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Review article

PHARMACOLOGICAL AND THERAPEUTIC APPLICATIONS OF SCORPION VENOM PEPTIDES: A REVIEW

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ABSTRACT

Introduction: In recent years, scorpion venom and its peptide compounds have attracted growing scientific interest. A remarkable biological diversity and strong therapeutic potential characterize these compounds.
Aims: to provide a comprehensive review of the therapeutic properties of scorpion venoms.
Methods: This analysis is based on a collection of 53 studies published between 2020 and 2025, all of which have strict inclusion criteria and are drawn from reliable sources, including specialized platforms such as PubMed, Web of Science, ScienceDirect, Scopus, and Google Scholar. The studies reviewed focus on the pharmacological effects of scorpion venom and chemical components.
Results: The collected data highlight the increased interest in scorpion-derived peptides as pharmacological tools in biomedical research, attributed to their diverse biological actions, including anticancer, antimicrobial, antiviral, antiparasitic, analgesic, antioxidant, immunomodulatory, and neuroprotective. Among the described mechanisms of action are the induction of apoptosis, disruption of cell membranes, modulation of intracellular signalling pathways, and inhibition of ion channels. Most studies on the subject demonstrate significant efficacy, with low toxicity observed in both in vitro cell cultures and in vivo murine models.
Conclusions: This review confirms the promising potential of scorpion venom peptides for developing novel therapeutic and biotechnological applications. However, it also emphasizes the necessity of further clinical research and standardized experimental protocols to fully harness their benefits.

KEYWORDS: SCORPION VENOM; PEPTIDES; THERAPEUTIC POTENTIAL; PHARMACOLOGICAL ACTIVITIES; REVIEW.

INTRODUCTION

Natural molecules play a crucial role in pharmaceutical and biomedical research. In recent years, the growing interest in natural compounds as sources of new therapeutics has drawn attention to animal venoms. Derived from various organisms, including plants, microorganisms, and animal venoms, these compounds exhibit remarkable biological properties with significant therapeutic potential. Among them, scorpion venoms have attracted particular attention from researchers due to their rich and diverse composition of bioactive molecules, including disulfide-bridged and non-disulfide-bridged peptides, neurotoxins, amino acids, nucleotides, and lipids (Javed et *al*., 2022). Neurotoxins, in particular, play a key role by selectively targeting ion channels in cell membranes, which can result in severe pathologies in cases of envenomation (Panayi *et al.*, 2024).

In addition to their toxicological impact, scorpion venoms have been used for centuries in traditional medicine in regions such as China, India, and Africa, highlighting their longstanding therapeutic relevance. For example, in China, fried scorpions are eaten as food, and scorpion-infused wines have been traditionally used to enhance immune function (Ding et *al*., 2014). Beyond their well-known toxic effects, scorpion venom also contains a variety of bioactive molecules with significant therapeutic potential. Recent studies have demonstrated that several peptides isolated from scorpion venom exhibit a wide range of pharmacological effects, including anticancer, antidiabetic, antioxidant, antimicrobial, anti-inflammatory, and immunomodulatory activities (El Hidan *et al.*, 2021; Chen *et al.*, 2024; Tobar *et al.*, 2024; Wang *et al.*, 2024; Xu *et al.*, 2025). Notably, compounds such as chlorotoxin and charybdotoxin appear particularly promising for treating cancer and cardiovascular diseases (Javed et *al*., 2022). These findings establish scorpion venom peptides and toxins as valuable lead compounds for the development of novel drugs.

To further strengthen this biomedical perspective, recent advances in proteomics, transcriptomics, and venom-gland genomics have greatly enhanced our understanding of scorpion venom composition, revealing a molecular diversity far greater than previously recognized. These technological advances have deepened our understanding of venom complexity and expanded the therapeutic possibilities associated with scorpion-derived molecules.

Moreover, the global rise in antimicrobial resistance and the urgent need for innovative anticancer therapies have intensified scientific interest in venom-derived molecules as alternative or complementary treatment options.

This review synthesizes recent findings on the therapeutic potential of scorpion venom-derived peptides, with a focus on studies published between 2020 and 2025. It aims to provide an updated and comprehensive overview of current research by identifying the most promising peptide candidates, analyzing their mechanisms of action, and evaluating their potential as innovative therapeutic agents.

MATERIALS AND METHODS

Research strategy, screening, and data extraction

A systematic methodological approach was employed to identify and analyze the most relevant publications dealing with scorpion venom peptides and their therapeutic applications. The literature search was conducted between March and May 2025 in five major scientific databases: *PubMed* (https://pubmed.ncbi.nlm.nih.gov/), *ScienceDirect* (https://www.sciencedirect.com/), *Web of Science* (https://www.webofscience.com), *Scopus* (www.scopus.com), and *Google Scholar* (https://scholar.google.com/). The search strategy was developed based on the problem studied, using the keywords scorpion venom or scorpion peptides related to therapeutic effects or biomedical applications, while excluding the term pathology. The following search string was used in databases: ("scorpion venom" OR "scorpion peptides") AND ("therapeutic effects" OR "biomedical applications") NOT "pathology". Only original, experimental, full-text articles published between 2020 and 2025 in English or French were included. On the other hand, studies of the topic, Review articles, conference abstracts, duplicates, and studies with weak methodology or articles unavailable in open access were excluded. The selected studies focused on *in silico*, *in vitro*, or *in vivo* experiments evaluating the therapeutic effects of scorpion venom or its isolated components. Those with inadequate controls, incomplete methodological descriptions, or a lack of reproducibility were excluded. The articles (title, abstract, full text) were sorted using the Rayyan QCRI platform, a tool specialized in managing systematic reviews. Two reviewers selected the studies independently and blindly. Disagreements were resolved by a third reviewer.

