

Review

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Review

# Scorpion Venom as a Source of Cancer Drugs: A Comprehensive Proteomic Analysis and Therapeutic Potential

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## Abstract

Scorpion venom has emerged as a promising source of anticancer compounds due to its diverse bioactive components, including neurotoxins, antimicrobial peptides, and enzymes. Proteomic analyses have characterized venom composition in several species, while further functional assays have clarified their anticancer mechanisms. This review synthesizes current knowledge on scorpion venom-derived peptides with demonstrated anticancer activity, which selectively target ion channels, induce apoptosis, or disrupt tumor microenvironments. Where available, we highlight proteomic studies that have identified these components and discuss their structural features relevant to drug design. We also examine clinical applications and the challenges in translating venom peptides into therapies. The crucial and growing role of proteomics in this field, particularly for venom fractionation, component identification, and structural characterization, is critically evaluated.

**Keywords:** proteomics; cancer; scorpion venom; natural products; anticancer peptides; targeted therapy; drug delivery

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## 1. Introduction

### 1.1. The Global Cancer Burden

Cancer remains a leading cause of mortality worldwide, with 20 million new cases and 9.7 million deaths reported in 2022 [1]. Projections suggest these numbers will increase significantly by 2040, with an estimated 29.9 million new cases annually, driven by population growth, aging, and changing exposure patterns to risk factors [1]. Despite significant advances in cancer treatment over the past decades, the need for more effective, targeted, and less toxic therapeutic options continues to drive research in this field.

Cancer is inherently complex, representing a group of related yet distinct diseases, each with unique molecular and cellular features [2]. This heterogeneity presents significant challenges in developing universal treatment approaches and necessitates exploring novel therapeutic strategies. The financial burden of cancer treatment, estimated to exceed \$245 billion annually by 2030 in the United States alone [3], further emphasizes the need for innovative and cost-effective treatment options.

### 1.2. Current Challenges in Cancer Treatment

Despite significant advancements in oncology, traditional cancer therapies continue to face substantial limitations that affect their efficacy and patient outcomes.

Chemotherapeutic agents, while effective against rapidly dividing cancer cells, often lack specificity, leading to collateral damage to healthy tissues. This non-selectivity results in a range of adverse effects, including myelosuppression, which increases infections risk, gastrointestinal toxicity, manifesting as mucositis and diarrhea; cardiotoxicity, particularly with anthracyclines like doxorubicin; neurotoxicity, secondary malignancies, and fertility issues. These side effects can significantly impair a patient's quality of life and may necessitate dose reductions or treatment discontinuation [4].

Drug resistance represents another major challenge in cancer treatment. Tumors may exhibit intrinsic resistance or develop acquired resistance over time. Mechanisms contributing to resistance include enhanced drug efflux via ATP-binding cassette (ABC) transporters, alterations in drug targets, increased DNA repair capabilities, activation of alternative survival pathways, metabolic reprogramming, and modifications within the tumor microenvironment [2,5–8]. These adaptations often necessitate changes in therapeutic strategies, which may lead to additional complications and diminished patient outcomes.

The blood-brain barrier (BBB) presents a significant challenge in treating brain tumors. Its selective permeability restricts the entry of many therapeutic agents into the central nervous system (CNS). Although tumors can disrupt the BBB, leading to the formation of a heterogeneous blood-tumor barrier (BTB), drug delivery remains inconsistent and often inadequate. This limitation hampers the efficacy of systemic therapies for brain malignancies [9–12].

The increasing costs of cancer treatments, particularly advanced therapies such as targeted agents and immunotherapies, pose significant barriers to access, especially in low- and middle-income countries. The financial burden extends beyond drug prices, including the need for specialized infrastructure and personnel. These economic challenges contribute to disparities in cancer care and outcomes globally.

### 1.3. Natural Products in Cancer Therapy

The limitations of conventional cancer treatments have driven renewed interest in natural products as sources of novel bioactive compounds. Historically, natural products have played a crucial role in drug discovery, with approximately 32.5% of approved drugs between 1981 and 2019 being derived from or inspired by natural sources [13], with plant-derived agents, such as taxanes and vinca alkaloids, transforming oncology practice. Animal venoms are an underexplored frontier, providing evolutionarily refined peptides with high specificity for ion channels and receptors, which are often dysregulated in cancer [14]. These venom-derived compounds exhibit distinct pharmacological advantages, including structural complexity enabling selective target engagement, multi-modal mechanisms of action that may circumvent drug resistance, and therapeutic indices often superior to synthetic molecules due to their biological optimization through natural selection [15–20].

### 1.4. Historical Use of Venom in Medicine

The therapeutic application of animal venoms has been documented for thousands of years across various cultures and medical traditions. Ancient Egyptian, Chinese, and Greek medical texts document the use of venoms to treat diverse pathologies, including pain, inflammatory conditions, neurological disorders, cardiovascular diseases, and cancer therapy. This empirical knowledge has provided valuable leads for contemporary drug discovery, yielding several clinically approved venom-derived therapeutics [14,15]. The journey from traditional remedy to approved drug is exemplified by captopril, the first venom-derived drug approved by the FDA in 1981. It was developed from the Brazilian *Bothrops jararaca* viper's venom, revolutionizing hypertension treatment as the first angiotensin-converting enzyme inhibitor [21,22]. Similarly, the anticoagulant eptifibatide (Integrilin®), developed from the pygmy rattlesnake (*Sistrurus miliarius barbourin*) venom

[23], the analgesic ziconotide (Prialt®), from the marine cone snail *Conus magus* [24], and exenatide (Byetta®) derived from Gila monster (*Heloderma suspectum*) venom for the treatment of type 2 diabetes [25] demonstrate venom’s capacity to address critical therapeutic needs. These successes have catalyzed the investigation of lesser-studied venoms, particularly scorpion toxins, for their unique pharmacologic properties, including anticancer potential.

1.5. The Promise of Scorpion Venom

Scorpion venoms have emerged as a promising source of anticancer compounds due to their distinctive biochemical characteristics. They present high-affinity targeting of ion channels and receptors overexpressed in tumors, along with the ability to cross the blood-brain barrier, enabling CNS tumor targeting. Furthermore, their multi-component compositions act synergistically, while their evolutionarily optimized molecular structures confer selective cytotoxicity against cancer cells. This review provides a systematic analysis of the proteomic complexity of scorpion venoms, their multimodal mechanisms of anticancer activity, and their potential for translational applications in oncology.

2. Composition and Biochemistry of Scorpion Venom

Scorpion venom represents a rich reservoir of bioactive compounds, comprising diverse proteins, peptides, enzymes, nucleotides, lipids, inorganic salts, free amino acids, and small molecules, demonstrating remarkable specificity in targeting cellular pathways [26,27]. Among these, proteins and peptides are the most pharmacologically significant, particularly for anticancer applications due to their high target selectivity and low off-target toxicity [28,29].

2.1. Proteomic Characterization of Scorpion Venom

Recent advances in high-throughput proteomics have revolutionized the characterization of scorpion venom, enabling comprehensive profiling of its complex molecular composition. State-of-the-art analytical techniques, such as nano-scale liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), combined with advanced bioinformatics pipelines, have enabled researchers to identify and quantify hundreds of unique proteins, peptides, and bioactive molecules within venom samples [30,31] (Table 1).

Table 1. Scorpion venom-derived peptides and proteins with demonstrated anticancer activity.

Peptide/Protein Name	Scorpion Source	Molecular Target	Primary Mechanism	Cancer Models Tested	Proteomics/ Mass Spectrometry Analysis	Key References
AcrAP1/AcrAP 2	<i>Androctonus crassicauda</i>	Cell membranes	They block the recognition and binding of the target DNA by the Cascade complex, preventing the subsequent degradation triggered by Cas3.	Prostate carcinoma cell line and Human lung adenocarcinoma	-	[28,32–34]
AGAP / AGAP-SYPU2	<i>Buthus martensii</i> Karsch	Voltage-gated sodium channels (Nav1.4, Nav1.5, Nav1.7)	Ion channel modulation, inhibition of proliferation and migration, apoptosis	Fibrosarcoma and Human Colon Cancer	MALDI-TOF-MS	[35–37]
Bengalin	<i>Heterometrus bengalensis</i>	Mitochondria (Bax/Bcl-2, cytochrome c	Intrinsic apoptosis: mitochondrial depolarization, cytochrome c release,	Human Leukemia (histiocytic lymphoma)	-	[38–42]

		release, caspase-9/-3)	PARP cleavage, HSP70/90 downregulation	and chronic myelogenous leukemia		
<b>BmK crude venom</b>	<i>Buthus martensii</i> Karsch	PI3K/Akt signaling, PTEN/p27 pathways	Oncogenic signaling inhibition; PTEN upregulation and Akt/Bad suppression; apoptosis in lymphoma cells	Human glioma, Human lymphoma, Human breast cancer and Human hepatoma	-	[43,44]
<b>BmKn2</b>	<i>Mesobuthus martensii</i> Karsch	Mitochondria (Bax/Bcl-2, caspase-9)	Apoptosis induction, ROS generation, mitochondrial dysfunction	Human oral squamous carcinoma	-	[45,46]
<b>BotCl</b>	<i>Buthus occitanus tunetanus</i>	ClC-3, MMP-2	Chlorotoxin-like; inhibition of migration and invasion in glioblastoma/breast cancer	Human glioblastoma and human breast cancer	-	[47–49]
<b>Chlorotoxin (CTX)</b>	<i>Leiurus hebraeus</i>	ClC-3 chloride channels, MMP-2	Inhibition of tumor cell invasion and migration	Malignant glioma	-	[49,50]
<b>Cm28</b>	<i>Centruroides margaritatus</i>	Potassium channel Kv1.3	Suppress T cell activation (IL-2R and CD40L)	Not tested	-	[51]
<b>Crude venom</b>	<i>Hottentotta saulcyi</i>	Na <sup>+</sup> and K <sup>+</sup> channels	Apoptosis induction through MCF-7 cells via TNF-α and caspase-3 upregulation	Colon Cancer	LC-MS/MS	[52,53]
<b>Gonearestide</b>	<i>Androctonus mauritanicus</i>	Cell membranes	Induces G1 cell cycle arrest in HCT116 colorectal cancer cells by dually targeting CDK regulators. It downregulates CDK4 and upregulates the CDK inhibitors p21 and p27, along with cyclin D3.	Prostate carcinoma cell line and Human lung adenocarcinoma	LC-MS/MS and MALDI-TOF	[54]
<b>Hemiscorpius lepturus crude venom</b>	<i>Hemiscorpius lepturus</i>	Bax, p53, caspase-3 activation, Bcl-2 suppression	Apoptosis induction in colon carcinoma and xenografts with low toxicity to normal cells	Colorectal cancer	-	[51,55]
<b>HsTX1</b>	<i>Heterometrus spinnifer</i>	Potassium channel Kv1.3	Suppress pathogenic effector memory T lymphocyte	Not tested	MALDI-TOF	[56]
<b>Iberiotoxin (IbTX)</b>	<i>Hottentotta tamulus</i> (syn. <i>Buthus/Mesobuthus tamulus</i> )	Potassium channels Kv1.1, Kv1.3	Blockade of K <sup>+</sup> currents, Ca <sup>2+</sup> dysregulation, apoptosis	Breast Cancer	-	[57–61].
<b>Margatoxin (MgTX)</b>	<i>Centruroides margaritatus</i>	Potassium channel Kv1.3	Suppression of proliferation and cell cycle regulation, tumor growth inhibition	Lung adenocarcinoma	-	[62]



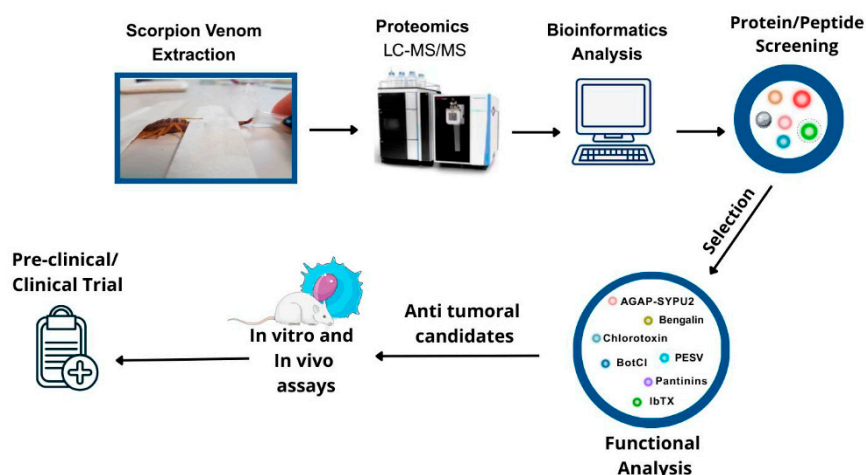
Maurocalcine (MCa)	<i>Scorpion maurus palmatus</i>	Ryanodine receptor (RyR1)	Ca <sup>2+</sup> release, cell-penetrating peptide, apoptosis and drug delivery	Breast Cancer	-	[63–66]
Neopladine 1 and 2	<i>Tityus discrepans</i>	Fas ligand → caspase-8 → Bid/tBid	Extrinsic apoptosis via death receptor pathway; cross-talk with intrinsic mitochondrial pathway	Breast Cancer	MALDI-TOF	[67]
Pantinins 1-3	<i>Pandinus imperator</i>	Cell membranes	Destabilizing and disrupting the membrane of target cells.	Breast adenocarcinoma and Prostate adenocarcinoma	Not specified	[68,69]
Smp43	<i>Scorpio maurus palmatus</i>	Mitochondria	Apoptosis induction by caspase-1 activation, triggering pyroptosis Apoptosis induction by reducing mitochondrial membrane potential	Human Lung Cancer	-	[70–73]
Smp24	<i>Scorpio maurus palmatus</i>	Mitochondria	(ΔΨ <sub>m</sub> ), increasing reactive oxygen species (ROS) production. Also, inducing apoptosis via caspase-1 activation triggering pyroptosis	Human Lung Cancer	-	[74,75]
TsAP-1 and TsAP-2	<i>Tityus serrulatus</i>	Cell membranes	Membrane disruption, cytotoxicity to cancer cells, apoptosis	Human Lung Adenocarcinoma, Prostate Adenocarcinoma, Human Squamous Carcinoma	MALDI-TOF/TOF	[76–78]
TsAP-S2	<i>Tityus serrulatus</i>	Mitochondria	Apoptosis induction through mitochondrial disruption and activation of caspase pathways	Not tested	ESI-MS	[77];
Vm24	<i>Vaejovis mexicanus smithi</i>	Potassium channel Kv1.3	Suppress pathogenic effector memory T lymphocyte	Breast Cancer	LC-MS/MS and MALDI-TOF	[79]

The key steps in venom proteomics typically begin with venom fractionation through chromatographic methods, such as high-performance liquid chromatography (HPLC) or size exclusion chromatography (SEC), followed by high-resolution mass spectrometric analysis for peptide sequencing and structural elucidation. Database mining using UniProt and VenomZone, together with bioinformatics analysis, is then employed to identify venom components and facilitate the discovery of previously unknown bioactive peptides with therapeutic potential, including anticancer properties [80]. This workflow is summarized in Figure 1.

