, Teleb *et al.*, 2022)
Smp24		24	↓Proliferation ↑Apoptosis ↓Tumor size	• KG1-a (myeloid leukemia) • CCRF-CEM (lymphoid leukemia) • HepG2 (hepatoma) ○ Lung cancer xenograft mouse model	(Harrison *et al*., 2016a, Elrayess *et al.*, 2019, Nguyen *et al.*, 2022, Guo *et al.*, 2022)
Bengalin	*Heterometrus bengalensis*	20	↓Proliferation ↑Apoptosis	• U937 (human leukemia) • K562 (chronic myelogenous leukemia)	(Das Gupta *et al.*, 2013).
BmKn2	*Mesobuthus martensii*	13	↓Proliferation ↑intrinsic apoptosis	• HSC4 (oral squamous carcinoma) • KB (mouth epidermoid carcinoma) • SW620 (colon cancer) • H460 (human lung adenocarcinoma)	(Arpornsuwan *et al.*, 2014, Satitmanwiwat *et al.*, 2016)
AcrAP1a **AcrAP2a**	*Androctonus crassicauda*	18	↓Proliferation ↑Cell lysis	• MB435s (breast carcinoma) • PC-3(prostate cancer) • MCF-7 (breast cancer)	(Du *et al.*, 2014)
Mauriporin	*Androctonus mauritanicus*	48	↓Proliferation	• PC-3, LnCAP, DU-145 (prostate cancers)	(Almaaytah *et al.*, 2013)
Gonearrestide		18	↓Proliferation ↑G1 cell cycle arrest ↓Tumor size	• HCT-116 (human colon cancer cell line) ○ HCT116 colon cancer xenograft model	(Li *et al.*, 2018)
Neopladine 1 **Neopladine 2**	*Tityus discrepans*	-	↑Apoptosis	• SKBR3 (human breast carcinoma)	(D'Suze *et al.*, 2010)
Pantinin	*Pandinus imperator*	13	↑Cytotoxicity ↑Apoptosis	• MDA-MB-231 (human breast adenocarcinoma) • DU-145 (prostate adenocarcinoma)	(Crusca *et al.*, 2018)
RK1	*Buthus occitanus*	14	↓Proliferation ↓Migration	• U87 (Glioblastoma) • IGR139 (Melanoma)	(Khamessi *et al.*, 2018)
TsAP-2	*Tityus serrulatus*	17	↓Proliferation	• NCI-H157 (human squamous carcinoma) • NCI-H838 (lung adenocarcinoma) • PC3 (prostate cancer) • MCF-7 (breast cancer) • U251-MG (human glioblastoma)	(Guo *et al.*, 2013)
AaeAP1a **AaeAP2a**	*Androctonus aeneas*	19	↓Proliferation	• NCI-H460 (lung adenocarcinoma) • MCF-7 (breast cancer) • PC3 (prostate cancer) • MDA-MB-435s (human breast carcinoma)	(Du *et al.*, 2015)
VmCT1 analogs	*Vaejovis mexicanus smithi*	14	↓Viability	• MCF-7 (breast cancer)	(Pedron *et al.*, 2018)

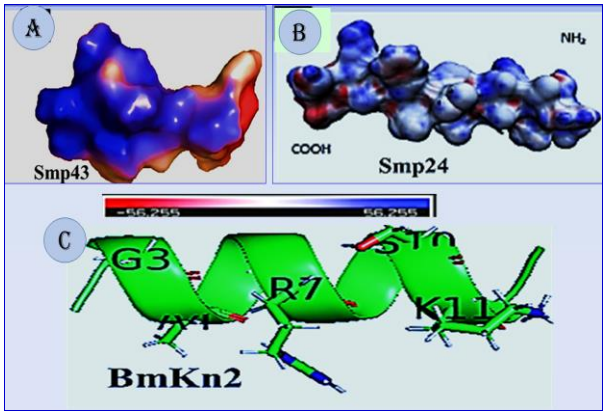

Figure (5): Structure of scorpion NDBP peptide toxins. A-B**:** 3D structure of Smp43 using the I-TASSER Server (Luo *et al.*, 2021b) and Smp24 (Rawson *et al.*, 2022), respectively. Blue highlights polar facets, and red highlights non-polar ones. C: 3D structure of BmKn2 using the I-TASSER Server (Luo *et al.*, 2021a).

on MAPK ERK 1/2 was selective, and it had no effect on JNK or p38 (Das Gupta *et al*., 2013). They were additionally, blocking ERK 1/2 and caspase-3 blocking ERK 1/2 and caspase-3 before bengalin administration activated the autophagy cascade in U937 cells (Das Gupta *et al.*, 2013, Ma *et al.*, 2017). It does not influence normal human lymphocytes but impacts chronic myelogenous leukemia (K562) by elevating the Bax/Bcl-2 ratio, caspase 3 and 9 expression, reducing mitochondrial membrane potential, and regulating heat shock proteins 70 and 90 (Gupta *et al.*, 2010).

