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Revisão

Crotamine: From Rattlesnake Toxin to a Multitarget Therapeutic Tool

Crotamina: Da Toxina de Cascavel a uma Ferramenta Terapêutica Multialvo

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ABSTRACT

Crotamine, a cationic peptide obtained from the venom of the snake *Crotalus durissus terrificus*, has emerged as a multifunctional biomolecule of growing interest in biomedical research. The molecule is recognized for its remarkable structural stability and its ability to efficiently cross cellular membranes, enabling rapid intracellular internalization. Crotamine exhibits a broad spectrum of biological activities, including antimicrobial, antifungal, antiviral, antitumor, immunomodulatory, analgesic, and emerging anti-obesogenic effects. Notably, the peptide demonstrates preferential uptake by rapidly dividing cells and interacts with nucleic acids, supporting its potential application as a carrier system for intracellular delivery. This review provides a critical synthesis of studies published between 2015 and 2025, addressing the structural characteristics, mechanisms of action, and biotechnological and pharmacological applications of crotamine. A total of 144 studies were identified and screened, of which 56 met the inclusion criteria and were included in the final qualitative synthesis. The available evidence positions crotamine as a promising peptide for the development of innovative therapeutic and biotechnological products, particularly in the context of drug delivery systems and targeted therapies. Nevertheless, despite these advances, additional *in vivo* and clinical investigations remain essential to fully establish its safety, efficacy, and translational potential.

Keywords: Therapeutic applications; biotechnology; *Crotalus durissus terrificus;* crotamine; bioactive peptides

RESUMO

A crotamina, um peptídeo catiônico obtido do veneno da serpente *Crotalus durissus terrificus*, tem emergido como uma biomolécula multifuncional de crescente interesse na pesquisa biomédica. A molécula é reconhecida por sua notável estabilidade estrutural e por sua capacidade de atravessar eficientemente membranas celulares, permitindo rápida internalização intracelular. A crotamina apresenta um amplo espectro de atividades biológicas, incluindo efeitos antimicrobianos, antifúngicos, antivirais, antitumorais, imunomoduladores, analgésicos e emergentes efeitos antiobesogênicos. Notavelmente, o peptídeo demonstra captação preferencial por células com alta taxa proliferativa e interage com ácidos nucleicos, sustentando seu potencial como sistema carreador para entrega intracelular. Esta revisão apresenta uma síntese crítica de estudos publicados entre 2015 e 2025, abordando as características estruturais, mecanismos de ação e aplicações biotecnológicas e farmacológicas da crotamina. Um total de 144 estudos foi identificado e triado, dos quais 56 atenderam aos critérios de inclusão e foram incorporados à síntese qualitativa final. As evidências disponíveis posicionam a crotamina como um peptídeo promissor para o desenvolvimento de produtos

terapêuticos e biotecnológicos inovadores, particularmente no contexto de sistemas de entrega de fármacos e terapias-alvo. Entretanto, apesar desses avanços, investigações adicionais *in vivo* e estudos clínicos permanecem essenciais para estabelecer plenamente seu perfil de segurança, eficácia e potencial translacional.

Palavras-chave: Aplicações terapêuticas; biotecnologia; *Crotalus durissus terrificus*; crotamina; peptídeos bioativos

INTRODUCTION

Crotamine is a venom-derived peptide purified from the rattlesnake *Crotalus durissus terrificus*, commonly known as the South American rattlesnake. This bioactive molecule has attracted scientific attention due to its diverse biological properties, particularly its antiproliferative, antimicrobial, and antifungal activities [1, 2]. Crotamine has a variety of biological functions and has been attracting scientific interest in recent years. Experimental evidence indicates that crotamine can internalize into multiple cell types, crossing cellular membranes and accumulating in the nucleus, which classifies it as a cell-penetrating peptide. This property enables its use as a marker of dividing cells, an intracellular tracking agent, and a DNA delivery carrier for eukaryotic cells [3, 4].

Crotamine primarily acts through interaction with and disruption of cellular lipid membranes, leading to loss of membrane integrity and subsequent microbial cell death [5, 6]. It exhibits low toxicity toward non-tumor mammalian cells and lacks hemolytic activity, suggesting a favorable safety profile for medical or industrial applications [7, 8]. One of the most relevant features associated with crotamine is its ability to penetrate cells without causing immediate damage, further supporting its classification as a cell-penetrating peptide. In addition to its cellular transport properties, crotamine displays antimicrobial and immunomodulatory activities, further expanding its biotechnological potential [9, 10].