The selection process was conducted in two stages: an initial analysis of titles and abstracts was used to preselect studies that met the inclusion criteria. A second phase consisted of an in-depth assessment of the methodological quality of the full texts. The data was then extracted manually, and a report was

completed for each study. This procedure included objectives, type of study, study methodology, and results. This information was organized and analyzed by theme to identify trends and group the articles into broad categories.

Our systematic search initially identified 930 potentially relevant articles. Following initial screening, we excluded 433 articles as irrelevant to the study topic, 283 review articles, and 113 duplicate publications. 100 articles were evaluated for eligibility. Of these, 47 full-text articles were excluded, and 53 were examined in detail. To ensure the rigor and transparency of the research process and to minimize potential bias or subjectivity. The screening and selection process was conducted in accordance with the PRISMA 2020 guidelines to ensure methodological rigor and transparency (Figure 1).

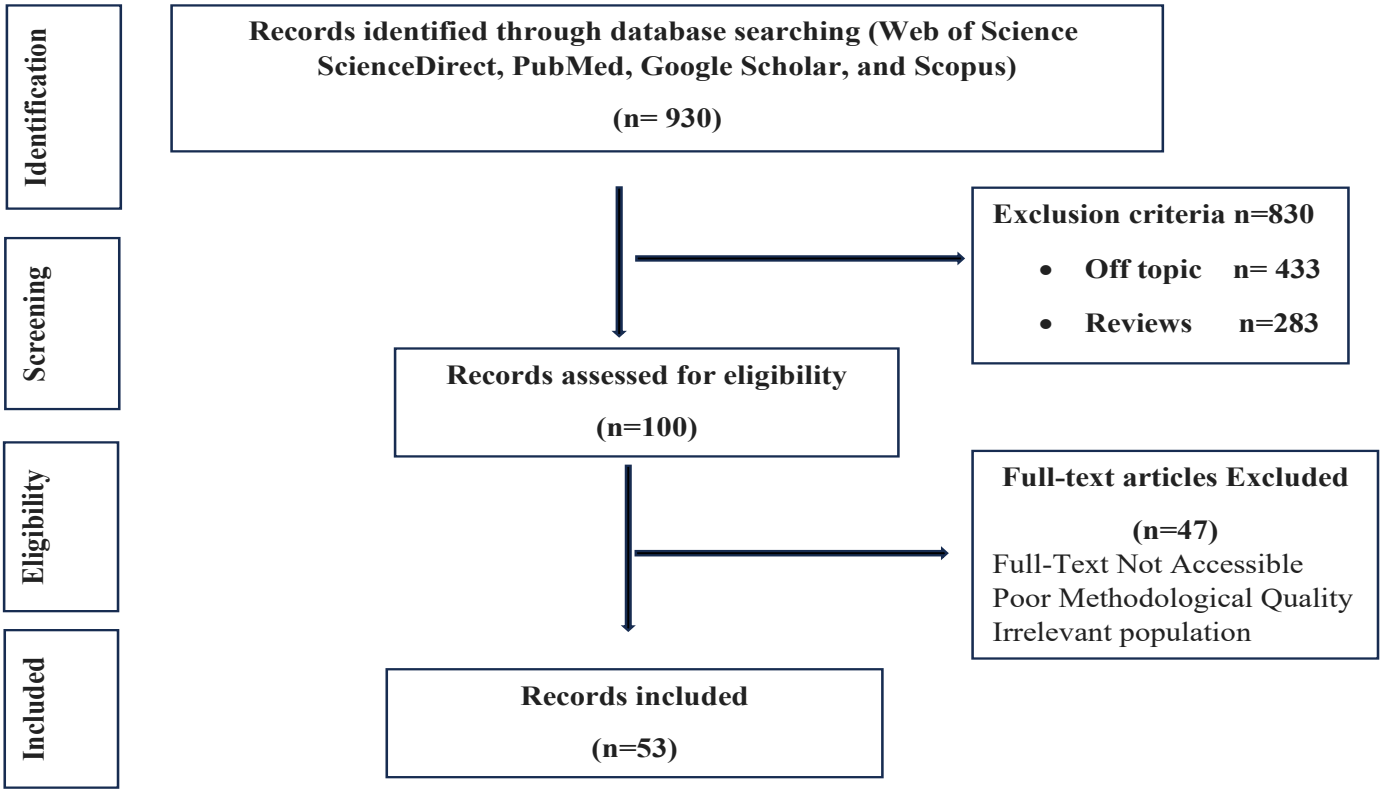

Figure 1. PRISMA flow diagram of study selection in the systematic review on scorpion venom-based therapeutics (January 2020– March 2025). A total of 930 articles were identified from the databases. After excluding 830 articles (433 off-topic, 283 reviews, 113 duplicates), 100 articles were evaluated for eligibility. Of these, 47 full-text articles were excluded, resulting in the final inclusion of 53 studies.