BmKn2 is an α-helical antimicrobial peptide (AMP) with an amidated C-terminus, consisting of 13 amino acids (Figure 5C) as described by Zeng *et al.* (2005). It is isolated from the venom of the scorpion *Mesobuthus martensii*. It has been demonstrated to inhibit the growth of HSC4 oral squamous carcinoma cells, KB (mouth epidermoid carcinoma) cells, and SW620 colon cancer cells (Table 2, Arpornsuwan *et al.*, 2014). This growth inhibition occurs via the activation of an intrinsic apoptotic pathway that is dependent on the tumor suppressor p53. In HSC4 and KB cells treated with BmKn2, there was a notable increase in the pro-apoptotic protein BAX, while the anti-apoptotic protein BCL-2 was downregulated. Additionally, levels of the initiator caspase-9 were significantly elevated, whereas caspase-8 levels remained unchanged. Furthermore, cells exposed to BmKn2 for both oral malignancies exhibited increased expression levels of the effector caspases-3 and -7 (Satitmanwiwat *et al.*, 2016). These findings suggest that BmKn2 may serve as a potential therapeutic agent in the treatment of certain cancers by modulating apoptotic pathways.

AcrAP1a and AcrAP2a are two cationic-modified analogs of AcrAP1 and AcrAP2 peptides derived from the Arabian scorpion, *Androctonus crassicauda* venom (Table 2). While the original peptides, AcrAP1 and AcrAP2, had limited effects on cancer cell lines, their modified forms with enhanced cationicity, particularly AcrAP1a, demonstrated potent influences on cell growth. These modified analogs exhibited diverse effects on cancer cell lines, showcasing both anti-proliferative and proliferative effects at varying concentrations. These anti-proliferative impacts are likely attributed to cell lysis. The proliferation of multiple cancer cell lines, including human lung adeno-carcinoma (H460), breast carcinoma (MB435s), tum-origenic breast cells (MCF-7), and prostate carcinoma (PC-3), was inhibited by the analogs at concentrations between 2 to 3.6 µM *(Du et al.*, 2014).

Mauriporin is isolated from *Androctonus mauritanicus* scorpion venom, and it comprises 48 amino acids (Table 2). It was discovered that Maur-iporin exhibited strong, selective cytotoxicity and antiproliferative effects against three distinct prostate cancer cell lines (LnCAP, PC-3, and DU-145). Moreover, at concentrations required to eliminate cancer cells, Mauriporin demonstrated reduced hemolytic activity against sheep erythrocytes. Even at an 80 µM concentration, The observed value is ten times greater than the IC_{50} values observed against prostate cancer cells., Mauriporin didn't show significant hemolysis, with the maximum observed percentage of hemolysis not surpassing 4.8% (Almaaytah *et al.*, 2013).

Gonearrestide peptide is isolated from *Androctonus mauritanicus* scorpion venom (Table 2**Error! Reference source not found.**). Gonearrestide, an extremely potent anticancer peptide, demonstrated minimal to no observed cytotoxic effects on epithelial cells and RBCs. In particular, it exhibited a consid-erable impact on HCT-116, a human colon cancer cell line. This peptide effectively hindered the proliferation of HCT-116 cells in a dose-dependent fashion, exerting a strong anti-proliferative influence. Additionally, Gonearrestide was observed to halt the cell cycle of HCT-116 cells during the G1 phase, thereby impeding their growth. Furthermore, experiments conducted in vivo using an HCT-116 colon cancer xenograft model revealed that Gonearrestide contributed to a dose-dependent reduction in tumor growth (Li *et al.*, 2018).