Recent studies have investigated its activity against clinically relevant bacteria and fungi, which is particularly significant in the current context of increasing antimicrobial resistance. These findings indicate that crotamine may serve as a model for the development of novel antimicrobial peptides or as a structural template for the synthesis of derived molecules with enhanced specificity and reduced toxicity. Given its structural and functional attributes, crotamine emerges as a biomolecule of considerable scientific relevance. Its study not only advances knowledge of animal toxins but also opens promising avenues for innovation in biomedicine, pharmacology, and biotechnology. Therefore, understanding its properties, mechanisms of action, and potential therapeutic applications is essential to support future strategies for clinical and technological exploitation, consolidating crotamine as a molecule of strategic interest in contemporary research.

METHODS

This study consisted of a literature review focused on biological properties, mechanisms of action, and therapeutic potential of crotamine, a peptide isolated from the venom of *Crotalus durissus terrificus*. The review question was structured according to a PICO strategy adapted for preclinical and experimental studies, as summarized in Table 1.

Table 1 - PICO strategy used to formulate the review question.

Component	Description
Population (P)	Experimental biological models, cancer cell lines, microorganisms, and in vivo systems evaluated in preclinical studies
Intervention (I)	Exposure or administration of crotamine derived from Crotalus durissus terrificus venom
Comparison (C)	Untreated controls, baseline experimental conditions, or conventional therapeutic approaches when applicable
Outcome (O)	Biological, pharmacological, antimicrobial, antitumor, anti-inflammatory, immunomodulatory, analgesic, anti-obesogenic, and biotechnological effects associated with crotamine

Source: Author, 2026

The literature search was conducted using PubMed, Scopus, and Web of Science databases. The literature search was performed between August and December 2025. Controlled vocabulary terms (MeSH) and Boolean operators (AND/OR) were applied when appropriate, particularly in PubMed searches. The search strategy was adapted according to the requirements of each database. In PubMed, the following search string was applied: ("crotamine" OR "Crotalus durissus terrificus toxin") AND ("antitumor activity" OR "antimicrobial activity" OR "cell-penetrating peptide" OR "biotechnological application"). Equivalent combinations of keywords and Boolean operators were adapted for Scopus and Web of Science databases.

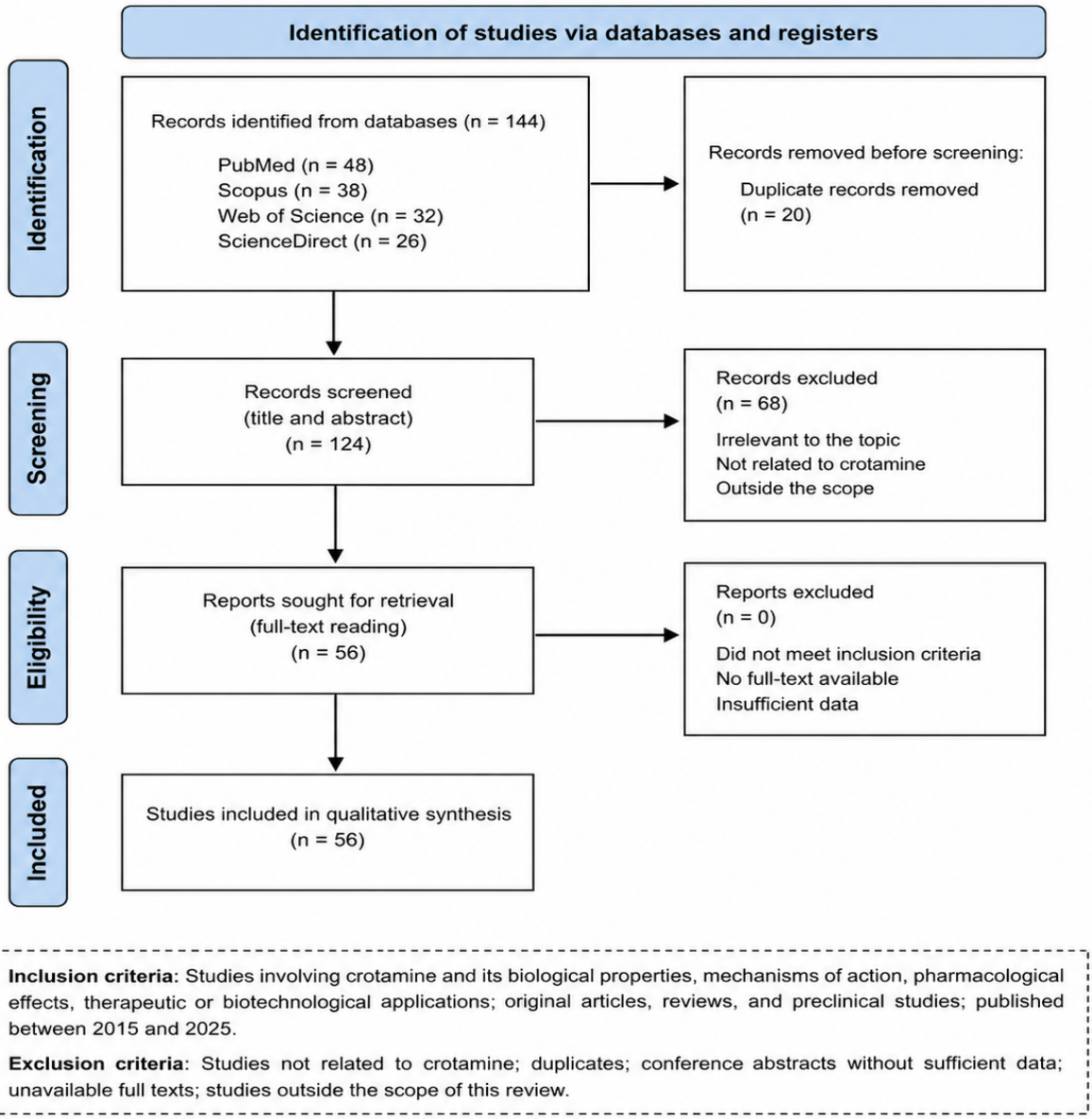
Articles published between 2015 and 2025 in English were considered eligible for inclusion. Original experimental and preclinical studies addressing the structure, biological activities, mechanisms of action, and therapeutic applications of crotamine were included. Duplicate records, studies without full-text availability, conference abstracts, editorials, and articles unrelated to the proposed topic were excluded.