Proteomic analyses across different species have provided insights into venom diversity and revealed evolutionary patterns in venom biochemistry, highlighting conserved elements that may serve as valuable leads for drug development [81,82]. This natural diversity in venom composition constitutes a vast molecular natural library of bioactive compounds, enabling targeted exploration for therapeutic applications.

Quantitative proteomics, including label-free, iTRAQ, and tandem mass tag (TMT)-based approaches, has further enhanced our understanding of venom composition by revealing the relative abundance of different constituents and their variability across species and environmental conditions [83]. These methods have also elucidated critical post-translational modifications (PTMs), such as disulfide bond formation, phosphorylation, and N-glycosylation in neurotoxins, which significantly influence protein stability and biological activity [84–86]. The integration of top-down (intact protein analysis) and bottom-up/shotgun (digested peptide analysis) proteomic strategies provide complementary insights into venom protein structure and function, facilitating the identification of promising therapeutic candidates.

Together, these advances not only deepen our understanding of venom composition but also accelerate the identification of bioactive candidates with anticancer potential, underscoring the importance of proteomics in drug development.



**Figure 1.** Workflow for the Discovery and Development of Scorpion Venom-Derived Anticancer Therapeutics.

## 2.2. Major Protein and Peptide Components of Scorpion Venom

The protein and peptide components of scorpion venom represent a complex mixture of bioactive molecules that constitute the molecular basis for its therapeutic potential. These components can be classified into several major groups based on their distinct structural and functional characteristics.

Neurotoxins represent one of the most abundant and well-studied groups, comprising both long-chain toxins that modulate voltage-gated sodium channels and short-chain toxins that target potassium and chloride channels [29,87–97]. These neurotoxins have shown promise in cancer therapy due to their ability to modulate ion channels that are crucial for cancer cell proliferation and migration, and are often dysregulated in cancer cells [98,99]. These interactions can disrupt cancer cell membrane potential, ultimately triggering apoptotic pathways. Of particular interest are certain short-chain peptides that exhibit the ability to cross the blood-brain barrier and specifically bind to cancer cell membranes, making them valuable candidates for treating neurological malignancies [27,100–102].

In addition to neurotoxins, scorpion venom contains antimicrobial peptides that demonstrate not only antimicrobial activity [103] but also exhibit potential anticancer properties through their membrane-disrupting mechanisms [70,104–106]. These peptides often exhibit selective cytotoxicity against cancer cells while showing minimal effects on normal cells, a characteristic that significantly enhances their therapeutic potential [74].

The venom also contains various enzyme inhibitors, particularly those targeting proteases that play crucial roles in cancer progression and metastasis [75,107–112]. Phospholipases represent another major component, capable of modifying cell membrane composition and triggering diverse cellular responses [99,113–119].

The disulfide-rich peptides are of pharmacological interest due to their remarkable stability conferred by multiple disulfide bonds and their high specificity for cellular targets, making them excellent candidates for drug development [84,120–122]. Recent research studies have identified novel peptides with unique mechanisms of action against cancer cells, including those that modulate the expression of tumor suppressor p53 or interfere with the PI3K/Akt signaling pathway, which is frequently dysregulated in cancer [28,123–125]. Additionally, the venom contains various bioactive amines and polyamines that can influence cellular signaling pathways, often synergizing with other venom components to enhance their cytotoxic effects [126–130].

Advances in proteomics and structural biology have enabled the optimization of these venom components for therapeutic applications. Strategies such as peptide cyclization and PEGylation have improved molecular stability, while conjugation techniques have enhanced tumor targeting specificity [16,19,131]. The multi-pathway inhibitory effects of certain venom components offer promise for overcoming drug resistance in cancer treatment [125].

The enzymatic components of scorpion venom represent a sophisticated array of biological catalysts that contribute significantly to its therapeutic potential [83]. These enzyme systems comprise diverse protein classes with distinct catalytic activities, including phospholipases, hyaluronidases, metalloproteases, and serine proteases [26,132,133]. Phospholipases, particularly PLA2, play a crucial role in membrane disruption and can trigger various cellular responses relevant to cancer therapy [134]. Hyaluronidases, often referred to as “spreading factors”, facilitate the distribution of other venom components by breaking down hyaluronic acid in the extracellular matrix (ECM) [135], a property that could be particularly advantageous in designing targeted drug delivery systems for cancer treatment. Metalloproteases present in scorpion venom can modulate the ECM, thereby affecting critical processes in cancer metastasis such as cell adhesion and migration [135]. The presence of serine proteases adds further complexity to the venom's enzymatic profile, given their ability to influence blood coagulation and inflammatory responses [134]. The coordinated action of these enzyme systems creates a complex network of biochemical reactions that can be potentially harnessed for therapeutic applications. A comprehensive understanding of their kinetics and regulatory mechanisms is essential for developing effective cancer treatments, as many of these enzymes exhibit substrate specificity or target cellular pathways implicated in cancer biology [136].

### 3. Molecular Mechanisms of Anticancer Activity

Scorpion venom components exert anticancer effects through diverse molecular mechanisms, including induction of apoptosis, cell cycle regulation, and modulation of ion channels. Rather than acting as non-specific cytotoxins, many peptides demonstrate selectivity for malignant cells by targeting signaling pathways, surface receptors, or membrane properties that are dysregulated in cancer. The following subsections provide an overview of the principal mechanisms, illustrated by representative venom-derived molecules (Figure 2). Detailed descriptions of individual peptides are provided in Section 4.



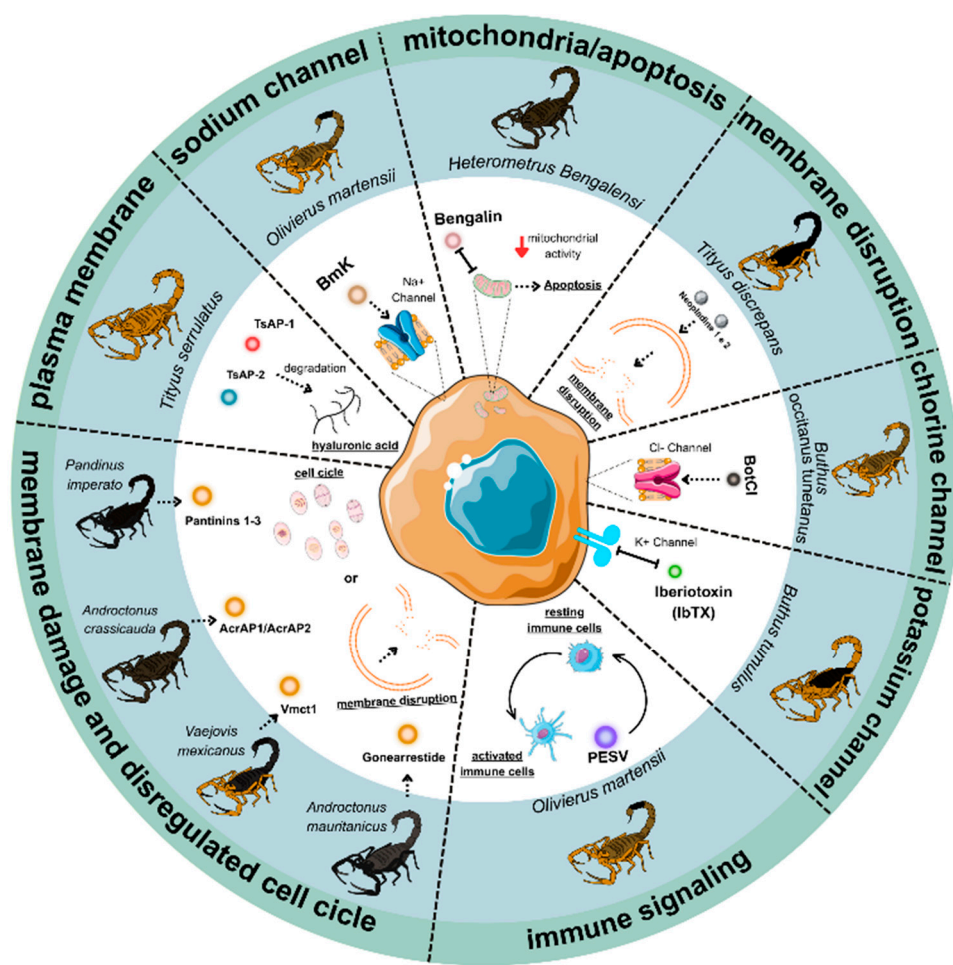


Figure 2. Mechanisms of Anticancer Action of Selected Scorpion Venom Peptides.

3.1. Induction of Apoptosis

The investigation of cell death pathways induced by scorpion venom components has revealed complex molecular mechanisms of action that selectively induce cancer cell death through both intrinsic and extrinsic apoptotic pathways. The intrinsic apoptotic pathway activation involves critical disruption of mitochondrial function, as demonstrated by Smp24, a peptide derived from *Scorpio maurus palmatus*. This peptide disrupts mitochondrial homeostasis by reducing the mitochondrial membrane potential ( $\Delta\Psi_m$ ), increasing reactive oxygen species (ROS) production, and inducing cytoskeletal reorganization in HepG2 cancer cells while exhibiting minimal toxicity toward normal LO2 liver cells [73,74]. Mitochondrial depolarization and ROS generation are hallmarks of caspase-3-mediated disruption of electron transport chain complexes I and II, a feedback mechanism that amplifies apoptotic signaling after cytochrome c release [32,137]. In addition, both Smp24 and Smp43 activate caspase-1, triggering pyroptosis in both myeloid (KG1-a) and lymphoid (CCRF-CEM) leukemia cells, again with minimal toxicity to non-tumor HaCaT cells [70].

Bengalin from *Heterometrus bengalensis* Koch exemplifies mitochondrial-targeting peptides, inducing cytochrome c release and caspase activation in leukemic cells [39]. Detailed proteomic and structural insights are discussed in Section 4.1.2. A similar mechanism is seen with peptide BmKn-2 from *Mesobuthus martensii* Karsch, which induces apoptosis in canine mammary gland tumor CHMp-5b and CHMPp-13a cell lines and in both human oral squamous carcinoma cells (HSC4) and human mouth epidermoid carcinoma cells (KB) via Bax/ Bcl-2 modulation and caspase 9 activation, while sparing normal human gingival and dental pulp cells [45,46]. Consistently, *Hemiscorpius lepturus* venom promotes Bax, caspase 3, and p53 overexpression alongside Bcl2 suppression in both CT26 colon carcinoma cells and xenograft tumors, with low cytotoxicity toward non-tumorigenic VERO cells [55].

Venoms also act on oncogenic signaling. *Buthus martensii* Karsch venom (BmK) selectively kills Raji and Jurkat lymphoma cells while sparing normal human peripheral blood lymphocytes. In Raji cells, BmK upregulated the tumor suppressor PTEN expression, decreasing Akt and Bad phosphorylation, thereby downregulating PI3K/Akt signaling. In PTEN-negative Jurkat cells, apoptosis proceeds through p27-mediated mechanisms, underscoring cell-specific vulnerabilities. Combining BmK with the Akt inhibitor LY294002 synergistically enhanced apoptosis, underscoring the therapeutic potential of venom-derived compounds in targeting oncogenic pathways [43].

The extrinsic apoptotic pathway is mediated through interactions with death receptors on cancer cell surfaces. Neopladines 1 and 2 from *Tityus discrepans* venom upregulate Fas ligand in SKBR3 breast cancer cells, promoting death-inducing signaling complex (DISC) formation, caspase-8 activation, and selective killing relative to non-malignant MA104 cells [67]. Similar receptor-driven effects have been reported in *Androctonus crassicauda* venom-treated HCT-8 colorectal cancer cells [28,32]. Activated caspase-8 also cleaves the BH3-only protein Bid, generating truncated Bid (tBid) that translocates to mitochondria, linking extrinsic and intrinsic pathways, thereby amplifying mitochondrial permeabilization and caspase-3 activation [28,32,138–142].

Taken together, these findings show that scorpion venoms exploit multiple cell death pathways, with selectivity for cancer cells driven by mitochondrial dysfunction, death receptor activation, and pathway cross-talk. Their multi-target nature, simultaneously inhibiting proliferation, angiogenesis, and metastasis, positions them as promising candidates for combinatorial anticancer therapies [44,143].

### 3.2. Cellular Signaling and Cycle Disruption

The impact of scorpion venom on cellular signal transduction pathways has been mapped through comprehensive phosphoproteomic analyses, revealing intricate networks of molecular interactions. Key targets include MAP kinases, PI3K/Akt, and JAK/STAT pathways, with venom peptides selectively inhibiting growth factor receptor signaling, disrupting crucial survival pathways in cancer cells. For example, *Buthus martensii* Karsch venom (BmK) upregulates PTEN in Raji lymphoma cells, suppressing PI3K/Akt via reduced Akt/Bad phosphorylation, while p27 mediates death in PTEN-negative Jurkat cells [43]. Temporal proteomics reveals sequential pathway activation, while protein-protein interaction studies highlight venom-induced disruption of cross-talk between survival pathways, potentially circumventing drug resistance.