RESULTS AND DISCUSSION

Anti-inflammatory and immunomodulatory effects

Peptides isolated from scorpion venom are recognized for their potent anti-inflammatory and immunomodulatory effects. For instance, the peptide BmKK2 from *Buthus martensii* Karsch (100 µg *in vitro*; 2–6 mg/kg *in vivo*) has been shown to inhibit macrophage activation by blocking the Kv1.3 channel. This blockade leads to a cascade of downstream effects, including reduced calcium influx, suppression of the NF-κB signaling pathway, and decreased TNF-α secretion. These therapeutic actions were confirmed in both *in vitro* cell cultures (BMDMs and HEK293T) and *in vivo* mouse models with a high-fat diet(Xu *et al.*, 2025). *In vitro* tests on BV2 microglial cells have shown that martensiiagm A (20

μM) effectively reduces pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) in the ELISA test, decreases oxidative stress, and improves mitochondrial potential, with efficacy comparable to that of melatonin (Li *et al.*, 2025). Similarly, DKK-SP1 (2 mg/kg) from *Buthus martensii* Karsch demonstrates potent anti-inflammatory activity, comparable to indomethacin, in murine models. It achieves this by reducing COX-2 and IL-6, increasing IL-10, and dose-dependently inhibiting the Nav1.8 channel (Liu *et al.*, 2021). Similarly, DKK-SP1 (2 mg/kg) from *Buthus martensii* Karsch demonstrates potent anti-inflammatory activity, comparable to indomethacin, in murine models. It achieves this by reducing COX-2 and IL-6, increasing IL-10, and dose-dependently inhibiting the Nav1.8 channel (Liu *et al.*, 2021). The venom of *Tityus sp.* has been shown to inhibit the multiplication of T lymphocytes (CD3+, CD4+, CD8+) cell subpopulations of RA patients and healthy controls and decreased IL-10 secretion, without affecting cell activation in vitro at concentrations of 252 μg/mL (Tobar *et al.*, 2024).

Anticancer properties of scorpion venom components

In several studies, scorpion venom toxins and peptides have demonstrated remarkable anticancer activity. These compounds have been extensively evaluated in vitro and, and more limited in vivo research, with their effects on diverse array of human tumor cell lines, the tested cell line include those derived from colorectal (Caco-2 and CT-26), glioblastoma (U87-MG and U87), breast (MCF-7, MDA-MB-231, and SUM149PT), hepatocellular carcinoma (HepG2), oral squamous carcinoma (SCC-9), prostate (PC3), cervical (HeLa), and neuroblastoma (SH-SY5Y), For comparison, the effects on normal human fibroblast cells (BJ) have also been investigated (table 1). Scorpion venom inhibits tumor cell proliferation, reduces viability, and limits metastatic migration, such as the promotion of apoptotic cell death with positive modulation of pro-apoptotic markers macrophage polarization from M2 to M1 phenotype, cell cycle arrest at specific phases, and increased reactive oxygen species (ROS) generation. (Amirgholami *et al.*, 2020; Aissaoui-Zid *et al.*, 2021; Pedron *et al.*, 2021; Ahmed *et al.*, 2022; Lafnoune *et al.*, 2022; Moslah *et al.*, 2022; Nguyen *et al.*, 2022; Cabral *et al.*, 2024; Hassan *et al.*, 2024; Sadeghi *et al.*, 2024; Zheng *et al.*, 2024; Chen *et al.*, 2025; Ghadiri *et al.*, 2025).

Table 1: Anticancer Activities of Peptides and Fractions Derived from Scorpion Venom (*In Vitro* and *In Vivo* Studies).