The study selection process followed PRISMA recommendations, including identification, screening, eligibility assessment, and inclusion stages. Initially, records retrieved from the databases were exported to the Rayyan software for organization and duplicate removal. Subsequently, titles and abstracts were screened according to the predefined eligibility criteria. Articles considered potentially relevant were evaluated through full-text reading, resulting in the final inclusion of 56 studies. The screening and selection process was conducted independently by two reviewers following predefined inclusion and exclusion criteria to minimize selection bias. Disagreements regarding study eligibility were resolved through discussion and consensus between the reviewers. The study selection process was conducted according to PRISMA recommendations, as illustrated in Figure 1.

Due to the heterogeneity of the included studies, involving predominantly experimental and preclinical designs, a standardized risk-of-bias tool was not uniformly applicable to all studies. Nevertheless, methodological quality was critically assessed according to study design, experimental clarity, reproducibility of methods, adequacy of controls, and consistency of reported outcomes.

Data extraction included information related to author/year, experimental model, crotamine therapeutic application, biological activity, and principal findings. The extracted information was organized descriptively and synthesized into summary tables to facilitate comparative analysis among the included studies. The main characteristics and findings of the studies included in this review are summarized in Supplementary Table S1.

Figure 1 – PRISMA flow diagram of study selection process.



Source: Author, 2026

REVIEW

Snake venoms constitute complex biochemical systems mainly composed of proteins and peptides, responsible for a broad spectrum of biological functions. With proteins and peptides representing approximately 90–95% venom composition. The extensive biochemical arsenal present in these venoms compromises molecules capable of modulating a wide range of biological functions with high specificity and selectivity for distinct pharmacological targets, such as receptors, ion channels, and enzymes [11–13].

Consequently, these molecules have been progressively utilized either as therapeutic agents or as template/prototypes for the development of novel pharmacological agents, some of which are already used in clinical settings e for the treatment of human

diseases. The South American rattlesnake *Crotalus durissus terrificus* is characterized by relatively simpler venom composition compared to other vipers or snake species belonging to the genus *Crotalus*. Despite this simplicity, its venom contains a set of toxins with significant potential for targeting diverse medical conditions, particularly in cardiovascular, antitumor, anti-inflammatory, immunosuppressive, analgesic, metabolic, and antimicrobial applications. Among the toxins produced by *Crotalus durissus terrificus*, crotamine stands out due to its strong clinical potential [14, 15].

Crotalus durissus terrificus belongs to the family Viperidae, subfamily *Crotalinae*. It is a venomous snake characterized by the presence of a loreal pit (thermosensory organ), a triangular head, a robust body, and a rattle at the tip of the tail composed of keratinous segments that produce sound when shaken a characteristic feature of the genus *Crotalus*. This species exhibits terrestrial and nocturnal habits and may exceed 1.50 meters in length [16, 17].

It is known for its neurotoxic, myotoxic, and coagulant venom, which is rich in gyroxin, crotamine, crotoxin, and convulxin [18, 19]. The species has a wide distribution throughout Latin America, extending from northern Argentina to the northern continental region, including, Argentina, Bolivia, Brazil, Colombia, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay and Venezuela with greater density and subspecies diversity in South America. Studies have reported an expansion of its geographical range toward previously forested areas, possibly associated with climate change and land-use alterations [20].