Proteomics also clarifies cell cycle interference, identifying venom interactions with cyclins, CDKs, and checkpoint regulators. High-throughput screens show venom peptides arresting the cell cycle at G1/S or G2/M transitions through post-translational modifications, such as phosphorylation of regulatory proteins. Quantitative proteomics demonstrates differential expression of cycle-related proteins in cancer versus normal cells, supporting selective toxicity. These insights have propelled targeted strategies to halt cancer proliferation.

## 4. Specific Anticancer Components in Scorpion Venom

### 4.1. Apoptosis induction

#### 4.1.1. TsAP-1 and TsAP-2 from *Tityus Serrulatus*

The 17-mer peptides TsAP-1 and TsAP-2, isolated from the venom of the Brazilian yellow scorpion *Tityus serrulatus*, demonstrate significant anticancer potential through selective cytotoxicity and apoptosis induction (see Section 3.1). While TsAP-1 exhibits modest activity against oral carcinoma (H157 cells,  $IC_{50} > 50 \mu M$ ), its cationic analog TsAP-S1 shows dramatically enhanced potency ( $IC_{50} = 2.5 \mu M$  in leukemia cells) through membrane disruption mechanisms [77]. TsAP-2 displays greater inherent activity, with an  $IC_{50}$  of  $4 \mu M$  in SKBR3 breast cancer cells, and its engineered analog TsAP-S2 achieves remarkable potency ( $IC_{50} = 0.83 \mu M$ ) while maintaining selectivity for cancer cells over normal cells. These peptides induce apoptosis through mitochondrial

disruption and activation of caspase pathways, as evidenced by their ability to suppress proliferation in multiple cancer cell lines, including glioblastoma (U251-MG) and prostate adenocarcinoma (PC-3), with minimal effects on non-malignant cells [77]. Further supporting their therapeutic potential, TsAP-2 and the structurally related peptide Stigmurin from *Tityus stigmurus* exhibit antiproliferative effects on tumor cells while demonstrating low cytotoxicity toward normal cells, highlighting their selectivity and safety profile [78]. The enhanced activity of cationicity-modified analogs (TsAP-S1 and TsAP-S2) underscores the importance of structural optimization for improving anticancer efficacy. These findings position TsAP-1 and TsAP-2 as promising candidates for targeted cancer therapy, with their mechanisms of action rooted in membrane interaction and apoptotic pathway activation. Further research is needed to elucidate their precise molecular targets and evaluate their efficacy *in vivo*.

#### 4.1.2. Bengalin from *Heterometrus Bengalensis* and Other Novel Peptides

Bengalin, a peptide isolated from the Indian black scorpion *Heterometrus bengalensis*, exemplifies how structural and proteomic analyses deepen our understanding of venom-derived anticancer compounds. Proteomic profiling has confirmed its abundance in crude venom and provided evidence of its selective enrichment in venom fractions with cytotoxic activity [144]. Structurally, Bengalin exhibits a disulfide-stabilized fold characteristic of scorpion toxins, conferring conformational stability and resistance to proteolytic degradation, properties that enhance its therapeutic potential [41]. Beyond its structural resilience, proteomic and immunoblotting studies have documented Bengalin's dual impact on cancer cells. It induces apoptotic signaling, evidenced by Bax/Bcl-2 modulation, cytochrome c release, and caspase cascade activation, while simultaneously engaging autophagic responses through Beclin-1 and Atg upregulation and LC3 conversion [38,39].

These molecular features correlate with selective cytotoxicity by inducing apoptosis in U937 and K562 leukemic cells through multiple pathways mediated by the increase of caspase-3 activity and mitochondrial disruption pathways [39,40] and autophagic cell death via inhibition of proliferative MAPK/ERK and PI3K/AKT pathways [38,39]. Although Bengalin has shown selective cytotoxic potential for leukemic cells [144], more studies are needed to investigate the exact mechanisms of action of this compound and perform *in vivo* assays to confirm its anti-tumorigenic activity.

#### 4.1.3. Neopladine 1 and Neopladine 2 from *Tityus Discrepans*

Neopladine 1 and 2, isolated from *Tityus discrepans* venom, represent novel anticancer compounds with unique mechanisms of action. These peptides exhibit selective anticancer activity against HER2-positive human breast carcinoma SKBR3 cells, inducing apoptosis while showing negligible effects on non-malignant MA104 monkey kidney cells [42,67,128]. Mass spectrometry analysis determined their molecular masses to be 29,918 Da (Neopladine 1) and 30,388 Da (Neopladine 2), and their N-terminal sequences were confirmed by Edman degradation. The peptides induce apoptosis in SKBR3 cells, with Neopladine 1 causing 6.3% apoptosis and Neopladine 2 causing 4.1% apoptosis after 5 hours of exposure; prolonged exposure increases this effect. Immunohistochemical studies indicate that neopladines bind to SKBR3 cell surfaces, upregulating FasL and Bcl-2 expression, which are critical in apoptosis signaling. Interestingly enough, the combined application of neopladines 1 and 2 reduced apoptosis but increased necrosis, suggesting complex interactions that require additional investigation [67].

### 4.2. Ion Channel Modulation

#### 4.2.1. AGAP-SYPU2 from *Buthus Martensii* Karsch

Analgesic Anti-tumor Peptide AGAP-SYPU2, a peptide isolated from *Buthus martensii* Karsch (BmK) scorpion venom, exhibits dual analgesic and antitumor activities [35,145]. Shao et al. purified AGAP-SYPU2 and demonstrated its strong analgesic effects against both visceral and somatic pain, with its mechanism involving inhibition of voltage-gated sodium channels, which are critical in pain

signaling. Although its onset of action is slower than morphine, it provides prolonged analgesic effects [36].

In cancer therapy, AGAP (a homolog of AGAP-SYPU2) shows promising antitumor properties. It prolonged survival by 36.05% in Ehrlich ascites tumor models and reduced tumor weight by 46.3% in S180 fibrosarcoma mouse models [36]. The peptide's anticancer activity is linked to its modulation of sodium channels such as Nav1.4, Nav1.5, and Nav1.7, which are overexpressed in cancer cells and contribute to proliferation and migration. Moreover, AGAP was able to inhibit the proliferation and migration of SHG-44 glioma cells, suggesting a shared mechanism involving sodium channel blockade [37]. The dual functionality of AGAP-SYPU2—both as an analgesic and antitumor agent—makes it clinically valuable, as it may improve patient survival without compromising quality of life. However, further research is needed to optimize its potency and evaluate its efficacy in other cancer types.

#### 4.2.2. BotCl from *Buthus Occitanus Tunetanus*

BotCl, a chlorotoxin-like peptide isolated from the venom of the scorpion *Buthus occitanus tunetanus*, has emerged as a promising anticancer agent due to its ability to target CIC-3 chloride channels, which are overexpressed in glioblastoma and breast cancer cells [47,48]. This peptide belongs to the chlorotoxin family, characterized by four disulfide bonds that confer structural stability and high binding affinity to tumor-specific ion channels and membrane receptors, such as matrix metalloproteinase-2 (MMP-2) [47,49]. BotCl shares significant sequence homology with chlorotoxin (CTX), a well-studied scorpion venom peptide currently in clinical trials for glioma imaging and therapy, suggesting similar mechanisms of action, including inhibition of tumor cell migration and invasion [47,49].

The anticancer properties of BotCl extend beyond glioblastoma. Its ability to reduce tumor viability in breast cancer models highlights its broad-spectrum potential, possibly through mechanisms involving chloride channel blockade and disruption of tumor microenvironment signaling [47,48]. Furthermore, BotCl's structural stability under varying pH and temperature conditions enhances its suitability for therapeutic development, including conjugation with imaging agents or cytotoxic drugs for targeted cancer therapy [48,146].

In summary, BotCl represents a novel chlorotoxin-like peptide with significant anticancer potential, supported by proteomic and structural analyses. Its ability to target CIC-3 channels and MMP-2 in glioblastoma and breast cancer positions it as a promising candidate for further preclinical and clinical evaluation, particularly in the development of tumor-specific diagnostic and therapeutic agents.

#### 4.2.3. Iberiotoxin (IbTX) from *Hottentotta Tamulus*

Iberiotoxin (IbTX), a 37-amino acid peptide derived from the venom of the scorpion *Hottentotta tamulus* (also known as *Buthus tamulus* or *Mesobuthus tamulus*), has emerged as a potent inhibitor of voltage-gated potassium channels, particularly Kv1.1 and Kv1.3, which are overexpressed in malignancies such as glioblastoma (U87), breast (MDA-MB-231), colon (LS174), cervical (HeLa), and ovarian (A2780) cancers [57–59]. This toxin shares 68% sequence homology with charybdotoxin (ChTX) but exhibits superior selectivity for large-conductance calcium-activated potassium (BKCa) channels, with an equilibrium dissociation constant (Kd) of 1.16 nM, making it one of the most potent blockers of this channel family [57,60,61,147].

IbTX's anticancer potential extends beyond direct channel blockade. In breast cancer models (MCF-7, MDA-MB-231), IbTX-sensitive currents were shown to modulate proliferation under conditions of elevated intracellular calcium, such as ATP stimulation [58]. This suggests a context-dependent role in tumor signaling, where IbTX could synergize with calcium-mobilizing therapies. Additionally, structural studies using synthetic chimeric peptides, such as IbTX-ChTX hybrids revealed that the toxin's C-terminal domain is critical for Kv1.1/1.3 selectivity, providing a template for designing targeted anticancer derivatives [148].



Despite its promise, challenges remain in translating IbTX into clinical applications due to its potential off-target effects on neuronal and cardiovascular Kv channels. However, advancements in bioconjugation—such as biotinylated IbTX for imaging BKCa distribution in cancer cells—highlight its utility as a molecular tool for tumor profiling and drug development [149]. Future research should explore engineered analogs with enhanced tumor specificity and delivery systems to harness IbTX's full therapeutic potential.

In summary, IbTX represents a structurally and functionally characterized scorpion venom peptide with validated anticancer activity, supported by proteomic and electrophysiological evidence. Its ability to target oncogenic potassium channels positions it as a promising candidate for further preclinical evaluation in calcium-driven malignancies [57,58,60].

### 4.3. Cell Cycle Arrest

#### 4.3.1. Gonearrestide from *Androctonus Mauritanicus*

Gonearrestide, an 18-amino acid peptide (2.2 kDa) isolated from the venom of *Androctonus mauritanicus*, represents a novel class of scorpion venom-derived compounds with potent anticancer activity. Identified through a high-throughput platform combining next-generation sequencing (NGS) transcriptomics and LC-MS/MS proteomics, this peptide was selected from 238 novel peptides discovered in scorpion venom libraries due to its selective cytotoxicity against cancer cells while sparing normal epithelial cells and erythrocytes [54].

The peptide's mechanism of action centers on inducing G1 cell cycle arrest in colorectal cancer cells (HCT116), achieved through dual modulation of cyclin-dependent kinase (CDK) regulators. Gonearrestide downregulates CDK4, a key driver of G1/S transition, while simultaneously upregulating the CDK inhibitors p21 and p27, as well as cyclin D3 [54]. This coordinated action effectively halts cancer cell proliferation, as demonstrated by RNA sequencing showing significant alterations in cell cycle-related gene expression profiles.

In preclinical validation, Gonearrestide exhibited broad-spectrum activity against multiple cancer cell lines while showing negligible toxicity to normal cells, a critical advantage over conventional chemotherapeutics. Its ability to inhibit primary colon cancer cells and solid tumors in vivo further underscores its therapeutic potential. The discovery of Gonearrestide exemplifies how integrated omics technologies (proteomics/transcriptomics) can accelerate the identification of bioactive venom peptides with precise mechanisms of action. Its cell cycle-specific targeting offers a template for developing novel anticancer agents that combine high potency with reduced off-target effects.

#### 4.3.2. PESV from *Buthus Martensii* Karsch

Mass spectrometry and molecular biology analyses of the *Buthus martensii* Karsch (BmK) venom have identified multiple bioactive components, including polypeptides with anticancer activity [121,150]. Comprising 50-60 amino acid peptides, the Polypeptide Extract from Scorpion Venom (PESV) interferes with tumor growth through both anti-proliferative and pro-apoptotic mechanisms. In preclinical models, it inhibited the angiogenesis and suppressed tumor growth of H22 hepatocellular carcinoma in murine models [151].

In human androgen-independent DU145 prostate cancer cells, PESV induces cell cycle arrest at the G1-phase by upregulating Kip1/p27 expression while downregulating cyclin E, thereby disrupting cyclin-dependent kinase (CDK) activity, a key driver of cancer progression, which is normally regulated by CDK inhibitors (CDKIs) [152,153]. This cell-cycle blockade is accompanied by apoptosis mediated through upregulation of the proapoptotic protein Bax and downregulation of the anti-apoptotic protein Bcl-2, highlighting PESV's dual regulatory impact on proliferation and survival pathways. Importantly, PESV demonstrates preferential cytotoxicity toward prostate cancer cells over normal prostate epithelial cells, highlighting its potential as a targeted therapeutic agent [152].



Although these findings support PESV as a promising candidate, its precise molecular targets and the identity of the active peptide(s) within the extract remain unresolved. Further studies across different prostate cancer models are needed to validate its efficacy and clarify the signaling cascades involved [152].