Scorpion species	Peptide/venom	Cancer type	Type of study	Dose	Results	References
Buthus occitanus	Fraction 3	Hepatocellularcarcinoma (HCC; MCTS cells)	*In vitro* (3D cell culture)	10 µg/mL	Significant tumor inhibition (78.91%) without toxicity to normal cells.	(Lafnoune *et al.*, 2022)
Leiurus quinquestriatus	FLV-SV	Colon cancer (Caco-2 cell)	*In vitro/ In vivo*	11,91 µg/mL	↓ IC50, bcl2, and increased apoptosis and P53	(Ahmed *et al.*, 2022)
Vaejovis mexicanus	VmCT1	Breast cancer (MCF-7)	*In vitro*	12.2 µg/mL.	Anionic membrane disruption, ↑ of the positive charge	(Pedron *et al.*, 2021)
Buthus martensii Karsch	PESV	Hepatocellularcarcinoma(HCC)	*In vivo*	40 mg/ kg	↓ Proliferation, Ki-67, and multiple metabolic modulation	(Zheng *et al.*, 2024)
Mesobuthus eupeus	Fraction 1	Colon cancer (CT-26)	*In vitro*	100 µg/ml	Reprogramming M2→M1, ↑ TNF-α, IL-1, IRF5, ↓ TGF-β, IL-10; ↓ CT-26 migration and proliferation.	(Sadeghi *et al.*, 2024)
Androctonus crassicauda	Fraction 2	Colon cancer (CT-26)	*In vitro*	100 µg/ml	M2→M1 reprogramming, ↓ CT-26 migration and proliferation.	(Ghadiri *et al.*, 2025)
Opisthacanthus madagascariensis	AC-AFPK-IsCT1/IsCT-P	Oral squamous cell carcinoma	*In vitro*	AC-AFPK-IsCT1 (90,5/84,4 µM); IsCT-P (96,5/81,3 µM	↑ p53 and caspases 3 and 8, ↓PCNA and cyclin D1, S-phase cell cycle arrest, ↓ proliferation	(Cabral *et al.*, 2024)
Buthus sindicus	Crude venom	Prostate (PC3), cervical (HeLa), neuroblastoma (U87-MG), normal human fibroblast cells (BJ)	*In vitro*	172 µg/mL HeLa, 171 µg/mL PC3, 237 U87-MG µg/mL	Cytotoxic for all cell lines, with a significant inhibitory effect on PC3 cells via apoptosis	(Hassan *et al.*, 2024)
Buthus martensii Karsch	BmK-M9	Breast cancer (MDA-MB-231, SUM149PT and MCF-7)	*In vitro/ In vivo*	Invitro:1.79-14.34 µg/mL In vivo: 1 mg/kg	↓ β-catenin expression, tumor proliferation, migration, and invasion	(Chen *et al.*, 2025)
Scorpio Maurus palmatus	Crude venom	Hepatocellular carcinoma (HepG2)	*In vitro/ In vivo*	1.79 – 14.34 µg/mL	↑ Apoptosis and ROS, cycle arrest, mitochondrial dysfunction	(Nguyen *et al.*, 2022)

Androctonus crassicauda *Mesobuthus eupeus* *Hemiscorpius lepturus*	Crude venoms	Colon cancer (CT26)	*In vivo*	A.crassicauda (65 µg/k) M. eupeus (125 µg/kg) H. lepturus (535 µg/kg)	↑ Inflammatory and CD+ + T lymphocytes, ↑ IL-12, and IFN-γ mRNA in the tumor microenvironment + 90% Inhibition	(Amirgholami *et al.*, 2020)
Androctonus australis	AaTs-1-2B, 4B, 8B	Glioblastoma (U87)	-	55.5–166.4 µg/mL	↑ p53, ERK1/2, AKT, ↓ proliferation, and migration	(Aissaoui-Zid *et al.*, 2021; Moslah *et al.*, 2022)

Neuroprotective effect

The SVHRSP peptide, extracted from the scorpion *Buthus martensii* Karsch, has shown promise in combating Parkinson's disease. According to researchers, it not only protects dopaminergic neurons and reduces neuroinflammation but also inhibits key enzymes like NLRP3 and NADPH oxidase 2 in rotenone-induced PD mouse models (200–400 μg/kg, twice a week for 5 weeks). Studies also indicate that it attenuates microglial activation and neurodegeneration *in vitro* (Zhang *et al.*, 2022). Furthermore, (Wu *et al.*, 2021) found that the peptide reduces the expression of iNOS and TNF-α both *in vivo* and *in vitro*, without causing toxicity, suggesting its therapeutic effect is linked to the suppression of the NF-κB and MAPK pathways. The SVHRSP peptide has also demonstrated neuroprotective properties in other models. In a C. elegans model of Parkinson's disease induced by 6-hydroxydopamine (6-OHDA), the peptide at a dose of 60.988 μg/mL notably reduced α-synuclein aggregation (Guo *et al.*, 2022).

Beyond Parkinson's, SVHRSP has shown potential as an antiepileptic agent. In both pentylenetetrazol (PTZ)-induced epileptic seizure models (acute: 7 days; chronic: 29 days) and NMDA-induced excitotoxicity *in vitro*, the peptide (160 μg/kg) reduced seizures, protected neurons, and improved memory. These effects are attributed to its ability to modulate the NMDA receptor and phosphorylated p38 MAPK protein expression (Sui *et al.*, 2024). This evidence supports its broad neuroprotective and antiepileptic potential.

Analgesic effects

Several peptides from the scorpion *Buthus martensii* Karsch have demonstrated potent analgesic effects.

Syb-prII-1: In a rat model of chronic infraorbital neuralgia, a 4.0 mg/kg dose of this peptide showed an analgesic effect comparable to morphine. Its mechanism involves dose-dependent inhibition of Nav1.8 channels and suppression of MAPK pathways (ERK, JNK, p38, CREB) (Bai *et al.*, 2022).

N58A: This peptide, also from *Buthus martensii Karsch,* alleviated facial pain and downregulated MAPK expression and phosphorylation, as well as Nav1.8/1.9 sodium channels, with an efficacy comparable to morphine but without its side effects at a dose of 4.0 mg/kg (Li *et al.*, 2021).

Makatoxin-3: From the same scorpion species, Makatoxin-3 (450 nmol/kg in mice) specifically targets the Nav1.7 channel. It produces potent analgesia that is not reversible by naloxone, indicating it is independent of opioid receptors and more effective than traditional NSAIDs and opioids (Chen *et al.*, 2022).