This species is widely distributed in Brazil, being more common in regions with dry climates and open vegetation, such as the Southeast (São Paulo, Minas Gerais, Espírito Santo), Midwest (Goiás, Mato Grosso, and Mato Grosso do Sul), South (Paraná and Santa Catarina), and the interior of the Northeast (Bahia, Piauí, Maranhão, and Pernambuco), especially in Cerrado and Caatinga ecosystems. It is rare or absent in dense Amazon rainforest areas and in humid coastal regions of the Atlantic forest. This species prefers open habitats, including grasslands, forest edges, and anthropized areas, and is frequently found in pastures and agricultural fields, which increases the risk of human–snake encounters [21, 22].

The venom of *Crotalus durissus terrificus* consists of a complex mixture primarily made up of the neurotoxic phospholipase A_2 (crotoxin), serine proteases, and other components such as convulxin and crotamine. Crotoxin is responsible for the high lethality of the venom, inducing neuromuscular paralysis, myotoxicity, and, in severe cases, acute renal failure. The venom composition is relatively simple, with a limited number of proteins accounting for most of its toxic effects, and it exhibits lower hemorrhagic activity compared to that of other rattlesnake species [23].

Crotamine is a major constituent of the venom of the South American rattlesnake *Crotalus durissus terrificus* (18,24). It represents one of the predominant toxins present in this venom, accounting for approximately 12–25% of its crude dry weight. Over the past decade, growing evidence from various studies suggests that this polypeptide shows significant potential increasing data from different research groups indicate that this polypeptide presents a substantial potential as a platform for biotechnological and biomedical applications [24–26].

The expression of crotamine can vary widely among individuals, even within the same geographic region. “The presence and concentration of crotamine in venom are modulated by genetic and environmental factors, as well as by variables such as sex, age, and captive conditions. Although time in captivity may reduce the overall toxicity of the venom, it does not necessarily alter the presence of crotamine, which, when detected, may account for up to approximately 20% of its composition. Crotamine is a venom-derived peptide with unique properties, exhibiting a broad spectrum of pharmacological activities, including antifungal, antiviral, antibacterial, antiplasmodial (*in vitro*), and antitumor effects, in addition to its therapeutic potential related to its ability to act as a cell-penetrating peptide [27, 28]. Crotamine is a venom-derived peptide with unique properties and exhibits a wide range of pharmacological activities, including antifungal, antiviral, antibacterial, antiplasmodial (in culture), and antitumor effects, among other therapeutic potentials, acting as a cell-penetrating peptide [29–31].

Structurally, crotamine displays a unique alpha/beta fold similar to that of human B-defensins and interacts with lipid membranes and ion channels, particularly sodium and potassium channels

[32, 33]. The structural similarity of crotamine to B-defensins contributes to its ability to interact with negatively charged membranes, a feature that is important for its antifungal activity [7, 34]. Crotamine is a low-molecular-weight mini-protein composed of approximately 42 amino acids and three disulfide bonds, which confer high conformational stability and resistance. This compact structure facilitates its interaction with different tissues and cell types, a fundamental characteristic underlying its pharmacological actions [8, 35, 36].

Crotamine stands out for its unique ability to cross biological membranes and selectively penetrate highly proliferative cells. This property makes crotamine a valuable platform for intracellular delivery of molecules, as well as for diagnostic applications and antitumor therapies [4, 37]. Crotamine crosses cellular membranes through electrostatic interactions at the cell surface, followed by endocytosis and release of endosomal contents into the cytosol. Once in the cytosol, crotamine interacts with DNA, interferes with replication, and induces apoptosis [10, 38].

Studies have demonstrated that crotamine exhibits affinity for nuclear structures, including chromosomes and centrioles. This feature makes it a potential vehicle for the targeted delivery of therapeutic molecules to the nucleus, such as plasmid DNA, oligonucleotides, or drugs that act at the genetic level. Its ability to cross the nuclear membrane without causing significant toxicity further expands its applications in gene therapy and molecular biotechnology [3, 39].

Crotamine contains a sequence rich in positively charged residues, such as lysine and arginine, which allows electrostatic interaction with negatively charged DNA or RNA molecules [3, 38]. This interaction leads to the formation of stable crotamine–nucleic acid complexes that can be internalized by cells via endocytosis. After cellular uptake, crotamine facilitates the escape of these complexes from the endosomal compartment and promotes the delivery of genetic material directly into the cytosol or even into the nucleus, particularly in dividing cells. This translocation occurs efficiently and with low cytotoxicity, a critical feature for safe therapeutic applications [3, 10, 40, 41].