#### 4.4. Membrane Disruption and Tumor Microenvironment

##### 4.4.1. Hyaluronidase BmHYA1 from *Buthus Martensii* Karsch

The hyaluronidase BmHYA1, isolated from the venom of the scorpion *Buthus martensi* Karsch (BmK), has emerged as a promising anticancer agent due to its ability to modulate the tumor microenvironment without observed toxic side effects [42,154–158]. This enzyme specifically targets hyaluronic acid (hyaluronan, HA), a key glycosaminoglycan polymer in the extracellular matrix (ECM), which promotes tumor progression by facilitating cancer cell migration, invasion, adhesion, and metastasis through interactions with CD44 receptors [156]. Elevated HA levels are associated with malignant phenotypes, as it provide a structural scaffold for tumor survival and activate signaling pathways via CD44, which is often overexpressed in cancer cells and generates oncogenic variants, such as CD44v6, through alternative splicing [159,160].

BmHYA1 exerts its anticancer effects by degrading HA, thereby disrupting HA-CD44 interactions, and sensitizing cancer cells to apoptosis by disrupting CD44-mediated survival signals, including TGF- $\beta$  activation and resistance to immune cytotoxicity [156]. This degradation reduces interstitial fluid pressure in tumors, enhancing the penetration of chemotherapeutic agents and improving drug delivery. In addition, BmK hyaluronidase was completely removed from triple-negative MDA-MB-231 breast cancer cells, downregulated CD44v6 expression, and inhibited HA-mediated oncogenic signaling [156]. The enzyme's specificity for HA makes it particularly effective against HA-rich cancers, such as breast and pancreatic carcinomas. Its dual role—as a standalone antitumor agent and a facilitator of combination therapies—highlights its therapeutic potential. However, further research is needed to fully elucidate its mechanisms and optimize its clinical application.

##### 4.4.2. RK1 from *Buthus Occitanus Tunetanus*

RK1, a 14-amino acid peptide isolated from the venom of the Tunisian scorpion *Buthus occitanus tunetanus*, represents a promising anticancer peptide with distinctive pharmacological properties. Biochemical and functional characterization has revealed that RK1 exhibits potent antitumor activity by simultaneously inhibiting cancer cell proliferation, migration, and angiogenesis without manifesting significant cytotoxicity toward normal cells, making it potentially effective against metastatic cancer. Moreover, RK1 demonstrated remarkable efficacy against glioblastoma (U87) and melanoma (IGR39) cell lines, with its mechanism of action involving the disruption of tumor cell adhesion and suppression of vascular growth, as evidenced by the chicken chorioallantoic membrane (CAM) assay [161].

Emerging evidence also indicates that RK1 may interfere with integrin-mediated pathways, which are critical for tumor cell adhesion, metastasis, and angiogenesis. This dual disintegrin-like activity, particularly on  $\alpha 1\beta 1$  and  $\alpha v\beta 3$  integrins, further expands its therapeutic potential by targeting the tumor microenvironment [161]. Given these multifaceted mechanisms, RK1 could serve as a foundational scaffold for developing novel anticancer therapeutics, either as a standalone agent or in combination with existing treatment modalities.

##### 4.4.3. Vmct1 from *Vaejovis Mexicanus*

Vmct1 is a 13-residue non-disulfide-bridged cationic peptide (NDBP) originally identified from the venom gland transcriptome of the scorpion *Vaejovis mexicanus*. With a net charge of +2, ~69% hydrophobicity, and an amphipathic  $\alpha$ -helical conformation, the native peptide exhibits antimicrobial activity but lacks significant anticancer effects. However, synthetic analogs of Vmct1 with lysine substitutions (Vmct1-K) were designed to enhance cationicity and bioactivity, resulting

in potent cytotoxicity against melanoma (B16-F10), breast (MCF-7), and cervical (HeLa) cancer cell lines ( $IC_{50}$ : 3.4 - 6.2  $\mu$ M), with minimal toxicity to non-tumoral VERO and red blood cells [34]. Mechanistic studies suggest a membrane-lytic mode of action. SEM images of Vmct1-K-treated cells revealed blebbing, wrinkling, and cell shrinkage, while increased propidium iodide uptake confirmed membrane disruption [34]. Together, these findings highlight Vmct1-K as a rationally optimized peptide with selective anticancer potential via direct membrane targeting.

#### 4.4.4. AcrAP1/AcrAP2 from *Androctonus Crassicauda*

AcrAP1 and AcrAP2 are non-disulfide bridged peptides (NDBPs) isolated from the venom of the Arabian scorpion *Androctonus crassicauda*, which exhibit selective antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* but exhibit no cytotoxic or antiproliferative effects on a panel of different human cancer cell lines. However, cationicity-enhanced analogues AcrAP1a and AcrAP2a, engineered by substituting polar residues with lysine, displayed significantly improved biological activity. These analogues exhibited potent antiproliferative effects against multiple human cancer cell lines, including lung adenocarcinoma (NCI-H460), breast carcinoma (MCF-7 and MDA-MB-435s), and prostate carcinoma (PC-3), with  $IC_{50}$  values ranging from 2.1 to 3.6  $\mu$ M. Interestingly enough, AcrAP1a also induced a paradoxical proliferative response in H460 and PC-3 cells at nanomolar concentrations, suggesting potential concentration-dependent dual effects that warrant further mechanistic investigation [33]. The enhanced anticancer activity of the analogues appears to correlate with their amphipathic  $\alpha$ -helical structures and increased net positive charge, promoting interactions with negatively charged components of cancer cell membranes. While direct evidence of membrane lysis was not provided, the observed cytotoxic effects are consistent with mechanisms reported for other cationic antimicrobial peptides. The rational design of AcrAP analogs achieved by substituting neutral residues with lysine, like Vmct1-K demonstrates how structural optimization can amplify anticancer effects while minimizing off-target toxicity [34]. In summary, these findings highlight the potential of venom-derived peptide templates for the rational design of anticancer agents. The structural optimization of AcrAP1/AcrAP2 into cationic analogues demonstrates a viable strategy to enhance bioactivity while maintaining selective toxicity, although concentration-dependent paradoxical effects underscore the need for thorough preclinical evaluation.

#### 4.4.5. Pantinins 1-3 from *Pandinus Imperator*

Pantinins 1-3 are a family of short, cysteine-free,  $\alpha$ -helical cationic peptides identified via cDNA cloning from the African scorpion *Pandinus imperator* venom gland transcripts. Their amphipathic helices underlie broad-spectrum antimicrobial activity, including potent effects against multidrug-resistant bacteria such as vancomycin-resistant *Enterococcus* strains (VRE) [68], which provides a rationale to explore their repurposing in oncology. Beyond their antibacterial profile, synthetic pantinin analogs have been shown to interact selectively with negatively charged membranes, producing membranolytic activity against human cancer cell lines while sparing erythrocytes, thus demonstrating low hemolytic potential [69].

This mode of action aligns with a growing class of anticancer antimicrobial peptides (AMPs) that exploit electrostatic differences in membrane lipid composition between malignant and healthy cells. While pantinins are  $\alpha$ -helical, their mechanism is conceptually parallel to that of engineered  $\beta$ -hairpin peptides such as SVS-1, which undergo membrane-induced folding into a cytotoxic conformation upon contact with tumor membranes [162]. Such comparisons highlight a broader principle: secondary structure plasticity, driven by the tumor microenvironment, underpins the selective cytotoxicity of many AMPs.

Recent reviews have highlighted the growing interest in antimicrobial peptides (AMPs) as dual-purpose agents with antimicrobial and anticancer potential [163]. Within this broader context, pantinins exemplify scorpion-derived AMPs that combine small size, a favorable safety profile, and well-defined helical structure, making them attractive scaffolds for further optimization. Strategies

such as enhancing cationicity or conjugating to delivery systems may improve their tumor specificity and therapeutic index.

#### 4.5. Multifunctional Peptides

##### 4.5.1. Chlorotoxin from *Leiurus Hebraeus* and Derivatives

Chlorotoxin (CTX) is a 36-amino acid peptide originally isolated and purified from the venom of *Leiurus hebraeus* (formerly *L. quinquestriatus hebraeus*) [164]. Structural analysis by NMR revealed a compact tertiary structure comprising an  $\alpha$ -helix packed against three antiparallel  $\beta$ -strands stabilized by four disulfide bonds, features that underlie its remarkable stability and high affinity for tumor cell membranes [165,166]. CTX selectively binds to gliomas and other neuroectodermal tumors, with negligible affinity for normal tissues [49,50,167,168], making it a valuable scaffold for tumor targeting.

Proteomics and mass spectrometry studies have been critical for defining CTX's molecular interactors. Affinity-column pull-downs combined with mass spectrometry further demonstrated that matrix metalloproteinase-2 (MMP-2) as a primary binding partner of CTX and revealed its association with a membrane complex containing MT1-MMP, TIMP-2, and  $\alpha v \beta 3$  integrin, implicating CTX in the modulation of pericellular proteolysis and adhesion [49,169]. These proteomic analyses reinforced earlier electrophysiology-based findings that CTX blocks glioma-enriched CIC-3 chloride channels involved in cell migration and cytoskeletal remodeling [170,171]. More recently, protein microarray profiling coupled with mass spectrometry validation identified cortactin, an actin-binding and Src kinase substrate linked to invasive cancers, as a novel CTX interactor, suggesting an additional mechanism for its anti-migratory effects and making it an important biomarker for invasive cancers [172]. Such mass spectrometry-based proteomics-driven discoveries have expanded the CTX interactome beyond MMP-2, CIC-3, and annexin A2, highlighting neuropilin-1 (NRP1) as another critical binding partner for tumor selectivity [173,174].

Recent proteomic surveys of Buthidae venoms have further contextualized chlorotoxin within the venom proteome. Using LC-MS/MS, Mabunda et al. (2025) identified chlorotoxin and CTX-like peptides as major cysteine-rich peptide families in *Leiurus hebraeus* venom. Importantly, integrative functional assays linked these CTX-containing fractions to cytotoxic and anti-migratory effects in glioma and melanoma cells, thereby bridging venom proteomics with cancer pharmacology. These findings reinforce the evolutionary conservation and therapeutic potential of CTX and highlight the value of advanced proteomics in connecting peptide abundance with functional anticancer activity [175].

Functional proteomic fragment mapping has shown that the C-terminal residues (29–36) of CTX retain partial activity, selectively inhibiting migration without fully blocking invasion [172]. This finding suggests that distinct CTX structural motifs may differentially regulate cytoskeletal versus proteolytic pathways. Internalization studies using live-cell imaging confirmed clathrin-mediated uptake of CTX derivatives [176], linking receptor binding with intracellular trafficking.

Building on these proteomics-driven insights, chlorotoxin has recently been incorporated into the design of chimeric antigen receptor (CAR) T cells. CLTX-CAR T cells employ the chlorotoxin peptide as a tumor recognition domain, redirecting T cell cytotoxicity against glioblastoma cells through MMP-2-associated binding. In a first-in-human Phase I clinical trial (NCT04214392), Barish et al. (2025) demonstrated the feasibility and safety of intracavitary administration of CLTX-CAR T cells in patients with recurrent glioblastoma. No dose-limiting toxicities or immunogenicity were observed, and three of four patients achieved transient stable disease with evidence of CAR T cell persistence and local cytokine induction in the tumor cavity. Although long-term clinical benefit remains to be established, this study represents the first clinical application of a venom-derived peptide as the targeting domain of a cellular immunotherapy and highlights the translational potential of CTX as a proteomics-validated tumor ligand [177].

From a translational perspective, synthetic CTX derivatives have been developed, notably TM-601, radiolabeled with iodine-131 ( $^{131}\text{I}$ -chlorotoxin), which demonstrated tumor-specific uptake and prolonged retention in Phase I/II clinical trials in malignant glioma [178–180]. Beyond therapy, proteomics-guided bioconjugates have supported CTX applications in diagnostics and imaging. BLZ-100 (Tumor Paint), a fluorescent CTX conjugate, enables intraoperative visualization of gliomas [181]. Nanotechnology-based delivery systems, such as CTX/mApoE-modified liposomes or MiniCTX shuttles, further enhance blood-brain barrier penetration and selective tumor targeting [182,183].

#### 4.5.2. Maurocalcine from *Scorpio Maurus Palmatus* and Related Peptides

Maurocalcine (MCA), a 33-amino acid peptide isolated from the venom of *Scorpio maurus palmatus*, exhibits dual functionality as a cell-penetrating peptide and a modulator of intracellular calcium signaling, with promising applications in oncology [63,184–186]. Structural analyses revealed three disulfide bonds and a cationic surface that facilitates membrane translocation, while its binding to ryanodine receptors (RyR1) triggers  $\text{Ca}^{2+}$  release from the endoplasmic reticulum [63,187]. Further studies have mapped its interaction with RyR1's cytoplasmic domain, identifying key residues, such as Lys20, critical for both receptor activation and cell penetration [63,66,188,189]. Interestingly enough, a short 9-amino acid derivative from MCA known as MCAUF1-9 showed very favorable cell-penetrating efficacy and may be used to specifically target cancer cells in vivo, due to its acidic pH that matches tumor acidic environments [190]. Moreover, MCA has been shown to overcome doxorubicin resistance in MDA-MB231 breast cancer cell line [64]. Another MCA derivative, Pt-1-DMCA, a platinum-maurocalcine conjugate, has been shown to induce apoptosis in human glioblastoma U87 cells through ROS-dependent modulation of the PI3K/AKT/OfoxO3a signaling pathway [65]. Furthermore, different studies have revealed novel applications for MCA in delivering therapeutic cargo to cancer cells [63,184–186,191]. Overall, MCA and its peptide derivatives' ability to efficiently cross cell membranes has made it an attractive candidate for drug delivery systems.

## 5. Cancer-Specific Targeting Mechanisms

### 5.1. Blood-Brain Barrier Penetration

The ability of certain scorpion venom components to cross the blood-brain barrier (BBB) has been extensively characterized, revealing unique structural and functional mechanisms that make them valuable for targeting brain cancers. Mass spectrometry-based proteomic studies and structural studies have identified specific post-translational modifications such as C-terminal amidation and disulfide bonds that enhance BBB penetration while preserving therapeutic efficacy [192–194].

Chlorotoxin, discussed in detail in Section 4.5.1, exemplifies a peptide capable of penetrating the blood-brain barrier and selectively targeting gliomas.