Other Scorpion Venom-Derived Analgesics

AGAP Peptide: This peptide inhibits TRPV1 and KCNQ2/3 channels and potentiates the effect of lidocaine in both *in vivo* and *in vitro* models of neuropathic pain, demonstrating a strong, dose-dependent antinociceptive effect (Kampo *et al.*, 2021).

Androctonus amoreuxi Crude Venom: Studies revealed that the crude venom of this scorpion has both peripheral and central analgesic effects, along with antipyretic and anti-inflammatory properties, in various mouse models at doses of 1/5 and 1/10 the LD50 (0.11 mg/kg and 0.22 mg/kg for mice)(Shoukry *et al.*, 2020).

Leptucin: Extracted from *Hemiscorpius lepturus,* Leptucin induced a significant analgesic effect (95-100%) in mouse hot plate and tail-flick tests at doses of 0.32, 0.48, and 0.64 mg/kg. It also demonstrated a safe profile without hepatic, renal, or cardiac toxicity (Bagheri-Ziari *et al.*, 2021).

Antibacterial effect

Several peptides derived from *A. amoreuxii* venom have demonstrated significant antimicrobial activity.

AamAP1-Lys-NH_2: This carboxy-amidated peptide, a modified version of AamAP1-Lys, shows potent bactericidal activity against Gram-negative bacteria like *E. coli* and *Acinetobacter baumannii* by causing membrane permeabilization. Its minimal biofilm inhibitory concentrations (MBICs) are 320/640 μg/mL against *E. coli* ATCC 700928 and 160/320 μg/mL against *A. baumannii* NICD 15283 biofilms. This makes it four times more effective than AamAP1-Lys against most clinical isolates and resistant strains of *A. baumannii* (NCTC 13302), with minimal inhibitory concentrations (MICs) around 9 μg/mL. While amidation increases its toxicity, it also improves the peptide's selectivity for bacteria over human cells (HepG2 and HaCat) (Van Wyk *et al.*, 2025).

A3a[I14W]: This peptide from *A. amoreuxii* is effective against *A. baumannii* (MICs = 8 µg/mL) and shows high in silico selectivity (Möller *et al.*, 2025).
GK-19: A derivative of *A.amoreuxii* Antimicrobial Peptide 1 (AamAP1), GK-19 exhibits broad-spectrum activity against both bacteria and fungi. It has very low MICs (3–10 µM), good stability, and acceptable tolerance in mice, with minimal hepatic and renal toxicity (Song *et al.*, 2022).

Other Scorpion Venom-Derived Antimicrobials

1,4-benzoquinone (blue): Isolated from *Diplocentrus melici*, this compound shows bactericidal activity against *A. baumannii* strains (MICs from 20–64 µg/mL). Notably, bacteria did not develop resistance to it even after 35 cycles of continuous exposure, unlike with ciprofloxacin or gentamicin (Gallegos-Monterrosa *et al.*, 2025).
IsCT-Δ6-8: An analog of IsCT from *Opisthacanthus madagascariensis*, this peptide exhibits potent anti-biofilm activity against *P. aeruginosa* at 150 µM without affecting bacterial growth. It targets virulence by reducing pyocyanin production and the release of inflammatory mediators like NO and IL-6 (Jantaruk *et al.*, 2024).
Crude Venoms: Bioactive fractions from the venoms of *Centruroides margaritatus*, *Tityus pachyurus*, and *T. metuendus* have shown activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, some of these fractions also demonstrated toxicity in murine or insect models and elicited a cross-immune response (Mendoza-Tobar *et al.*, 2021).

Antifungal Effect

Several peptides have demonstrated significant antifungal activity, often outperformed conventional drugs and targeted drug-resistant strains.
Css54, a peptide from *Centruroides suffusus* venom, has potent fungicidal activity against *Candida albicans*, including fluconazole-resistant strains. Its MIC is significantly lower than fluconazole's (2 µM vs. 16 µM). It works by inducing oxidative stress and membrane alteration, while showing moderate cytotoxicity and low hemolysis (Park *et al.*, 2024).
Ts8/Ts8+ propeptides from *Tityus serrulatus* exhibit antifungal effects against *Pichia pastoris* at very low concentrations (0.005 and 0.01 µg/mL). Their mechanism involves the induction of pro-inflammatory cytokines and nitric oxide (NO) release (Cordeiro *et al.*, 2022).
Peptides from *Tityus stigmurus*, when encapsulated in chitosan nanoparticles, show enhanced antifungal effects against *Candida tropicalis* and *C. parapsilosis,* with MICs of 5.5 µg/mL and 11.1 µg/mL, respectively (Gláucia-Silva *et al.*, 2024).
The GK-19 peptide, derived from *Androctonus amoreuxi* venom, has broad antifungal activity against *C. krusei, C. albicans*, and *C. glabrata.* It has low MICs (5-10 µM) and demonstrates good stability and low hepatic and renal toxicity (Song *et al.*, 2022).