Crotamine exhibits significant antiviral activity *in vitro* studies, particularly against enteroviruses, which are responsible for neurological infections and hand, foot, and mouth disease. Experimental evidence has demonstrated that crotamine can inhibit up to 99% of viral replication, acting both through direct virucidal effects and by blocking post-entry stages of the viral life cycle within host cells. This activity shows high selectivity, efficacy, and low cytotoxicity even under conditions of high viral load, indicating promising therapeutic potential. However, the antiviral activity of crotamine appears to be virus-specific, as it has not shown relevant activity against other viruses such as dengue and yellow fever viruses. To date, the available evidence is limited to cell-based assays, with no confirmation in animal models or clinical studies, which precludes definitive conclusions regarding its safety and effectiveness in living organisms. Nevertheless, additional studies indicate that crotamine also exhibits antimicrobial, antifungal, and immunomodulatory effects, inducing the production of inflammatory mediators as well as nitric oxide, which may indirectly contribute to its antiviral activity [42, 43].

Crotamine has also attracted attention due to its antimicrobial activity, particularly against eukaryotic microorganisms such as yeasts and fungi. Studies have shown that this peptide exhibits significant antifungal activity, inhibiting the growth of species such as *Candida albicans*, *Cryptococcus neoformans*, and other pathogenic yeasts, while displaying low activity against Gram-positive and Gram-negative bacteria [35, 44].

Its activity is associated with its positive charge, which enables structures of the fungal plasma membrane and cell wall, resulting in increased membrane permeability and cell lysis. In addition, crotamine can penetrate fungal cells and interfere with intracellular processes essential for survival and cell division [45]. Crotamine also enhances the effects of conventional antifungal agents, such as fluconazole, against *C. albicans* and *C. tropicalis* [35, 44].

The potential application of crotamine as a molecular template for the design of new antimicrobial compounds is further reinforced by their low toxicity toward non-tumor mammalian cells, making it a promising candidate for future investigations and the development of antimicrobial therapeutic strategies.[37]. Crotamine represents a valuable tool in the fight against multidrug-resistant pathogens, with

prospective applications in medicine and biotechnology ([8]. Electron microscopy studies confirm ultrastructural alterations in *C. albicans* following exposure to crotamine. The mechanism involves the generation of oligomeric pores in cellular membranes; a strategy shared with defensins [5, 7].

Recent evidence suggests that crotamine is capable of stimulating innate immune responses by enhancing the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, as well as by promoting the activation of neutrophils and macrophages, which play central roles in the early response to pathogens. These findings indicate that crotamine may act as a modulator of the immunological microenvironment, thereby facilitating the activation of host defense mechanisms. This immunomodulatory effect is likely associated with its capacity to interact with cellular membranes and pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), leading to the activation of intracellular signaling pathways that ultimately result in the production of inflammatory mediators [46–48].

Furthermore, crotamine promotes cytokine secretion and enhances macrophage phagocytic activity and nitric oxide (NO) production, upregulating both gene expression and protein levels of TNF-α and inducible nitric oxide synthase (iNOS). It induces macrophage activation through NF-κB–dependent signaling pathways, thereby modulating the host immune response. These properties highlight its potential as an immunostimulatory peptide and suggest its possible application as a therapeutic agent aimed at macrophage activation in clinical settings [1, 48].

Studies have shown that this toxin is capable of disrupting the cell cycle and inducing programmed cell death (apoptosis) in different cancer cell lines, including melanoma, hepatocellular carcinoma, leukemias, and sarcomas. This selectivity is attributed to the fact that tumor cells generally exhibit higher expression of sulfated proteoglycans on the cell surface, which facilitates crotamine interaction and internalization. Once inside the cell, crotamine can interfere with organelles such as the cells nucleus and lysosomal compartments; and modulate intracellular signaling cascades associated with cell survival [49, 50].

Given the selective cytotoxicity exhibited by venom components toward tumor cells in comparison to healthy cells, the development of novel anticancer strategies based on bioactive compounds from rattlesnake venom may provide advantages over conventional therapies, such as chemotherapy and radiotherapy, which are known to also damage normal cells. In this context, compounds derived from the venom of the rattlesnake Crotalus durissus terrificus emerge as promising alternatives for the treatment of tumors resistant to currently available drugs [29, 51, 52].

"Crotamine has exhibited pronounced analgesic and anti-inflammatory effects in experimental murine models of pain, significantly attenuating nociceptive behaviors and paw edema. Moreover, TNF-α levels, a key pro-inflammatory mediator, were substantially reduced in treated animals, indicating that its anti-inflammatory activity is associated with modulation of this cytokine. Notably, the pharmacological actions of crotamine were not reversed by naloxone, an opioid receptor antagonist, suggesting that its mechanism of action is independent of classical opioid pathways, such as those induced by morphine. This non-opioid mechanism highlights crotamine as a promising candidate for the design of novel therapeutics targeting pain and inflammation, with the potential to provide safer and more effective alternatives that circumvent the risks of tolerance and dependence commonly associated with opioid-based treatments [53, 54].