Neopladine 1 (29.918 kDa) and Neopladine 2 (30.388 kDa) peptides are isolated from *Tityus discrepans* scorpion venom (Table 2). Both peptides prompt programmed cell death in human breast carcinoma SKBR3 cells by attaching to the SKBR3 cell surface, initiating the expression of FasL and BcL-2 (D'Suze *et al.*, 2010).

Pantinin is an antimicrobial peptide with 13 amino acids each. They are isolated from *Pandinus imperator* scorpion venom (Table 2). Cell viability experiments demonstrated that pantinin displayed greater efficacy on tumor cells compared to healthy fibroblasts (HGF-1), demonstrating a preference for cancer cells. Apoptosis induced by pantinin in cancer cells was shown, through flow cytometry analysis, to occur thro-ugh a mechanism distinct from that observed in fibroblasts (Crusca *et al.*, 2018).

However, RK1 is a 14 amino acid peptide, isolated from *Buthus occitanus tunetanus* scorpion venom (Table 2), showed capability of hindering the migr-ation, growth, and angiogenesis in U87 (Glioblastoma) and IGR39 (Melanoma) cell lines (Khamessi *et al.*, 2018).

TsAP-2 is another peptide, consisting of 17 amino acid, was isolated from *Tityus serrulatus* scorpion venom (Table 2). This peptide demonstrated its ability to induce cytotoxicity, resulting in anti-proliferative effects for various cancer cell lines, including MCF-7 (breast carcinoma), PC3 (prostate carcinoma), H157 (squamous carcinoma lung), H838 (adenocarcinoma lung), and U251-MG (glioblastoma) (Guo *et al*., 2013). Meanwhile, AaeAP1a and AaeAP2a peptides, are isolated from *Androctonus aeneas* scorpion venom and have 19 amino acid residues (Table 2). Both peptides induce cytotoxicity in a dose-dependent manner, inhibiting the proliferation of MCF-7 (breast cancer), NCI-H460 (lung adenocarcinoma), PC3 (prostate cancer), and MDA-MB-435s (human breast carcinoma) cell lines (Du *et al.*, 2015).

VmCT1 is a 14 amino acid peptide (Phe–Leu–Gly–Ala–Leu–Trp–Asn–Val–Ala–Lys–Ser–Val–Phe–NH_2). This peptide is derived from *Vaejovis mexicanus smithi* scorpion venom (Table 2), [Lys]3-VmCT1-NH2 and [Lys]11-VmCT1-NH2 analogs, featuring introduced Lys residues on the hydrophilic face of VmCT1, demonstrated a propensity for anticancer activity. At 25 μmol/L, they reduced the number of viable MCF-7 breast cancer cells by approximately 50% within 24 hours. Notably, [Lys]3-VmCT1-NH2 maintained about 90% viability in human breast epithelial cells, indicating potential as templates for designing peptides with reduced cytotoxic effects on healthy cells. Additionally, [Glu]7-VmCT1-NH2 analog, with a substitution of a Glu residue on the hydrophilic face, exhibited a tendency towards MCF-7 anti-cancer activity by reducing cell viability using MTT assay. Importantly, it selectively targeted cancer cells without reducing viable human breast epithelial cells, even at higher concentrations. Atomic force microscopy (AFM) assays suggested that this peptide disrupted cancer cell membranes, potentially explaining its mechanism of action (Pedron *et al.*, 2018).

DICUSSION

The findings stemming from scorpion venom-derived peptides, particularly their diverse and promising applications in cancer therapeutics, represent a compelling avenue in oncological research. These peptides exhibit multifaceted mechanisms of action, exploring their potential as novel agents for targeting various aspects of cancer progression, including invasion, metastasis, angiogenesis, and cell proliferation across different cancer types (Abdel Fattah *et al.*, 2024; Xu *et al*., 2016). Scorpion venom-derived peptides, exemplified by chlorotoxin (CTX) and its analogs, have garnered significant interest in cancer therapeutics due to their unique properties. CTX, a 4 kDa peptide derived from *Leiurus quinquestriatus* scorpion venom, exhibits remarkable anti-invasive properties, particularly in glioma cells. It impedes the epithelial-mesenchymal transition (EMT) in these cells and demonstrates a specific interaction with MMP-2 isoforms, resulting in the inhibition of both MMP-2 enzymatic activity and surface expression. This characteristic interaction underscores its potential in mitigating glioma metastasis. This characteristic interaction underscores its potential in mitigating glioma metastasis (Farsi and Fard, 2023).