Mechanistically, venom peptides, such as the other CTX derivative MiniCTX3, exploit endogenous transport systems such as receptor-mediated transcytosis, to cross the BBB, as revealed through protein-protein interaction networks and surface plasmon resonance (SPR) assays [182]. Other peptides, including BmK components such as BmKCT from *Buthus martensii* modulate BBB permeability by downregulating tight junction proteins, enhancing drug delivery to brain tumors [27,44,195]. These insights have spurred the development of targeted delivery systems, such as CTX-conjugated nanoparticles, which enhance chemotherapeutic uptake in glioblastomas while minimizing off-target effects [47,196,197].

### 5.2. Molecular targeting Mechanisms

Scorpion venom peptides exhibit precise molecular targeting, disrupting key pathways in cancer cells. Several studies including proteomic analysis have revealed that these peptides interact with ion channels, matrix metalloproteinases, growth factor receptors, and integrins, leading to selective cytotoxicity.



### 5.2.1. Ion Channel Interactions

Many scorpion venom peptides exert anticancer effects by modulating ion channels. AGAP from *Buthus martensii* inhibits voltage-gated sodium channels (Nav1.4, Nav1.5, Nav1.7 and Nav1.8), which are overexpressed in breast, prostate, and colon cancers, disrupting tumor proliferation, inducing apoptosis, migration, and metastasis [29,35,98,198–200]. Chloride channels, particularly overexpressed in gliomas, are another key target. BotCl, a chlorotoxin-like peptide from *Buthus occitanus tunetanus*, selectively blocks ClC-3 chloride channels in glioblastoma and breast cancer, impairing migration [48]. In addition, CTX has also been described to target MMP-2 and ClC-3 on the surface of human glioma cells, inhibiting glioma cell invasion [49,164,169,171], as well as voltage-activated chloride channels in glioma cells that facilitate cell volume changes essential for migration and invasion [201].

Potassium channels are often found to be expressed differently in cancer cells compared to normal cells. Iberiotoxin (IbTX), derived from *Buthus tumulus*, targets Kv1.1 and Kv1.3 potassium channels, triggering calcium dysregulation and apoptosis in cervical and ovarian cancers [58].

### 5.2.2. Receptor-Mediated Effects

Scorpion venom components also act through receptor-mediated mechanisms. The tetrapeptide AaTs-1 from *Androctonus australis* antagonizes formyl-peptide receptor-like 1 (FRL-1) in glioblastoma, upregulating p53 while suppressing ERK/p38/JNK signaling [123]. Although the direct receptor target of BmK AGAP has not been identified, evidence suggests that it modulates receptor-associated signaling pathways. In breast cancer cells, BmK AGAP downregulates pentraxin-3 (PTX3), a molecule involved in receptor–ligand interactions within the tumor microenvironment. This leads to suppression of the NF- $\kappa$ B/Wnt/ $\beta$ -catenin axis, ultimately reducing stemness and epithelial–mesenchymal transition (EMT) [145]. Neopladines 1 and 2 from *Tityus discrepans* upregulate Fas ligand (FasL) in breast cancer cells, activating extrinsic apoptosis [67].

## 6. Immunomodulatory Effects

Scorpion venom contains a diverse array of bioactive peptides that can modulate both innate and adaptive immune responses. These peptides have been shown to influence immune cell function, including the repolarization of immune cells and the enhancement of antigen-specific responses.

### 6.1. Innate Immune Response Modulation

Proteomic analyses have revealed that scorpion venoms contain diverse proteins and peptides that modulate innate immune responses relevant to cancer. Several biochemical and mass spectrometry-based proteomic analyses have revealed that scorpion venom contains peptides and proteins with potential bioactive properties, including immunomodulatory effects, which can influence innate immune cells. Cota-Arce and colleagues have identified several proteins derived from the *Centruroides limpidus* venom, including neurotoxins, metalloproteases, phospholipases, hyaluronidases, and antimicrobial peptides. Among them, fractions CIF8 and CIF9 were able to induce the anti-inflammatory IL-10 while suppressing the pro-inflammatory IFN- $\gamma$  in CD4<sup>+</sup> T cells via Ca<sup>2+</sup> channel modulation [202]. Moreover, they trigger innate immune crosstalk by activating macrophages and dendritic cells, evidenced by elevated IL-12 and TNF- $\alpha$  in co-cultures. IL-10 suppression could counteract tumor-associated immunosuppression, while Ca<sup>2+</sup> channel-targeting toxins may disrupt cancer cell signaling [202]. Overall, this study demonstrated that these venom-derived proteins can shift the immune response toward Th1, Th2, or Th17 profiles, indicating their potential as modulators of T cell-mediated immunity that may be able to further explore their role in immune regulation relevant to cancer immunotherapy.

Another venom component, the peptide Css54 isolated from *Centruroides suffusus suffusus* has demonstrated significant immunomodulatory effects. Css54 enhances macrophage phagocytic activity while reshaping cytokine production. It suppresses IL-6, increases the anti-inflammatory IL-10, and modestly elevates IL-12p70 and TNF- $\alpha$ , with minimal impact on IFN- $\gamma$ . This balanced



immunomodulation suggests an ability to promote antimicrobial defense while dampening excessive inflammation [203]. These results position Css54 as a dual-function peptide with potential therapeutic applications in infection control and immune regulation, and they further raise the prospect of exploiting Css54 to modulate the tumor microenvironment by reinforcing innate immune mechanisms while preventing chronic inflammation.

The venom's ability to modulate toll-like receptor (TLR) signaling pathways is particularly noteworthy for its potential initial immune response against cancer cells. The peptide Ts1 isolated from *Tityus serrulatus* venom activates TLR2, TLR4, and CD14 on macrophages. This triggers MyD88-dependent NF- $\kappa$ B activation and TLR4-dependent, MyD88-independent c-Jun activation, as well as engagement of the ERK1/2 and p38 MAPK pathways, culminating in the release of TNF- $\alpha$  and IL-6 [204].

Venom-induced immune modulation has emerged as an important mechanism with potential application in cancer therapy. Several studies demonstrate that scorpion venoms can regulate macrophage polarization, shifting cells between pro-tumorigenic M2 and anti-tumorigenic M1 phenotypes [205]. Venom from *Heteroctenus junceus* (previously known as *Rhopalurus junceus*) was shown to modulate pro-inflammatory cytokine production in F3II mouse mammary tumor cells, significantly reducing IL-6 and IL-1 $\beta$  while elevating TNF- $\alpha$  and IL-12, consistent with interference in the NF- $\kappa$ B pathway [206]. Oral administration of *H. junceus* venom in F3II tumor-bearing mice suppressed tumor growth and decreased serum TNF- $\alpha$  levels, indicating systemic immunomodulation [207]. These dual effects on cytokine regulation suggest that venom-derived molecules may repolarize tumor-associated macrophages from an M2- to an M1-like state, thereby reprogramming the tumor microenvironment toward an anti-tumor phenotype. Supporting this concept, studies with *T. serrulatus* venom show that macrophage responses are mediated by TLR2/TLR4/CD14 recognition, engaging NF- $\kappa$ B-linked pathways, which can be negatively modulated by PPAR- $\gamma$  activity [204,208]. Collectively, these findings highlight scorpion venom as a source of immunomodulatory peptides with the potential to enhance antitumor immunity through macrophage reprogramming.

In another study, the toxic fraction FTox-G50 from *Androctonus australis hector* venom promoted M1 macrophage polarization in adipose tissue, increasing nitric oxide NO production and upregulating IL-12p40, IL-23, and NOS2 while suppressing M2 markers Arg1 and IL-10, in a TNF- $\alpha$ -dependent manner [209].

This modulation of innate immunity shows potential in cancer treatment, as it can help overcome the immunosuppressive tumor microenvironment and promote anti-tumor responses without causing systemic toxicity.

## 6.2. Adaptive Immunity Enhancement

The impact of scorpion venom on adaptive immunity has emerged as a crucial area of investigation in cancer immunotherapy.

Notably, scorpion venom can act as an adjuvant, promoting Th1-type adaptive immunity and increasing antibody avidity, which may improve the neutralizing capacity of antibodies against systemic threats. For example, the scorpion venom from *Hottentotta rugiscutis* exhibits adjuvant properties by enhancing adaptive immunity, specifically promoting HBsAg-specific Th1 responses and increasing antibody avidity, which may improve neutralizing capacity against pathogens. This effect is mediated through neuroendocrine-immune interactions, including upregulation of nerve growth factor (NGF) and corticosterone (CORT), leading to activation of splenocytes and sustained IL-1 $\beta$  production (Santhosh et al., 2022).

Conversely, certain scorpion venom peptides selectively suppress pathogenic effector memory T lymphocytes by blocking Kv 1.3 potassium channels. For instance, HsTX1 from *Heterometrus spinifer* is a potent Kv1.3 inhibitor (IC<sub>50</sub>  $\approx$  12 pM) [56]. Likewise, Vm24 from *Vaejovis mexicanus smithi* exhibits extremely high specificity and affinity for Kv1.3 (K<sub>d</sub>  $\approx$  2.9 pM,  $\sim$ 1500-fold selectivity),

attenuating human CD4<sup>+</sup> T<sub>EM</sub> cell activation, cytokine production, and proliferation upon stimulation [79,211,212].

Recent studies identified Cm28, a peptide from *Centruroides margaritatus*, as a high-affinity inhibitor of Kv1.2 and Kv1.3 channels. In human CD4<sup>+</sup> effector memory T cells, Cm28 suppressed activation markers such as IL-2R (CD25) and CD40L, underscoring its potential as an immunomodulatory agent [51].

This mechanism, classically explored in autoimmunity, may also be exploited in cancer, where Kv1.3 contributes to shaping the tumor-immune interface. In head and neck cancer, Kv1.3<sup>high</sup> CD8<sup>+</sup> tumor-infiltrating lymphocytes have been identified as functionally competent effectors [213]. Supporting this rationale, margatoxin (MgTx), another Kv1.3 inhibitor from *C. margaritatus*, has demonstrated both in vitro and in vivo efficacy against A549 human lung adenocarcinoma, where it suppressed tumor cell proliferation, modulated cell-cycle regulators, and significantly reduced tumor growth in xenograft models [62]. These findings suggest that Kv1.3 inhibition may reprogram immune responses within the tumor microenvironment, potentially reducing Treg activity while preserving cytotoxic T-cell function.

Beyond Kv1.3-targeting peptides, other venom-derived molecules contribute to adaptive immune modulation. For example, peptides AK and GK from *Buthus martensii* suppress TNF- $\alpha$ /EGFR/STAT3 signaling pathway, downregulating pro-inflammatory cytokines such as TNF- $\alpha$  and oncogenic drivers such as c-Myc while upregulating tumor suppressors (p53/PTEN). In gastric cancer models, these effects may help reverse immune evasion and restore antitumor immunity [214]. Collectively, these mechanisms underscore the potential of scorpion venom peptides to act either as immune adjuvants or as selective immunomodulators, thereby broadening their applicability in cancer immunotherapy.

### 6.3. Cytokine Profile Alterations

The manipulation of cytokine profiles by scorpion venom components represents a significant breakthrough in understanding their therapeutic potential. Different scorpion venoms are able to modulate cytokine networks through specific toxins, influencing both pro- and anti-inflammatory responses. FTox-G50 from *Androctonus australis* hector was shown to polarize adipose tissue macrophages (ATMs) toward an M1 phenotype, characterized by upregulated IL-12p40, IL-23, and NOS2 (iNOS) expression, while suppressing M2 markers such as Arginase-1 (Arg1) and IL-10. This shift is TNF- $\alpha$ -dependent, as demonstrated by the reversal of M1 gene expression upon etanercept (TNF- $\alpha$  antagonist) treatment [209]. Similarly, *T. serrulatus* venom (TsV) triggers systemic release of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IFN- $\gamma$  in severe envenomation cases [215]. In contrast, *Leiurus macroctenus* venom exhibits an atypical immunomodulatory profile, reducing pro-inflammatory cytokines (IL-6, IL-8, IL-1 $\beta$ ) while elevating anti-inflammatory IL-4, IL-10, and IFN- $\gamma$  in rat lungs, suggesting species-specific immune reprogramming [216]. The antimicrobial peptides BmKn1, BmKn2, and BmKn2-7 from *Mesobuthus martensii* further illustrate this duality, dampening TNF- $\alpha$  and IL-1 $\beta$  in *Litopenaeus vannamei* shrimp infected with *Vibrio parahaemolyticus*, while enhancing immune enzymes like phenoloxidase and complement component C3 [217]. Proteomic analyses of *Hottentotta saulcyi* venom reveal additional complexity, notably the dominance of Na<sup>+</sup>- and K<sup>+</sup>-channel-targeting peptides, as well as a substantial lipid component (~1.2% dry weight), characterized via LC-MS/MS [52].

These findings underscore the potential of venom components to recalibrate immune responses, though their clinical translation requires further exploration of dose-dependent effects and signaling pathways.

### 6.4. Immune Cell Activation and Regulation

Scorpion venom components selectively target immune cells, influencing their activation and functional polarization. For example, the TzII and TzIII fractions of *Tityus zulianus* venom selectively activate human neutrophils, inducing PKC-dependent ROS production, an effect blocked by PKC inhibition [218]. Mass spectrometry has proven indispensable in characterizing such fractions: recent

MALDI-TOF and LC-MS/MS analyses revealed that specific peptide components remain non-neutralized after antivenom interaction, as shown in *Odonthobuthus doriae* venom [219]. These findings underscore that non-neutralized low-molecular-weight peptides may persist and retain biological activity, providing a molecular basis for their selective engagement with neutrophil membranes. However, this effect is cell-type-specific, as eosinophils show negligible respiratory burst compared to neutrophils, reflecting distinct localization and regulatory mechanisms of the NADPH oxidase complex [114]. In macrophages, the  $\beta$ -toxin Ts1, also known as Ts $\gamma$ , from *T. serrulatus* venom, is recognized by TLR2, TLR4, and CD14, leading to MyD88-dependent NF- $\kappa$ B activation and triggering the release of IL-6, TNF- $\alpha$ , and nitric oxide (NO) [204,220]. Ts1 has been previously sequenced as a 61-amino-acid  $\beta$ -toxin, confirming its identity and structural class [221]. Conversely, Meuk7-3 from *Mesobuthus eupeus* suppresses effector memory T cells by blocking Kv1.3 channels, a strategy relevant for autoimmune diseases [222]. The Scorpine peptide from *Pandinus imperator* exemplifies dual functionality, activating phagocytes while exhibiting antimicrobial properties, though its precise immune targets remain under investigation [223]. Proteomic gaps persist for several scorpion venoms, including *Androctonus crassicauda*, despite its medical importance and demonstrated biological activities. These studies highlight the potential of venom-derived peptides to modulate immune cell function, with implications for treating inflammatory disorders and cancer.