Computational and experimental studies indicate that crotamine interacts with multiple metabolic targets related to obesity, including the glucagon-like peptide-1 receptor (GLP-1R). These interactions may modulate pathways involved in appetite control, glucose metabolism, and thermogenesis, thereby contributing to its anti-obesogenic effects [55]. By contributing to reduced weight gain and increasing adipose tissue browning, in addition to improving glucose tolerance and insulin sensitivity, crotamine has therefore been proposed as an anti-obesogenic peptide [15, 56].

Studies have not reported significant toxicity in organs or tissues, even following prolonged administration. Positive metabolic effects, for example reductions in cholesterol and triglyceride levels, were more evident in non-tumor-bearing animals, indicating benefits beyond their antitumor activity [49, 56].

FINAL CONSIDERATIONS

Crotamine emerges as a multifunctional biomolecule of considerable scientific interest, integrating distinctive structural attributes with a wide spectrum of biological activities. Its capacity to penetrate cellular membranes, modulate immune responses, interact with nucleic components, and exert antimicrobial, antifungal, antiviral, antitumor, analgesic, and anti-inflammatory effects underscores its substantial therapeutic potential. Furthermore, its preferential selectivity toward cells with high proliferation rates, low cytotoxicity to normal tissues, and remarkable structural stability reinforce its value as a promising prototype for the development of innovative pharmacological agents.

Collectively, the studies reviewed indicate that crotamine may act not only as a direct therapeutic molecule but also as a versatile platform for therapeutic delivery systems and gene transfer applications. Nevertheless, despite these encouraging results, comprehensive in vivo investigations and well-designed clinical studies remain essential to thoroughly characterize its safety profile, biodistribution, therapeutic efficacy, and potential adverse effects.

Despite the promising biological and therapeutic properties of crotamine, some limitations remain evident in the current literature. Most available studies are preclinical, involving *in vitro* or animal experimental models, with a limited number of clinical investigations. In addition, considerable heterogeneity exists regarding crotamine dosage, experimental conditions, and therapeutic approaches, which makes direct comparisons between studies difficult. These limitations highlight the need for further standardized and clinical studies to better establish the safety, efficacy, and translational potential of crotamine for biomedical applications.

Supplementary Table S1. Summary of experimental and preclinical studies evaluating the biological and therapeutic applications of crotamine derived from ***Crotalus durissus terrificus.***

Title	Year	Study model	Therapeutic application	Crotamine dosage/ concentration	Main findings
Insights into the mechanism of crotamine and potential targets involved in obesity-related metabolic pathways	2024	Computational / Experimental	Anti-obesogenic activity	Not applicable	Identified metabolic pathways and molecular targets potentially associated with anti-obesity effects of crotamine
Antinociceptive and anti-inflammatory effects of recombinant crotamine in mouse models of pain	2021	*In vivo*	Anti-inflammatory / Analgesic	1–10 mg/kg	Reduced nociception and inflammatory response in murine models
The antineoplastic potential of crotoxin isolated from *Crotalus durissus terrificus* snake venom on oral squamous cell carcinoma	2023	*In vitro* / Experimental	Antitumoral	Not reported	Demonstrated cytotoxic and antineoplastic effects against oral squamous carcinoma cells
Acute toxicity, antinociceptive, and anti-inflammatory activities of the orally administered crotamine in mice	2021	*In vivo*	Anti-inflammatory / Analgesic	1–20 mg/kg	Demonstrated low toxicity and significant anti-inflammatory and analgesic activity
Cytotoxic effect of crotoxin on cancer cells and its antitumoral effects correlated to tumor microenvironment: A review	2023	Review	Antitumoral	Not applicable	Summarized antitumoral effects of crotoxin and its interaction with tumor microenvironment
The secreted metabolome of hela cells under effect of crotamine, a cell-penetrating peptide from a rattlesnake using NMR-Based metabolomics analyses	2022	*In vitro*	Cell-penetrating peptide / Metabolomics	1–5 µM	Identified metabolic alterations induced by crotamine in HeLa cells
Intradermal application of crotamine induces inflammatory and immunological changes *in vivo*	2019	*In vivo*	Immunomodulatory / Inflammatory	10 µg	Induced inflammatory and immunological alterations following intradermal administration
Immunotherapeutic potential of crotoxin: Anti-inflammatory and immunosuppressive properties	2018	Review	Immunomodulatory	Not applicable	Discussed anti-inflammatory and immunosuppressive therapeutic potential
Report of the Vth workshop of the spanish national network on mycotoxins and toxigenic fungi and their decontamination processes	2021	Review / Scientific report	Toxicology / Biological activity	Not applicable	Discussed advances in toxin research and decontamination strategies involving bioactive compounds
***In vitro* antifungal activity of three synthetic peptides against *Candida auris* and other *Candida* species of medical importance**	2023	*In vitro*	Antifungal	10–40 µM	Demonstrated antifungal activity against Candida species including Candida auris
Effect of proteins isolated from Brazilian snakes on enterovirus A71 replication cycle: An approach against hand, foot and mouth disease	2023	*In vitro*	Antiviral	Not reported	Inhibited enterovirus A71 replication cycle
Nucleic acid drugs: Recent progress and future perspectives	2024	Review	Drug delivery / Nucleic acid therapeutics	Not applicable	Discussed advances in nucleic acid therapeutics and intracellular delivery systems