Moreover, CTX treatment shows promise in reducing vascularization in brain sections implanted with rat glioma cells, indicating its efficacy in controlling angiogenesis within tumors. Analogous peptides to CTX, such as BmKCT and AaCtx, exhibit similarities in their interactions with MMP-2 receptors in glioma cells, indicating comparable potential in inhibiting glioma cell growth and metastasis. BmKCT, derived from *Buthus martensii* scorpion venom, has shown efficacy in hindering glioma cell growth by specifically targeting MMP-2 and impeding chloride channel activity analogous to CTX (Boltman et al., 2023).

Recent studies have further elucidated the anticancer mechanisms of scorpion venom peptides. For instance, Smp24 has been shown to induce apoptosis and disrupt mitochondrial function in HepG2 hepatoma cells through multiple pathways, including cell cycle arrest and autophagy modulation (Nguyen *et al.*, 2022). These findings highlight the potential of scorpion venom-derived peptides as effective agents in cancer therapy and underscore the need for continued research into their mechanisms of action and therapeutic applications (Nguyen *et al.*, 2022). However, structural disparities, such as the absence of negatively charged amino acids in specific regions, might account for varying effectiveness in inhibiting migration and invasion compared to CTX. Scorpion venom-derived peptides extend their therapeutic implications beyond glioma treatment, demonstrating versatility across diverse cancer types and therapeutic interventions. Peptides like AGAP and its recombinant variant rAGAP display substantial anticancer activities by disrupting cell proliferation, migration, and the expression of proteins like VEGF and MMP-9, implicating their involvement in various signaling pathways.

Remarkably, scorpion peptides like Cn2 exert extensive effects encompassing apoptosis, cell proliferation, cytoskeletal rearrangement, RNA processing, and energy metabolism (Escalona *et al.*, 2014). Cn2's multifaceted impact on cellular pathways beyond sodium channel modulation highlights its potential in cancer therapeutics, providing avenues for further investigation and potential therapeutic targeting. Several scorpion venom-derived peptides, including Smp43, Smp24, Mauriporin, and VmCT1, exhibit potent anti-cancer effects against various cancer cell lines. Their ability to induce apoptosis, disrupt membrane integrity, arrest the cell cycle, and inhibit proliferation showcases their potential as effective agents against different cancer types, paving the way for novel therapeutic interventions in oncology. Furthermore, the observed selectivity of these peptides towards cancer cells over healthy cells is an encouraging aspect for their future clinical application.

Despite these promising findings, further exploration and detailed investigation are warranted to comprehend the molecular mechanisms underlying these peptides' actions and to optimize their efficacy. Moreover, structural modifications and targeted delivery systems might enhance specificity and reduce potential off-target effects, thereby increasing their translational potential in clinical applications.

In essence, scorpion venom-derived peptides present a promising landscape for the development of innovative anticancer therapeutics, diagnostic tools, and targeted drug delivery systems. While CTX remains a frontrunner for brain glioma malignancies, further exploration, and structural modifications of these peptides hold the potential to enhance their efficacy and reduce cytotoxic effects on healthy cells, propelling their translation into clinical applications and advancing cancer treatment modalities.

In general, natural-based toxin sources have shown considerable promise in cancer research, particularly through peptides derived from medicinal plants, various marine and terrestrial organisms, and scorpion venom as well (Abdel Fattah *et al.*, 2024; Abdelaal *et al*., 2024; Eltamany *et al*., 2014). For instance, crude extracts from Red Sea sponges such as *Spheciospongia vagabunda* and *Negombata corticata*, along with soft corals like *Sarcophyton glaucum* and *Sarcophyton auritum*, have demonstrated significant efficacy against HepG2 liver cancer cells and MCF-7 breast cancer cells (Eltamany *et al*., 2014). Similar to the peptides from scorpion venom, these marine extracts exemplify the impressive diversity of natural compounds that can combat cancer through various mechanisms, including inducing apoptosis and inhibiting tumor growth. The exploration of bioactive compounds from natural sources is critical, as they not only provide potential therapeutic agents but also enhance the effectiveness of existing treatments. Recent studies have highlighted the role of natural compounds in modulating autophagy pathways, which can be pivotal in overcoming treatment resistance in cancers such as hepatocellular carcinoma (HCC) (Abdel Fattah *et al*., 2024). Further investigation into these naturally occurring toxins may lead to the development of innovative therapies that could synergize with established treatments, thereby improving patient outcomes.