Antiviral effects

Scorpion venom components have also shown efficacy against several viruses, both in vitro and in silico.
BmKn2-T5, an analog from *Mesobuthus martensii,* showed dose-dependent inhibition of EV71, DENV, ZIKV, and HSV-1 viruses *in vitro*. This peptide works by specifically targeting non-structural viral proteins (Xia *et al.*, 2024).
A synthetic peptide from *Tityus obscurus* was found to reduce SIVmac251 viral replication in human leukocytes. At concentrations from 0.39 to 6.24 µM, it also modulated pro- and anti-inflammatory cytokines (e.g., IL-4, IL-6, IFN-γ) with low cellular toxicity (da Mata *et al.*, 2020).
ODAMP2 and ODAMP5, two peptides from *Odontobuthus doriae*, showed high binding affinity to the RBD domain of the SARS-CoV-2 Spike protein in *in silico* studies, suggesting they have promising antiviral potential (Soorki, 2025).
Chlorotoxin, from *Leiurus quinquestriatus*, inhibits the neuropilin-1 (NRP1) receptor, a cofactor for SARS-CoV-2 cellular entry. This effect has been demonstrated *in vitro* on purified proteins and *in silico* (Sharma *et al.*, 2021).
LaPLA2-1, a phospholipase from *Liocheles australasiae,* efficiently inhibited the infection of Flaviviridae viruses, including HCV, DENV, and JEV, with IC_{50} values of 2.0, 3.4, and 5.7 ng/mL, respectively, and exhibited low cytotoxicity *in vitro* (Miyashita *et al.*, 2021).

Anti-parasitic activity

Antimalarial: Synthetic peptides from *Vaejovis mexicanus* venom, specifically $[Arg]_3$-VmCT1-NH_2 and $[Arg]_7$-VmCT1-NH_2, have inhibitory effects against *Plasmodium gallinaceum* with low cytotoxicity on normal cells (Pedron *et al.*, 2021).

Antitoxoplasmosis: The venom of *Hemiscorpius lepturus* and its F5 fraction significantly inhibit *Toxoplasma gondii* tachyzoites *in vitro* (Rostamkolaie *et al.*, 2022). Similarly, the venom of *Tityus serrulatus* (TsV) and its F6 fraction exert antiparasitic activity against *T. gondii* by inducing pro-inflammatory cytokines like IL-12 and TNF-α, and stimulating nitric oxide (NO) production. The mimetic peptides Pep1 and Pep2a also reduced the brain parasite load in infected mice (de Assis *et al.*, 2021).

Antihydatidosis: The crude venom of *Androctonus crassicauda* at 100 µg/mL exhibits a scolicidal effect, destroying all protoscolices of *Echinococcus granulosus* after 240 minutes of incubation (Al-Malki et Abdelsater, 2020).

Antileishmaniasis: The crude venom of *Brotheas amazonicus* and *Tityus metuendus* showed lethal activity against *Leishmania guyanensis* and *Leishmania amazonensis*, respectively (Pereira *et al.*, 2023). The venom of Tityus meaingens also demonstrated a dose-dependent leishmanicidal effect against *Leishmania amazonensis* (Pereira *et al.*, 2023).

Antitrypanocidal: The Ts7 peptide from *Tityus serrulatus* venom has trypanocidal activity by stimulating NO and pro-inflammatory cytokine production (TNF-α, IL-12) via activation of the MAPK pathway (p38, JNK, ERK) (Pimentel *et al.*, 2021).

Antioxidant effect

Although some scorpion venoms have pro-oxidative properties, several peptides derived from them have shown potent antioxidant effects.

Stigmurin, from *Tityus stigmurus,* demonstrated over 70% hydroxyl radical scavenging efficiency at a concentration of 10 µM (Gláucia-Silva *et al.*, 2024).

HL-7 and HL-10, peptides from *Hemiscorpius lepturus*, were shown to decrease levels of malondialdehyde (MDA) a marker of oxidative stress, and increase the activity of antioxidant enzymes like superoxide dismutase and catalase (Setayesh-Mehr, Ghasemi et Asoodeh, 2021).

Other peptides that reduce oxidative stress include Martensiiagm A from *Buthus martensii* (Li *et al.*, 2025), SVHRSP from *Buthus martensii* Karsch (Guo *et al.*, 2022), and kaliotoxin (KTX) from *Androctonus australis* (Ladjel-Mendil *et al.*, 2025).

Our paper provides an updated overview of scorpion venom research, focusing on the most recent experimental advances, specifically studies published since 2020. This review integrates the latest discoveries, innovative experimental approaches, and newly identified or re-evaluated peptides. It presents a current and comprehensive perspective on the therapeutic potential of scorpion venom, emphasizing its remarkable pharmacological value across various therapeutic fields. These include neurodegenerative diseases, pain management, inflammatory and oxidative stress-related conditions, as well as microbial and viral infections. The structural and functional diversity of these bioactive peptides endows them with unique therapeutic properties, often characterized by high selectivity and low toxicity, making them promising candidates for the development of new therapeutic agents.