Title	Year	Study model	Therapeutic application	Crotamine dosage/ concentration	Main findings
Recent advances and prospects of nucleic acid therapeutics for anti-cancer therapy	2024	Review	Antitumoral / Drug delivery	Not applicable	Reviewed therapeutic applications of nucleic acid delivery systems in cancer
Intraspecific differences in the venom of *Crotalus durissus cumanensis* from Colombia	2022	Experimental / Venomics	Venom characterization	Not applicable	Demonstrated compositional variations in venom according to geographic distribution
Membrane-modifying properties of crotamine, a small peptide-toxin from *Crotalus durissus terrificus* venom	2014	Experimental / *In vitro*	Membrane interaction	1–20 µM	Demonstrated membrane-disruptive and membrane-modifying effects
Synthetic polypeptide crotamine: Characterization as a myotoxin and as a target of combinatorial peptides	2022	Experimental	Myotoxic activity	1–10 µM	Characterized biological and myotoxic properties of synthetic crotamine
Global trend in research conducted on crotamine: A bibliometric analysis	2024	Bibliometric analysis	Scientific production / Biotechnology	Not applicable	Evaluated global scientific trends and publication patterns involving crotamine
Effects of crotamine in human prostate cancer cell line	2024	*In vitro*	Antitumor	0.1–10 µM	Demonstrated cytotoxic effects against prostate cancer cells
Crotamine in *Crotalus durissus*: Distribution according to subspecies and geographic origin, in captivity or nature	2020	Experimental / Venomics	Venom characterization	Not applicable	Demonstrated variation in crotamine distribution according to subspecies and geographic origin
Global proteomic and functional analysis of *Crotalus durissus collilineatus* individual venom variation and its impact on envenoming	2019	Proteomic / Experimental	Venom characterization	Not applicable	Identified proteomic variations and functional differences among venom samples
Crotamine: Function diversity and potential applications	2016	Review	Biotechnology / Therapeutic applications	Not applicable	Summarized biological activities and therapeutic potential of crotamine
In-Depth Venome of the Brazilian Rattlesnake *Crotalus durissus terrificus*: An Integrative Approach Combining Its Venom Gland Transcriptome and Venom Proteome	2018	Proteomic / Experimental	Venomics / Proteomics	Not applicable	Characterized venom gland transcriptome and venom proteome composition
Global change explains the neotropical rattlesnake *Crotalus durissus* (Serpentes: Viperidae) range expansion in South America	2023	Ecological study	Geographic distribution	Not applicable	Demonstrated environmental factors associated with species range expansion
Geographic variation of individual venom profile of *Crotalus durissus* snakes	2020	Experimental / Venomics	Venom characterization	Not applicable	Demonstrated geographic variation in venom composition
***Crotalus durissus terrificus* crotapotin naturally displays preferred positions for amino acid substitutions**	2017	Molecular / Experimental	Structural biology	Not applicable	Identified amino acid substitution patterns in crotapotin molecules
Biological and medical aspects related to South American *Rattlesnake Crotalus durissus* (Linnaeus, 1758): A view from Colombia	2022	Review	Biological activity / Toxicology	Not applicable	Reviewed biological, toxicological, and medical aspects of Crotalus durissus