#### 6.5. Potential for Immunotherapy Enhancement

Scorpion venom peptides offer promising avenues for cancer immunotherapy by targeting hallmarks of malignancy. Chlorotoxin (CTX) from *Leiurus hebraeus* binds glioma-specific chloride channels and MMP-2, inhibiting metastasis and enhancing blood-brain barrier penetration for drug delivery [49,146]. Its 4 kDa structure, confirmed by MALDI-TOF MS, underpins its clinical use in tumor imaging, such as CTX-Cy5.5 for fluorescence-guided surgery [44,49]. Similarly, BmK-AGAP from *Buthus martensii* Karsch exhibits analogous antitumor and immunomodulatory activities, though its characterization extends beyond RP-HPLC to include genomic and functional analyses (Y. Zhang et al., 2025).

The Kv1.3 blockers, such as Meuk7-3 from *Mesobuthus eupeus*, demonstrate translational potential by suppressing autoreactive T cells in autoimmune diseases, with MALDI-TOF and structural modeling confirming their ion channel-targeting motifs [222].

*Androctonus crassicauda* venom and its peptides further expand this repertoire, inducing apoptosis and cell-cycle arrest in MCF-7 cells, with caspase-3 involvement; transcriptomic and proteomic studies of *A. crassicauda* venom glands detail the underlying peptide diversity [33,117,122,224-227].

Challenges include scalable production, addressed via heterologous expression in *Escherichia coli*, and precise immune modulation to increase bioactivity capabilities and avoid cytokine storms (Y. Zhang et al., 2025).

Together, these components highlight the dual utility of venom peptides: as direct cytotoxic agents and as immune modulators to enhance checkpoint inhibitor therapies.

## 7. Diagnostic Applications

Scorpion venom-derived peptides have emerged as innovative tools for tumor marking and imaging, owing to their high affinity for cancer-specific targets. Among them, chlorotoxin (CTX) has been extensively studied as a tumor-targeting agent due to its ability to selectively bind glioma and other tumor cells. Building on this specificity, synthetic derivatives such as BLZ-100 (tozuleristide, Tumor Paint) have been developed by conjugating CTX to fluorescent dyes, enabling real-time intraoperative visualization of tumor margins.

Preclinical studies demonstrated that CTX-based probes selectively label glioma, medulloblastoma, sarcoma, prostate, and colorectal tumors in mouse models, with near-infrared fluorophores offering optimal intraoperative imaging [197,228]. Comparative oncology trials in dogs

confirmed safety and effective tumor visualization [229], highlighting the translational value of this approach [230]. Toxicology studies in multiple species, including rodents, dogs, and non-human primates, further established a favorable safety profile [231].

In humans, BLZ-100 has progressed to Phase 2/3 trials for pediatric central nervous system tumors, demonstrating safe administration and improved surgical precision through fluorescence-guided resection. Beyond gliomas, BLZ-100 has shown promise in identifying other lesions, such as cerebral vascular malformations [232], as well as non-melanoma skin cancers and melanoma, where it achieved accurate tumor imaging at clinically feasible doses [233]. These results underscore the potential of CTX-based probes to improve tumor visualization across diverse cancer types while maintaining low systemic toxicity.

### 7.1. Early Detection Methods

For early detection of *Hottentotta tamulus* (syn. *Mesobuthus tamulus*) envenomation, mass spectrometry-based proteomics was able to identify a rich repertoire of low-molecular-mass toxins, particularly Na<sup>+</sup> and K<sup>+</sup> ion-channel toxins that comprise a majority of the venom proteome [234]. To improve detection sensitivity in plasma, acetonitrile precipitation has been used to enrich these low-abundance peptides while simultaneously depleting high-molecular-weight plasma proteins, thereby facilitating their identification by mass spectrometry [235,236].

Although the direct application of gold nanoparticle (AuNP)–antibody conjugates and localized surface plasmon resonance (LSPR) biosensors to scorpion venom toxins has not yet been reported, AuNP-based platforms are well established in clinical diagnostics for providing rapid (often <10 min) colorimetric readouts and picomolar sensitivity for diverse biomolecules [237–239]. This suggests that similar systems could, in principle, be adapted for the ultrasensitive detection of scorpion venom peptides in envenomed patients. Such an approach would not only accelerate diagnosis in clinical settings but also establish a foundation for broader applications in oncology and precision medicine.

The specificity of venom peptide recognition, exemplified by Tamapin, a K<sup>+</sup> channel toxin targeting SK2 [240], and  $\alpha$ -neurotoxins acting on Na<sup>+</sup> channels, underscores the potential of scorpion toxins as molecular probes. In oncology, chlorotoxin from *Leiurus hebraeus* provides a precedent: it binds selectively to tumor-associated receptors such as MMP-2 in gliomas and has been widely employed in tumor-targeting bioconjugates for both imaging and therapeutic applications (Deshane et al., 2003).

Beyond diagnostics, this dual-use paradigm offers therapeutic opportunities. Kv10.1 (Eag1), a voltage-gated K<sup>+</sup> channel aberrantly expressed in many cancers, represents a validated pharmacological target [241–243]. Conjugation of venom-derived peptides such as chlorotoxin or venom-derived cell-penetrating peptides (CPPs) to nanocarriers—including AuNPs, chitosan, polyethylene glycol (PEG), and polyethylenimine (PEI)—has been shown to improve tumor-selective delivery and anti-tumor efficacy while minimizing off-target effects [244–246]. By bridging diagnostics and therapy, this translational framework highlights the untapped potential of scorpion venom peptides in oncology and points toward their integration into next-generation precision medicine [235].

### 7.2. Biomarker Development

In biomarker discovery, untargeted UHPLC-QTOF-MS metabolomic profiling of hepatocellular carcinoma (HCC)-bearing mice treated with scorpion venom peptide extract (PESV) from *Buthus martensii* revealed 111 significantly altered serum metabolites (48 in negative ion mode, 63 in positive ion mode), highlighting major disruptions in pathways such as aminoacyl-tRNA biosynthesis, amino acid metabolism, glutathione metabolism, protein transport, protein digestion and absorption, and cAMP signaling [247]. These findings position PESV-induced metabolic signatures as potential diagnostic and therapeutic biomarkers in HCC. The observed pathway-level perturbations suggest that scorpion venom peptides could modulate key metabolic networks relevant to tumor progression and therapy. Future studies should clarify whether these shifts intersect with known cancer-related



mechanisms, including immune evasion, nitrogen metabolism, or drug resistance. Bridging these metabolomic insights with venom peptide pharmacology may open avenues for developing venom-based diagnostics and therapeutic strategies in precision oncology.

### 7.3. Therapeutic Monitoring

The neurotoxic properties of *Odontobuthus doriae* venom, which disrupts ion channels and neurotransmitter activity, also make it a promising candidate for diagnostic applications. Recent advances in plasmonic biosensing technology have enabled the detection of venom-induced neurotoxicity in human serum through circular dichroism (CD) measurements. By employing an achiral gold-coated plasmonic nanostructure, researchers demonstrated that minute changes in venom concentration alter the Stern layer's action potential, shifting the sensor's refractive index and producing measurable CD responses. This method achieved high sensitivity (27.4 at 520 nm) and rapid detection, offering a potential tool for diagnosing envenomation or monitoring venom-derived therapeutics. Such biosensors could be adapted to detect cancer-specific biomarkers, leveraging venom components' selective binding properties to improve early diagnosis and personalized treatment strategies [248].

### 7.4. Integration with Current Diagnostic Tools

Integration with current diagnostic tools further expands the clinical potential of venom-based agents. For instance, chlorotoxin (CTX) has been combined with MRI and near-infrared fluorescence in preclinical studies for glioblastoma detection [49,249,250]. In addition, CTX-drug conjugates such as CTX-onconase have shown increased antitumor efficacy in glioma models compared to unconjugated mixtures [251], while CTX-decorated liposomal nanoparticles have effectively delivered siRNA or antisense oligonucleotides to glioblastoma cells in vitro and in vivo [252]. Despite these promising results, challenges remain in translating these approaches into routine clinical use, particularly regarding standardization, scalability, and regulatory approval. Nonetheless, the high specificity of CTX for tumor cells, its modular platform design, and its blood-brain-barrier permeability position it as a valuable adjunct to conventional diagnostic and therapeutic strategies for glioblastoma and related malignancies.

## 8. Drug Development and Delivery Systems

### 8.1. Peptide Modification Strategies

The development of peptide modification strategies for scorpion venom components represents a critical advancement in cancer drug development. Mass spectrometry analysis has identified key modification sites, such as disulfide bridges in chlorotoxin (CTX), which enhance structural stability and target specificity for glioma cells [253,254]. The PEGylation of CTX demonstrated that PEG-CTX conjugates significantly improved tumor-targeting efficiency, as evidenced by an 8-fold increase in glioma accumulation compared to unmodified CTX when delivered via polyamidoamine (PAMAM) dendrimer nanoparticles [255]. This modification not only enhanced systemic circulation but also preserved CTX's binding affinity to matrix metalloproteinase-2 (MMP-2), a receptor overexpressed in gliomas, enabling precise intracellular delivery of therapeutic genes such as TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) [255].

Moreover, recent studies with *Tityus stigmurus* venom-derived peptides demonstrate that PEGylation strategies can be extended to other venom components for cancer applications, as evidenced by PLA-PEG encapsulation of Stigmurin analogs (S1 and S2), which reduced hemolysis by 20% while maintaining antiproliferative activity against macrophage-like RAW264.7 cancer cells, highlighting the dual benefit of improved safety and retained bioactivity in venom-based nanotherapeutics [256].

Cyclization of BmK peptides from *Buthus martensii* has been shown to enhance their therapeutic potential. In the case of Buthicyclin, a cyclic peptide derived from Defensin 4 (BmKDfsin4), the



introduction of a disulfide bond between terminal cysteine residues improved structural stability and prolonged serum half-life [257]. The peptide's high binding affinity to opioid receptors (Mu/Kappa/Delta types) and low toxicity profile (LD50 > 20 mg/kg, <5% hemolysis at 4 mg/mL) suggests its scaffold could be repurposed for targeting cancer-associated receptors, such as opioid growth factor receptor (OGFR), which is implicated in tumor proliferation and metastasis [257].

### 8.2. Nanoparticle-Based Delivery

Nanoparticle delivery systems have revolutionized venom peptide therapeutics by addressing challenges such as rapid degradation and poor tissue penetration while improving controlled release, stability, and cellular uptake, all with reduced toxicity [258]. Gold nanoparticles, for instance, have shown promise in cancer treatment due to their ability to be co-functionalized with targeting ligands like peptides and stabilizing agents such as polyethylene glycol (PEG), enhancing cellular uptake while maintaining stability under physiological conditions [244–246]. This approach reduces non-specific protein adsorption and immune clearance, positioning gold nanoparticles as promising candidates for targeted drug delivery and imaging in oncology [259].

The anticancer potential of scorpion venom has been further demonstrated through liposomal encapsulation of venoms from *Androctonus bicolor*, *Androctonus crassicauda*, and *Leiurus quinquestriatus*, which significantly enhances their anti-cancer efficacy against colorectal cancer cells (HCT-8). Venom-loaded liposomes exhibited superior stability, controlled release, and increased cytotoxicity compared to free venoms, as evidenced by reduced cell viability, elevated reactive oxygen species (ROS) generation, and induction of apoptosis and cell cycle arrest at the G0/G1 phase. This nano-delivery system not only improved the therapeutic index of the venoms but also minimized non-specific toxicity, underscoring its potential as a targeted and efficient strategy for cancer therapy [28].

Chitosan nanoparticles (CN) have emerged as another promising platform for venom-based cancer therapies. For example, CN enhanced antimicrobial activity of *Tityus stigmurus* venom (Tsv) through high encapsulation efficiency (>78%), stability, and controlled release, with a small particle size (<180 nm) and positive charge (+23 to +28 mV) that improves cellular interactions [260]. Similarly, Rebbouh et al (2020) demonstrated the efficacy of CN in detoxifying and delivering the neurotoxin Aah II from *Androctonus australis hector* venom. The nanoparticles achieved 96.66% encapsulation efficiency and a biphasic release profile (55% within 8 hours and 80% over 5 days), significantly reducing toxicity while enhancing immunogenicity. Immunized mice survived lethal toxin doses (up to 8 LD50), highlighting the potential of CN for venom-based therapies [261].

These properties are particularly advantageous for antitumor applications, as chitosan's biocompatibility and mucoadhesive nature can enhance tumor targeting and retention. By encapsulating venom peptides with known anticancer properties, CN could enhance therapeutic efficacy while minimizing systemic toxicity. Such an approach leverages the dual benefits of detoxification and controlled delivery, offering a promising strategy for developing targeted cancer therapies.

### 8.3. Targeted Delivery Systems

Targeted delivery systems have been refined through different experimental insights. For example, chlorotoxin CTX-conjugated iron oxide nanoparticles displayed significantly enhanced internalization in glioma cells, with approximately 50% higher uptake in C6 glioma cells compared to untargeted nanoparticles, supporting their role in improving tumor-specific delivery [262]. Beyond demonstrating selective binding and uptake, such systems also open opportunities for integration with proteomic strategies to profile nanoparticle-cell surface protein interactions, enabling a deeper understanding of receptor landscapes that mediate efficiency and refining future venom-based nanocarriers [263].