In terms of anti-cancer treatments, several peptides derived from scorpion venoms, such as AaTs-1 (*Androctonus australis*), BmK-M9 (*Buthus martensii* Karsch), and FLV-SV (*Leiurus quinquestriatus*), effectively inhibit tumor proliferation and induce programmed cell death. These effects are mediated by the activation of the p53 pathway, regulation of the Bax/Bcl-2 genes, and inhibition of the Wnt/β-catenin signaling pathway. These peptides show high selectivity for cancer cells, which they preferentially target due to their affinity for over-expressed receptors such as NRP1 or FPRL1, or their ability to penetrate altered cell membranes (Aissaoui-Zid *et al.*, 2021; Moslah *et al.*, 2022; Chen *et al.*, 2025; El-Qassas, Abdelatti et El-Badri, 2025). This selectivity is observed in both *in vitro* and *in vivo* models. Our results are consistent with those of Al-Asmari et *al*. (2016), who demonstrated that the venom of *Androctonus crassicauda* induced an increase in apoptotic cells, reactive oxygen species, and cell cycle arrest in breast and colorectal cancer cells (Al-Asmari, Islam et Al-Zahrani, 2016). Similarly, scorpion peptides target ion channels to inhibit cancer cell growth and metastasis (Srairi-Abid *et al.*, 2019). The venom of *A.amoreuxi* has shown potential cytotoxic effects on tumour cells via antiproliferative, apoptotic, and antiangiogenic activities (Salem *et al.*, 2016). Although most studies have shown that peptides and crude scorpion venoms have promising anti-cancer effects, these effects have mostly been reported only *in vitro* in cell lines, thus limiting the

transposition of results to humans, and few studies have thoroughly assessed selectivity towards healthy cells or long-term systemic toxicity. The diversity of the cell lines examined, the lack of dose standardization administered, and the variability of the proposed mechanisms complicate any rigorous comparison.

Other peptide fractions or whole venoms modulate both the tumor microenvironment and immune responses, notably by promoting the polarization of macrophages towards a pro-inflammatory M1 phenotype, associated with an increase in the production of cytokines (TNF-α, IL-12, IFN-γ) and NO. The venoms of *Mesobuthus eupeus* and *Androctonus crassicauda* are particularly active in this area, participating in an amplification of anti-cancer responses (Sadeghi *et al.*, 2024; Ghadiri *et al.*, 2025). In addition, peptides such as BmKK2 (*Buthus martensii* Karsch) and sVmKTx (*Vaejovis mexicanus smithi*) selectively target the Kv1.3 potassium channel, involved in the activation of effector memory T lymphocytes offering therapeutic prospects in the treatment of autoimmune diseases (Csoti *et al.*, 2022; Xu *et al.*, 2025). In 2019, the venom of the scorpion *Androctonus amoreuxi* showed promising therapeutic potential against rheumatoid arthritis thanks to its analgesic, antioxidant, and anti-inflammatory effects, without causing any notable side effects (Hassan *et al.*, 2019). Research has shown that SVHRP and SVHRSP have neuroprotective properties, indicating their potential in the fight against neurodegenerative diseases such as Parkinson's disease and epilepsy. Indeed, these studies have demonstrated an improvement in memory, a reduction in neuronal loss, and a reduction in inflammation of the nervous system (Zhang *et al.*, 2022, 2023).

On the antimicrobial side, several scorpion peptides show potent bactericidal activity, sometimes enhanced by encapsulation techniques (such as chitosan) or molecular engineering (Gláucia-Silva *et al.*, 2024). Their mechanisms of action are based mainly on the induction of oxidative stress, disruption of cell membranes (Luo *et al.*, 2021), and inhibition of biofilm formation (Jantaruk *et al.*, 2024), with efficacy in some cases surpassing that of conventional antibiotics. The low risk of resistance development observed with certain derivatives reinforces their interest in dealing with multi-resistant bacterial strains (Zhao *et al.*, 2021; Gallegos-Monterrosa *et al.*, 2025). This is in line with the results of studies published before the analyzed period, such as the bactericidal capacity of Uy234, Uy17, and Uy192 on multi-resistant pathogenic bacteria (Cesa-Luna *et al.*, 2019). The peptide Css54, derived from *Centruroides suffusus suffusus,* acts by disrupting the integrity of the cell membrane, inducing membrane depolarization and generating fatal oxidative stress for *Candida albicans* (Park *et al.*, 2024).

Scorpion venom exhibits remarkable anti-parasitic activity against Plasmodium gallinaceum*, Echinococcus granulosu, Leishmania guyanensis, Leishmania amazonensis,* and *Toxoplasma gondii* by reducing their growth and replication and by inducing oxidative stress or the immune response (de Assis *et al.*, 2021; Pedron *et al.*, 2021; Pimentel *et al.*, 2021; Al-Malki *et al.*, 2022; Rostamkolaie *et al.*, 2022; Pereira *et al.*, 2023). However, it should be noted that these activities are mainly observed at relatively high concentrations and that exploration of *in vivo* activity remains relatively limited. The enzymatic stability, selectivity towards human cells, and optimal formulation of these peptides deserve particular attention.

Certain peptides, such as chlorotoxin (ClTx), ODAMP2, ODAMP5, and BmKn2-T5, also exert direct antiviral activity by disintegrating the viral envelope, which prevents the entry and intracellular replication of viruses such as SARS-CoV-2, SIV, hepatitis C virus HCV, dengue fever (DENV), herpes simplex virus type 1 (HSV-1), and JEV (da Mata *et al.*, 2020; Miyashita *et al.*, 2021; Sharma *et al.*, 2021; Xia *et al.*, 2024; Soorki, 2025). In 2012, a study demonstrated that the Kn2-7 synthetic peptide from BmKn2 (*Mesobuthus martensii* Karsch) could inhibit HIV-1 by direct interaction with the viral particle (Chen *et al.*, 2012). rEv37 from *Euscorpiops validus* can inhibit DENV, HCV, ZIKV, and HSV-1 infections in a dose-dependent manner at non-cytotoxic concentrations (Li *et al.*, 2019). Obviously, these results are still mainly preliminary and need to be validated by mechanistic studies and *in vivo* infectious models.