Title	Year	Study model	Therapeutic application	Crotamine dosage/ concentration	Main findings
Fauna digital do Rio Grande do Sul	2019	Ecological / Taxonomic	Species distribution	Not applicable	Documented fauna distribution and ecological aspects in Rio Grande do Sul
Bioprospection of rattlesnake venom peptide fractions with anti-adipose and anti-insulin resistance activity *in vitro*	2024	*In vitro*	Anti-obesogenic	1–50 µg/mL	Demonstrated anti-adipogenic and insulin resistance-modulating activity
The chemistry of snake venom and its medicinal potential	2022	Review	Biotechnology / Drug discovery	Not applicable	Reviewed medicinal applications of snake venom compounds
Snake venoms in drug discovery: Valuable therapeutic tools for life saving	2019	Review	Drug discovery	Not applicable	Discussed therapeutic applications of venom-derived bioactive molecules
Emerging antifungal targets and strategies	2022	Review	Antifungal	Not applicable	Reviewed novel antifungal therapeutic targets and strategies
Interaction of the rattlesnake toxin crotamine with model membranes	2014	Experimental / *In vitro*	Membrane interaction	0.5–10 µM	Demonstrated interaction of crotamine with lipid membrane models
Revisiting the potential of South American rattlesnake *Crotalus durissus terrificus* toxins as therapeutic, theranostic and/or biotechnological agents	2022	Review	Biotechnology / Therapeutic applications	Not applicable	Discussed therapeutic and biotechnological potential of rattlesnake toxins
Crotamine induces browning of adipose tissue and increases energy expenditure in mice	2018	*In vivo*	Anti-obesogenic	10 µg	Increased thermogenesis and adipose tissue browning in mice
Cell-penetrating peptides derived from animal venoms and toxins	2021	Review	Cell-penetrating peptides	Not applicable	Discussed CPP applications from venom-derived molecules
Crotamine cell-penetrating nanocarriers: Cancer-targeting and potential biotechnological and/or medical applications	2020	Review	Drug delivery / Antitumor	Not applicable	Discussed applications of crotamine as a cancer-targeting nanocarrier
Antineoplastic properties and pharmacological applications of *Crotalus durissus terrificus* snake venom	2022	Review	Antitumor	Not applicable	Reviewed antineoplastic properties of rattlesnake venom compounds
A native CPP from rattlesnake with therapeutic and theranostic properties	2022	Review	Cell-penetrating peptide / Theranostics	Not applicable	Discussed theranostic and intracellular delivery applications
State of the art in the studies on crotamine, a cell penetrating peptide from South American rattlesnake	2014	Review	Cell-penetrating peptide	Not applicable	Summarized structural and biological properties of crotamine
Mechanistic insights into functional characteristics of native crotamine	2018	Experimental	Biological activity	Not reported	Investigated functional and mechanistic properties of native crotamine
Co-Localization of crotamine with internal membranes and accentuated accumulation in tumor cells	2018	*In vitro*	Antitumoral / Cell internalization	1–5 µM	Demonstrated preferential accumulation in tumor cells

Title	Year	Study model	Therapeutic application	Crotamine dosage/ concentration	Main findings
Biophysical and pharmacological characterization of a full-length synthetic analog of the antitumor polypeptide crotamine	2020	Experimental	Antitumor	1–10 µM	Characterized pharmacological and antitumoral properties of synthetic crotamine
Crotamine derived from *Crotalus durissus terrificus* venom combined with drugs increases *in vitro* antibacterial and antifungal activities	2024	*In vitro*	Antimicrobial / Antifungal	0.5–10 µg/mL	Enhanced antimicrobial activity when combined with conventional drugs
Effects of the natural peptide crotamine from a South American rattlesnake on *Candida auris*, an emergent multidrug antifungal resistant human pathogen	2019	*In vitro*	Antifungal	10–80 µM	Demonstrated activity against multidrug-resistant Candida auris
Oral treatment with a rattlesnake native polypeptide crotamine efficiently inhibits the tumor growth with no potential toxicity for the host animal and with suggestive positive effects on animal metabolic profile	2018	*In vivo*	Antitumoral	1 µg	Reduced tumor growth without significant toxicity
South American rattlesnake cationic polypeptide crotamine trafficking dynamic in *Plasmodium falciparum* infected erythrocytes: Pharmacological inhibitors, parasite cycle and incubation time influences in uptake	2022	*In vitro*	Antiparasitic	1–5 µM	Demonstrated crotamine internalization dynamics in Plasmodium falciparum infected erythrocytes
Crotamine stimulates phagocytic activity by inducing nitric oxide and TNF-α via p38 and NFκ-B signaling in RAW 264.7 macrophages	2016	*In vitro*	Immunomodulatory	1–10 µM	Activated macrophages and increased inflammatory mediator production
Pharmacological characterization of crotamine effects on mice hind limb paralysis employing both ex vivo and in vivo assays: Insights into the involvement of voltage-gated ion channels	2018	*In vivo*	Pharmacological activity / Ion channel modulation	1–10 µM	Demonstrated involvement of voltage-gated ion channels in crotamine-induced neuromuscular effects
Inhibition of malaria parasite Plasmodium falciparum development by crotamine, a cell-penetrating peptide from snake venom	2016	*In vitro*	Antiparasitic / Antiplasmodial	1–5 µM	Inhibited Plasmodium falciparum development and demonstrated antiparasitic activity
Long-term safety of targeted internalization of cell penetrating peptide crotamine into renal proximal tubular epithelial cells *in vivo*	2019	*In vivo*	Cell-penetrating peptide / Toxicological evaluation	1–10 µM	Demonstrated long-term safety and low toxicity associated with crotamine internalization
Multiple effects of toxins isolated from *Crotalus durissus terrificus* on the hepatitis C virus life cycle	2017	*In vitro*	Antiviral	0.1–10 µM	Demonstrated inhibition of hepatitis C virus replication and interference in viral life cycle stages

Source: Prepared by the authors, 2026

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