A particularly relevant innovation has been the development of dual-targeting systems designed to overcome both the blood–brain barrier (BBB) and the tumor microenvironment. In this context,

Yue and colleagues engineered PEGylated liposomes conjugated with OX26, an antibody against the transferrin receptor, together with CTX, thereby coupling BBB transcytosis with glioma-specific targeting [264]. The dual-targeting lipoplexes successfully transported therapeutic plasmid DNA across the BBB in vitro and in vivo, decreased C6 glioma cell viability to nearly 46% in a co-culture BBB model, and achieved marked tumor reduction and prolonged median survival (46 days versus 13 days in controls) in rat glioma models. Histopathological and immunohistochemical analyses confirmed that the therapeutic effect was mediated by targeted hTERTC27 gene expression within the tumor site, underscoring the complementary roles of OX26 in mediating BBB transport and CTX in conferring tumor selectivity [264].

Collectively, these findings illustrate how venom-derived ligands such as CTX can be integrated into multifunctional delivery platforms to improve targeting precision and therapeutic efficacy. The combination of proteomic insights into receptor expression with rational design of dual-targeted nanocarriers may pave the way for next-generation scorpion venom-based therapeutics capable of addressing both systemic delivery challenges and the heterogeneity of tumor microenvironments.

## 9. Clinical Studies and Trials

### 9.1. Preclinical Studies

Extensive preclinical research has laid a robust foundation for the clinical translation of scorpion-venom-derived peptides. Venomics analysis combining transcriptomics and proteomics, has catalogued venom constituents with high resolution, allowing the identification of chlorotoxin (CTX)-like peptides with anticancer potential. Early venomic efforts provided the essential sequence-level starting points for functional studies [167,265]. Biochemical and structural analyses subsequently mapped CTX mechanisms of action, revealing direct interactions with tumor-associated membrane proteins, such as MMP-2 and NRP1. These interactions clarified the mechanism of cellular uptake and CTX retention within glioma models [49,174].

In vivo studies in rodents and other models reinforced these findings by demonstrating selective tumor binding, effective intratumoral localization, and pronounced antitumor activity of CTX-based agents [168,174]. Imaging-enabled preclinical studies with radiolabeled or fluorescent CTX conjugates tracked biodistribution and tumor localization in real time, thereby visually substantiating CTX's tumor-targeting capabilities [50,266]. These cumulative preclinical data collectively supported first-in-human testing of CTX-derived agents [52,174], providing the rationale for translation into early-phase clinical trials.

Another significant preclinical development in this domain is the discovery and characterization of the peptide Gonearrestide, an anticancer peptide derived from the Moroccan fat-tail *Androctonus mauretanicus* scorpion venom. This peptide was identified using an integrated high-throughput platform combining next-generation transcriptome sequencing (NGS) and MS/MS proteomic analysis, which enabled the screening of over 200 novel peptides and rational functional selection [54]. Gonearrestide showed potent in vitro activity, inducing G1 cell-cycle arrest and inhibiting proliferation in human colorectal cancer cells. Mechanistically, it inhibited cyclin-dependent kinase 4 (CDK4) while upregulating key cell-cycle regulators p21, p27, and cyclin D3. Its antitumor activity extended to in vivo xenograft mouse models, confirming potent reduction of tumor growth, with minimal toxicity toward noncancerous epithelial cells and erythrocytes [54]. Systematic reviews further acknowledge Gonearrestide as a leading example of venom-derived peptides with translational potential [26].

Collectively, these investigations highlight how the synergy of molecular venomics, proteomic mapping, and imaging technologies accelerates bench-to-bedside development of scorpion venom-derived peptides. This multidisciplinary approach has not only identified promising excipient peptides such as CTX and Gonearrestide but also elucidated their mechanisms of action, helping bridge molecular discovery with early-phase clinical exploration.

9.2. Clinical Trials

Phase I clinical evaluation of scorpion venom-derived compounds has marked an important step toward their translation into oncology. Among these, chlorotoxin (CTX)-based constructs are the most extensively studied, with two agents: TM-601 and BLZ-100 (Tozuleristide), advancing into first-in-human clinical trials. These compounds were initially designed to assess safety, pharmacokinetics, and tumor-targeting or intraoperative imaging capabilities, and they represent distinct but complementary applications of venom peptides in oncology (Table 2).

9.2.1. TM-601 (<sup>131</sup>I-chlorotoxin conjugate)

TM-601 is a synthetic chlorotoxin analog radiolabeled with iodine-131 (<sup>131</sup>I), for targeted radionuclide delivery to gliomas. In a Phase I single-dose, open-label trial, 18 adult patients with recurrent high-grade gliomas received intracavitary administration of <sup>131</sup>I-TM-601 following tumor resection [179]. The compound showed selective tumor uptake and prolonged intracavitary retention for up to 14 days, with minimal systemic distribution and rapid clearance of non-bound peptide within 24 to 48 hours. Importantly, the therapy was well tolerated, and no dose-limiting toxicities were reported. Clinical outcomes were encouraging at 180 days post-treatment, several patients exhibited stable disease or partial radiographic responses, and two remained without evidence of disease for more than 30 months [179]. These findings confirmed the safety and tumor-targeting specificity of <sup>131</sup>I-TM-601, providing the basis for subsequent multicenter Phase II studies that further validated its tolerability and suggested signals of tumor control in subsets of patients [173].

9.2.2. BLZ-100 (Tozuleristide, “Tumor Paint”)

BLZ-100, also known as tozuleristide or “Tumor Paint,” represents a diagnostic and surgical innovation derived from chlorotoxin. It consists of chlorotoxin conjugated to a near-infrared fluorophore, enabling real-time intraoperative visualization of tumors [228]. In a Phase I dose-escalation trial in adults with newly diagnosed or recurrent gliomas, BLZ-100 demonstrated a favorable pharmacokinetic profile, absence of dose-limiting toxicities, and robust tumor-specific fluorescence that facilitated surgical delineation of tumor margins [181]. Beyond gliomas, early-phase evaluations have extended its application to breast carcinoma, neck squamous cell carcinoma, cutaneous malignancies, and cerebral vascular malformations, where it has similarly provided intraoperative contrast and improved visualization of neoplastic and malformed tissue [232,233,267,268].

Taken together, these first-in-human studies illustrate the translational trajectory of scorpion venom-derived peptides from preclinical discovery to clinical application. TM-601 highlights the potential of chlorotoxin analogs for selective delivery of therapeutic radionuclides to malignant gliomas, while BLZ-100 demonstrates their utility as tumor-targeted imaging agents capable of enhancing surgical precision. Both exemplify how venomomic and proteomic research can yield clinically valuable innovations at the interface of targeted therapy and image-guided oncology.

**Table 2.** Clinical trials of scorpion venom-derived compounds.

Compound Name	Trial Phase	Condition	Key Findings	Status
Chlorotoxin (CITx) / TM-601	Phase I/II	Recurrent high-grade glioma (glioblastoma, anaplastic astrocytoma)	Selective tumor binding; safe intratumoral use; prolonged tumor retention; limited systemic toxicity	Completed Phase I/II; discontinued for glioma therapy, redirected to imaging and drug-delivery applications
BLZ-100 (Tumor Paint, Tozuleristide, Chlorotoxin-ICG conjugate)	Phase I/II	Pediatric and adult brain tumors, breast cancer, sarcoma	Enabled real-time intraoperative tumor visualization; improved surgical margin delineation; well tolerated	Ongoing Phase II (pediatric brain tumors, solid tumors); active in translational oncology
Chlorotoxin–nanoparticle conjugates	Preclinical / Translational	Glioblastoma, metastatic tumors	Enhanced blood–brain barrier penetration; targeted imaging and therapeutic delivery in animal models	Preclinical; advancing toward first-in-human evaluation
Other venom-derived peptides (Bmk peptides, Bengalin, Neopladines, Maurocalcine)	Preclinical	Leukemia, breast cancer, glioblastoma, colon carcinoma	Demonstrated apoptosis induction, cell cycle arrest, and tumor inhibition in vitro and xenograft models; low toxicity to normal cells	Preclinical only; not yet in clinical trials

10. Current Challenges and Future Directions

10.1. Production and Scale-up Issues

The production and scale-up of scorpion venom–derived therapeutics remain major challenges in their development as anticancer agents. The structural complexity of venom peptides, particularly their disulfide-rich scaffolds, makes large-scale synthesis and recombinant expression technically demanding. Recombinant systems, including bacterial, yeast, and insect cell hosts, have been explored to produce bioactive peptides, although maintaining proper folding and disulfide connectivity is a persistent obstacle [27,136]. Mass spectrometry and proteomic analyses have been essential for characterizing venom components and verifying recombinant products, confirming sequence integrity, disulfide patterns, and post-translational modifications. These analytical approaches support quality control and help ensure batch-to-batch consistency. However, true large-scale manufacturing remains difficult, and further advances in expression technologies, folding strategies, and purification methods are required before venom-derived peptides can be produced reliably for widespread clinical use.

10.2. Regulatory Considerations

The regulatory development of scorpion venom–derived therapeutics presents unique challenges, particularly related to product characterization, manufacturing consistency, and safety evaluation. The structural complexity of venom peptides, including their disulfide-rich scaffolds and post-translational modifications, necessitates sophisticated analytical methods to meet regulatory standards. Mass spectrometry and proteomic approaches have been valuable in supporting early-stage product characterization by providing detailed molecular fingerprints, verifying disulfide connectivity, and assessing purity. These analyses contribute to quality control and the establishment of critical quality attributes, which are central to regulatory submissions [27,136]. However, the integration of proteomic tools into regulatory processes for venom-derived therapeutics remains largely preclinical and supportive, rather than being mandated for safety monitoring or biomarker validation. Future regulatory pathways may benefit from standardized and validated proteomic methodologies; however, conventional analytical chemistry and pharmacology approaches currently remain the backbone of regulatory compliance.

10.3. Cost and Accessibility

The production and scale-up of scorpion venom–derived therapeutics face substantial hurdles that stem from the structural complexity and heterogeneity of venom peptides, many of which are disulfide-rich and require precise folding and post-translational features to retain activity. As a result, development programs increasingly favor synthetic or recombinant routes over direct venom

extraction, but these approaches introduce manufacturing challenges in expression, folding, and downstream purification. Proteomics-driven venomomics-centered on high-resolution LC-MS/MS has become indispensable for defining critical quality attributes (identity, purity, isoform composition, and stability) and for establishing batch comparability, thereby informing process optimization and release testing. These analytical requirements, together with the need for controlled production of correctly folded peptides, contribute to the overall complexity and cost of goods, and they help explain why only a few scorpion-toxin candidates (e.g., chlorotoxin derivatives) have advanced clinically while no scorpion-venom drug has yet reached the market. Current literature highlights these scientific and technological bottlenecks and points to ongoing advances in recombinant expression, folding strategies, and high-throughput venomomics as levers to improve manufacturability and scalability, though further optimization and standardization will be needed before routine, cost-efficient production is achieved [26,269–271].

#### 10.4. Research Gaps

Comprehensive venomomics has clarified that major knowledge gaps still limit the development of scorpion venom-derived therapeutics for cancer. Large portions of the venom peptidome remain insufficiently characterized across species, with unresolved questions about isoform diversity, post-translational modifications, and their impact on stability and bioactivity [80,86,175,193,219,272–277]. Proteomics and transcriptomics have mapped candidate toxins and hinted at complex mechanisms, yet for lead bioactive peptides such as chlorotoxin, target engagement and downstream pathways remain debated, underscoring the need for rigorous mechanism-of-action studies in relevant cancer models and microenvironments [49,169,278–280]. Furthermore, translational gaps persist: there are no validated proteomic biomarkers for patient selection, pharmacodynamic readouts, or resistance monitoring in clinical settings, reflecting the absence of efficacy-focused trials to generate such data. While [<sup>131</sup>I]-TM-601 has undergone Phase I-II clinical trials for recurrent glioma, these studies were primarily safety-oriented and did not include broad biomarker development [177,179]. Addressing these gaps will require standardized, cross-lab venomomics workflows, including top-down and de novo analysis, to define critical molecular features. Systematic studies of PTMs and structure–function relationships, and integrated preclinical pipelines that couple proteomics with functional assays to prioritize truly druggable venom leads [44,80,174,277,281,282].

#### 10.5. Future Research Directions

The future development of scorpion venom-derived cancer therapeutics holds significant promise, with proteomic and transcriptomic analysis continuing to guide discovery and preclinical evaluation. Venomomics approaches integrating mass spectrometry-based proteomics and sequencing have expanded the catalog of bioactive peptides, enabling the identification of novel components with potential therapeutic applications [80]. Efforts to improve specificity and efficacy increasingly rely on structural and proteomic characterization of toxin–target interactions, exemplified by ongoing studies on chlorotoxin derivatives [175]. Advances in delivery systems, including nanoparticle formulations and peptide conjugates, are being investigated to improve stability and tumor selectivity. Although not yet widely applied to scorpion toxins, nanoparticle delivery of venom-derived peptides in broader venom research demonstrates proof-of-concept potential [283].

Looking ahead, the integration of artificial intelligence with proteomic datasets offers a path toward accelerating venom peptide discovery and prioritizing candidates with favorable properties [284,285]. Combination therapies also represent a promising avenue, as proteomic profiling can reveal synergistic effects between venom peptides and established anticancer agents [44]. Finally, the application of proteomic biomarkers to stratify patients and guide treatment design remains largely speculative, but it represents an important goal for developing personalized venom-derived therapeutics. Collectively, these strategies are expected to produce more effective and targeted interventions while addressing current translational limitations.