Ongoing research into marine-derived peptides underscores their potential to serve as complementary agents in cancer therapy, emphasizing the need for continued exploration of the vast biodiversity available in natural environments for novel anticancer strategies. As scientists continue to uncover the mechanisms by which these compounds exert their effects, it becomes increasingly evident that integrating natural products into cancer treatment paradigms could significantly enhance therapeutic efficacy and patient quality of life.

CONCLUSION

The exploration of scorpion venom peptides as potential therapeutic agents in cancer treatment is a rapidly evolving field, driven by the urgent need for more effective therapies against various malignancies, including metastatic cancers. Recent studies have highlighted the diverse array of bioactive peptides present in scorpion venom, which exhibit unique mechanisms of action that could be harnessed for anticancer applications. Research indicates that the initial interaction between venom peptides and target molecules is a pivotal step in mediating their anticancer effects. These peptides predominantly exert their influence through interactions with cellular membranes, although they also engage in critical intracellular interactions with proteins and DNA. This multifaceted mode of action positions scorpion venom peptides as promising candidates for cancer therapy, particularly because they may offer a more favorable safety profile compared to traditional chemotherapeutic agents, which often carry significant toxicity risks. The therapeutic potential of scorpion venom peptides lies not only in their ability to induce apoptosis and inhibit tumor proliferation but also in their capacity to modulate immune responses and disrupt key signaling pathways involved in cancer progression. For instance, specific peptides have been shown to block ion channels that are dysregulated in cancer cells, thereby impeding cell migration and invasion while promoting apoptosis. This pleiotropic activity underscores the importance of characterizing each peptide's unique molecular interactions to fully exploit their therapeutic benefits. The ongoing evaluation of the distinct properties and interactions of individual venom peptides will be crucial in advancing the development of peptide-based therapies. In conclusion, this review synthesizes current knowledge regarding the anticancer mechanisms of specific scorpion venom peptides, providing insights into their molecular actions and therapeutic potential. By proceeding our understanding of these peptides, we can overlay the way for innovative treatment strategies that influence their unique properties, ultimately contributing to more effective and less toxic cancer therapies. Continued research in this area holds promise for translating these findings into clinical applications, potentially revolutionizing the strategy for cancer treatment.

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البيتيدات المضادة للسرطان المستخلصة من سم العقارب التي تعيش في بيئات حيوية متنوعة

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الملخـص العـربي

يُعد السرطان من أكبر التحديات الصحية على مدار الخمسين سنه الماضية مسببا اعدادا هائلة من الوفيات على مستوي العالم. على الرغم من التقدم في تقنيات الجراحة والعلاجات المساعدة لعلاج السرطان، فإن معدل انتشار السرطان بشكل عام ارتفع بشكل حاد خلال الثلاثة عقود الماضية. ايضاً، إن مقاومة بعض الخلايا السرطانية لموت الخلايا المبرمج، وكذلك نمو الورم سريعا مجددا بعد الاستجابة الأولية لأدوية العلاج الكيميائي، تظل من المشكلات السريرية المهمة. وبالتالي، هناك حاجة ماسة لتطوير عوامل مضادة للسرطان ذات انتقائية وفعالية عالية مع سمية وآثار جانبية منخفضة للتغلب على المشاكل المرتبطة بأدوية السرطان التقليدية. لقد تم استخدام الأدوية المفصولة من السموم لمئات السنين. ومع ذلك، فإن الأدوية المضادة للسرطان المفصولة من السموم نادرة في السوق. وذلك لأن آلية عمل العديد من هذه الأدوية ، بما في ذلك البيتيدات المفصولة من سم العقرب، غير معروفة. إن سم العقرب يحتوي على العديد من المركبات البيولوجية النشطة. وقد أظهرت عدة ببتيدات فُصلت من سم العقرب تأثيراً طبياً واعداً بفضل التقدم في فصل البيتيدات وتوصيفها والطرق التكنولوجية الحيوية. وبالتالي، ظهرت ببتيدات العقرب كمصدر واعد ومحتمل للعلاج المضاد للسرطان. يسلط هذا البحث الضوء بشكل عام على آلية العمل المضادة للسرطان لبعض البيتيدات المستخلصة من السموم المفصولة من مختلف العقارب التي تعيش في البيئات المختلفة.