About analgesic activity, several peptides derived from scorpion venom have demonstrated effective pain reduction by modulating nociceptive ion channels. These include Leptucin from *Hemiscorpius lepturus*, Makatoxin-3 and N58A from *Buthus martensii* Karsch, whose inhibition of sodium and calcium channels reduces the transmission of nociceptive signals (Shoukry *et al.*, 2020; Bagheri-Ziari *et al.*, 2021; Li *et al.*, 2021; Chen *et al.*, 2022). Other studies confirm the analgesic efficacy of peptides such as ω-Buthitoxin-Hf1a from *Hottentotta franzwerneri* (Wang *et al.*, 2024), BotA from *Buthus occitanus tunetanus* (Maatoug *et al.*, 2018), and BmK AGP-SYPU1 from *Buthus martensii* Karsch (Wang *et al.*, 2011), which also act via the selective inhibition of ion channels involved in nociception.

Finally, very few studies have focused on the antioxidant properties of scorpion venom. This could be explained by the fact that peptides extracted from venom are generally associated with pro-oxidant effects, inducing oxidative stress in human bodies. However, some of these molecules behave oppositely, such as

Stigmurin from *Tityus stigmurus*, which has an antioxidant effect by reducing free radicals and neutralizing reactive oxygen species (ROS) before they damage cell membranes and macromolecules (Daniele-Silva *et al.*, 2021). However, *in vivo* evidence is still insufficient to confirm these properties in a real disease context.

Certain scorpion peptides are classified according to their target type of activity (anti-inflammatory, anti-cancer, analgesic, etc.). They share several mechanisms of action, such as the induction of oxidative stress and the disruption of cell membranes. These mechanisms occur across multiple types of effects, such as anti-cancer, anti-microbial, and even anti-viral effects. This versatility could enhance the treatment of complex diseases in several ways, particularly cancers associated with chronic infections or autoimmune diseases.

This review reveals an impressive reservoir of bioactive peptides, but several limitations must be considered. Most of the studies listed in this review and others already published are preclinical, conducted *in vitro* or on animal models. In addition, the lack of standardization in peptide extraction, purification, and testing protocols makes it difficult to compare results directly between studies. Furthermore, the venoms of many scorpion species have yet to be exploited, and a thorough characterization of venom composition is essential to better understand the mechanisms of action of each component while avoiding the harmful effects of others.

One of the main obstacles encountered in the use of this therapeutic treasure is its toxicity, which limits its application in the pharmaceutical field. To validate the therapeutic use of venom, it is essential to include an in-depth toxicological study to ensure short- and long-term safety by analyzing hemolytic, histopathological, and chronic toxicity in addition to behavioral observations, the absence of visible events, and preliminary evaluations.

In addition, the development of synthetic peptides inspired by natural venoms is opening up new prospects. These analogues can be designed to improve stability, enhance biological activity, or reduce toxicity. By modifying their structure, it is possible to increase their efficacy while maintaining an optimal safety profile. This capability represents a significant advantage in the search for new therapies derived from scorpion venoms.

Despite these limitations, scorpion venom peptides now appear to be serious therapeutic candidates, with a multi-target pharmacological profile, increased specificity of action, and high potential for pharmaceutical innovation. To improve the clinical transposition of these peptides, efforts need to be focused on: developing more relevant *in vivo* models, developing stable and targeted formulations (nanoparticles, peptide modifications), and biotechnological production of standardized, safe, and economically viable peptides. The integration of high-throughput screening technologies, structural bioinformatics, and peptide engineering tools will also enable us to better predict the efficacy, stability, and molecular interactions of these compounds.

CONCLUSIONS

This systematic review highlights the significant therapeutic potential of peptides derived from scorpion venom. Their unique structural diversity and high target specificity demonstrate remarkable efficacy across multiple medical domains. These effects have been observed in oncology, infectiology (bacteriology and virology), neurology, as well as in the treatment of inflammation and chronic pain. This analysis validates the functional richness of these peptides and their growing scientific interest as potential alternatives to conventional therapies. Nevertheless, despite the significant progress made both in the laboratory and in clinical settings, their application remains limited by many obstacles, including residual toxicity, poor biological stability, and a lack of methodological standardization between studies. From this perspective, integrating these peptides into targeted therapeutic approaches, supported by vectorization technologies and bioengineering, could represent a major advance in managing complex pathologies, including drug-resistant cancers, emerging viral infections, and refractory neuropathic pain.

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Authors contributions

SN: Conceptualization; Methodology; Investigation; Formal analysis; Visualization; Writing – original draft; Writing – review & editing.

BB: Conceptualization; Methodology; Validation; Writing – review & editing.

AE: Conceptualization; Methodology; Validation; Writing – review & editing.

AK: Writing – review & editing.

OT: Conceptualization; Methodology; Supervision; Validation; Writing – review & editing.

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