## 11. Conclusion and Future Perspectives

Scorpion venom represents a highly diverse natural library of peptides and proteins with unique structural and functional characteristics, making them valuable candidates for anticancer drug development. Proteomic advances have been pivotal in uncovering this molecular diversity, enabling the identification of novel bioactive compounds and mapping their mechanisms of action at unprecedented resolution. These peptides have demonstrated the capacity to selectively target ion channels, disrupt tumor-supportive signaling pathways, induce apoptosis, and remodel the tumor microenvironment while often sparing healthy cells. In addition, the capacity of some venom-derived peptides, such as chlorotoxin, to cross the blood-brain barrier highlights their translational potential in targeting aggressive and otherwise inaccessible tumors.

Despite these advances, important challenges remain. The clinical development of venom-derived therapeutics is hindered by obstacles such as large-scale peptide synthesis, in vivo stability, pharmacokinetics limitations, delivery strategies, and the risk of off-target effects. Addressing these barriers will be essential to enable the translation from preclinical to clinical application. In this regard, the future of scorpion venom-based drug discovery is closely linked to the evolution of proteomic technologies. Single-cell venom gland proteomics promises to delineate precise cellular origins of toxins, uncovering rare peptides and clarifying the understanding of the regulation of venom biosynthesis. Top-down proteomics will allow comprehensive characterization of intact venom proteins and their native post-translational modifications, providing insights into proteoforms that directly correlate with biological activity. Furthermore, interactomics will be key to systematically mapping the binding partners of venom peptides within cancer cells, validating molecular mechanisms, and identifying opportunities for rational combination therapies.

Beyond discovery, proteomics will play a pivotal role in addressing translational challenges. Advanced mass spectrometry will ensure batch-to-batch consistency during manufacturing by confirming sequence integrity, disulfide connectivity, and overall purity. Furthermore, proteomic data will guide the rational design of optimized analogs with improved stability, reduced immunogenicity, and improved pharmacological profiles through strategies such as peptide cyclization and PEGylation. The integration of proteomic biomarkers into preclinical and clinical settings could also help stratify patients, monitor therapeutic efficacy, and quickly identify mechanisms of resistance.

Looking ahead, the integration of proteomics with transcriptomics, structural biology, computational modeling, and synthetic biology will be crucial to optimizing venom-derived therapeutics. Strategies such as nanoparticle conjugation or imaging probes, and targeted delivery strategies may enhance efficacy and minimize off-target effects. Moreover, the immunomodulatory and tumor-microenvironment-modulating properties of certain venom peptides highlight promising synergies with immunotherapies and standard treatments.

In summary, scorpion venom remains an underexploited source of bioactive molecules with significant potential in oncology. By combining high-throughput omics technologies, nanotechnology, medicinal chemistry, artificial intelligence, and translational research may transform these natural peptides into clinically relevant anticancer agents. Realizing this promise will require sustained interdisciplinary collaboration to overcome current barriers and accelerate innovation. While significant progress has been made, key proteomic gaps remain, particularly in the detection of low-abundance peptides, characterization of post-translational modifications, and integrating with other omics layers such as transcriptomics and structural biology. Future advances in multi-omics and computational approaches will be critical to translating scorpion venom peptides into effective therapeutic tools against cancers resistant to conventional treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

$\Delta\Psi_m$	Mitochondrial membrane potential.
A2780	Human Ovarian Cancer Cell Line A2780.
Aah II	<i>Aah II</i> neurotoxin.
AaTs-1	<i>Androctonus australis</i> Toxin-1.
ABC	ATP-binding cassette.
AcrAP1	<i>Androctonus crassicauda</i> Antimicrobial Peptides 1.
AcrAP2	<i>Androctonus crassicauda</i> Antimicrobial Peptides 2.
AGAP	Analgesic-Antitumor Peptide.
AGAP-SYPU2	Analgesic-Antitumor Peptide Variant SYPU2.
AI	Artificial intelligence.
AK	Adenylate kinase.
Akt	Protein Kinase B.
AMPK	AMP-Activated Protein Kinase.
AMPs	Antimicrobial Peptides.
AP-1	Activator Protein 1.
Arg1	Arginase-1.
ATMs	Tumor-Associated Macrophages.
ATP	Adenosine Triphosphate.
AuNP-antibody	Gold nanoparticle conjugated to antibody.
B16-F10	Murine Melanoma Cell Line B16-F10.
Bax	Bcl-2-Associated X Protein.
BBB	Blood-Brain Barrier.
Bcl-2	B-cell Lymphoma 2.
BKCa	Large-Conductance Calcium-Activated Potassium Channel.
BLZ-100	Chlorotoxin-based Tumor Paint Bioconjugate.
BmHYA1	<i>Buthus martensii</i> Karsch Hyaluronidase 1.
BmK	<i>Buthus martensii</i> Karsch.
BmKCT	<i>Buthus martensii</i> Karsch chlorotoxin.
BmKDfsin4	Derived Defensin-4 peptide.
BmKn1	Antimicrobial peptides derived from <i>Buthus martensii</i> Karsch venom.
BmKn2-7	Anticancer peptides derived from <i>Buthus martensii</i> Karsch venom.
BotCl	<i>Buthus occitanus tunetanus</i> Chloride Channel Blocker.
BTB	Blood-tumor barrier.
Buthicyclin	Cyclic peptide derived from Defensin-4.
C3	Complement component 3.
C6	Glioma cell line.
Ca <sup>2+</sup>	Calcium ion.
CAM	Chorioallantoic Membrane.
Caspase-3	Effector caspase enzyme.
CD	Circular dichroism.
CD40L	CD40 ligand.
CD44	Cluster of Differentiation 44.
CD44v6	CD44 Variant Isoform 6.

CDK	Cyclin-Dependent Kinase.
CDK4	Cyclin-Dependent Kinase 4.
CDKI	Cyclin-Dependent Kinase Inhibitor.
CDKIs	Cyclin-Dependent Kinase Inhibitors.
CDKs	Cyclin-dependent kinases.
cDNA	Complementary DNA.
ChTX	Charybdotoxin.
CIF8	Cancer Inhibitory Fractions 8.
CIF9	Cancer Inhibitory Fractions 9.
CIC-3	Chloride Channel Protein 3.
Cm28	<i>Centruroides margaritatus</i> peptide/toxin.
CN	Chitosan nanoparticles.
CNS	Central nervous system.
CORT	Cortistatin.
Css54	Cationic antimicrobial peptide 54.
CTX	Chlorotoxin.
D3	Cyclin D3.
DISC	Death-inducing signaling complex.
DNA	Deoxyribonucleic acid.
DU145	Human Prostate Carcinoma Cell Line DU145.
ECM	Extracellular Matrix.
EGFR	Epidermal Growth Factor Receptor.
ELISA	Enzyme-linked immunosorbent assay.
ERK1/2	Extracellular Signal-Regulated Kinases 1/2.
F3II	Murine mammary adenocarcinoma cell line F3II.
FasL	Apoptosis-inducing ligand binding to Fas receptor.
FDA	Food and Drug Administration.
FoxO	Forkhead Box O.
FPRL-1	Formyl Peptide Receptor-Like 1.
FTox-G50	Scorpion venom fraction Toxin G50.
G0	Cell cycle phases of resting.
G1	Gap 1 phase of the Cell Cycle.
GK	Glucokinase.
H22	Murine Hepatocellular Carcinoma Cell Line H22.
H460 / NCI-H460	Human Non-Small Cell Lung Carcinoma Cell Line.
HA	Hyaluronic Acid.
HBsAg-specific	Hepatitis B surface antigen-specific.
HCC	Hepatocellular carcinoma.
HCT116	Human Colorectal Carcinoma Cell Line HCT116.
HCT-8	Colorectal cancer cell line.
HeLa	Human Cervical Cancer Cell Line HeLa.
HER2	Human epidermal growth receptor 2.
HPLC	High-Performance Liquid Chromatography.
HSP70	Heat shock protein 70.
HSP90	Heat shock protein 90.
HsTX1	<i>Heterometrus scaber</i> toxin 1.
hTERTC27	C-terminal 27 kDa polypeptide fragment of human telomerase reverse transcriptase.
HUVEC	Human Umbilical Vein Endothelial Cells.
IbTX	Iberiotoxin.
IC <sub>50</sub>	Half Maximal Inhibitory Concentration.
IFN-γ	Interferon-gamma.
IGR39	Human Melanoma Cell Line IGR39.
IL-10	Interleukin-10.
IL-12p40	Interleukin-12 subunit p40.
IL-12p70	Biologically active heterodimeric form of interleukin-12.
IL-1β	Interleukin-1 beta.
IL-23	Interleukin-23.
IL-2R	Interleukin-2 receptor.

IL-4	Interleukin-4.
IL-6	Interleukin-6.
IL-8	Interleukin-8.
iTRAQ	Isobaric tags for relative and absolute quantification.
JAK	Janus kinase.
Kd	Equilibrium Dissociation Constant.
Kv1.1	Voltage-gated Potassium Channel Subfamily A Member 1.
Kv1.3	Voltage-gated Potassium Channel Subfamily A Member 3.
Kv10.1	Voltage-gated potassium channel 10.1.
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry.
LD50	Median lethal dose.
LS174	Human Colon Adenocarcinoma Cell Line LS174.
LSPR	Localized plasmon resonance.
M1 macrophages	Classically activated macrophages.
M2 macrophages	Alternatively activated macrophages.
MALDI-TOF MS	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry.
MAP kinases	Mitogen-activated protein kinases.
MAPK p38	p38 Mitogen-Activated Protein Kinase.
MCa	Micaelase.
MCF-7	Human Breast Cancer Cell Line MCF-7.
MDA-MB-231	Human Triple-Negative Breast Cancer Cell Line.
MDA-MB-435s	Human Breast Carcinoma Cell Line.
Meuk7–3	Peptide fraction Meuk7–3.
MgTX	Margatoxin.
MiniCTX3	Charybdotoxin analogue peptide.
MMP-2	Matrix metalloproteinase-2.
MRI	Magnetic resonance imaging.
MS	Mass spectrometry.
MS/MS	Tandem mass spectrometry.
MT1-MMP	Membrane-Type 1 Matrix Metalloproteinase.
mTOR	Mechanistic Target of Rapamycin.
MyD88	Myeloid Differentiation Primary Response 88.
NADPH	Nicotinamide Adenine Dinucleotide Phosphate.
Nav1.4	Voltage-gated Sodium Channel, Alpha Subunit 1.4.
Nav1.5	Voltage-gated Sodium Channel, Alpha Subunit 1.5.
Nav1.7	Voltage-gated Sodium Channel, Alpha Subunit 1.7.
Nav1.8	Voltage-gated Sodium Channel, Alpha Subunit 1.8.
NCI-H460	Human Lung Cancer Cell Line NCI-H460.
NDBP	Non-Disulfide Bridged Peptide.
NF-κB	Nuclear Factor kappa-light-chain-enhancer.
NGF	Nerve growth factor.
NGS	Next-generation sequencing.
NOS2	Inducible Nitric Oxide Synthase.
NRP1	Neuropilin-1.
OGFR	Opioid growth factor receptor.
FOXO3a	Forkhead box O3a.
p21	Cyclin-dependent kinase inhibitor 1A.
p27	Cyclin-dependent kinase inhibitor 1B.
p53	Tumor suppressor protein.
PAMAM	Polyamidoamine.
PARP	Poly polymerase.
PC-3	Human Prostate Carcinoma Cell Line PC-3.
PEG	polyethylene glycol.
PEG-CTX	Polyethylene glycol–chlorotoxin conjugate.
PEGylation	Polyethylene glycol conjugation.
PESV	Polypeptide Extract from Scorpion Venom.
PI3K	Phosphatidylinositol 3-Kinase.
PLA-PEG	Polylactic acid–polyethylene glycol copolymer.



PLA2	Phospholipase A2.
PPAR	Peroxisome Proliferator-Activated Receptor.
PTEN	Fosfatase supressora tumoral.
PTMs	Post-translational modifications.
RAW264.7	Macrophage-like cell line.
RK1	Scorpion-derived Peptide from <i>Buthus occitanus tunetanus</i> .
ROS	Reactive oxygen species.
S1 / S2	Designations of Stigmurin analogues.
S180	Murine Sarcoma Cell Line S180.
SDS-PAGE	Sodium Dodecyl Sulfate–Polyacrylamide Gel Electrophoresis.
SEC	Size exclusion chromatography.
SEM	Scanning Electron Microscopy.
SHG-44	Human Glioma Cell Line SHG-44.
SPECT	Single-Photon Emission Computed Tomography.
SPR	Surface plasmon resonance.
STAT3	Transcription factor.
STAT	Signal transducer and activator of transcription.
SVS-1	Anticancer Beta-Hairpin Peptide SVS-1.
TAMs	Tumor-associated macrophages.
tBid	Truncated Bid.
TfR	Transferrin receptor.
TGF-β	Transforming Growth Factor Beta.
Th1 / Th2 / Th17 cells	T helper cell subsets.
TIMPs	Tissue Inhibitors of Metalloproteinases.
TLR2	Toll-Like Receptors 2.
TLR4	Toll-Like Receptors 4.
TM-601	Synthetic Chlorotoxin Derivative Radiolabeled with Iodine-131.
TME	Tumor Microenvironment.
TMT	Tandem mass tags.
TNF-α	Tumor Necrosis Factor-alpha.
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand.
TRPV1+	Transient Receptor Potential Vanilloid 1–positive.
Ts1	Major neurotoxin from <i>Tityus serrulatus</i> venom.
Tsv	<i>Tityus stigmurus</i> venom.
TzII	<i>Tityus zulianus</i> toxin isoforms II.
TzIII	<i>Tityus zulianus</i> toxin isoforms III.
U87	Human Glioblastoma Cell Line U87.
UHPLC-QTOF-MS	Liquid chromatography coupled to mass spectrometry.
VERO	African Green Monkey Kidney Epithelial Cell Line VERO.
Vm24	Peptide from <i>Vaejovis mexicanus</i> .
Vmct1	<i>Vaejovis mexicanus</i> cationic peptide 1.
Vmct1-K	Lysine-substituted variant of Vmct1.
VRE	Vancomycin-Resistant Enterococcus.
α1β1	Alpha-1 Beta-1 Integrin.
αvβ3	Alpha-V Beta-3 Integrin.

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