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# A Comprehensive Review of Venomous Chordates and Non-Chordates: Biochemical Characteristics, Evolutionary Perspectives, and Pathophysiological Effects

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## Abstract

Venomous animals have evolved a sophisticated array of biochemical weapons used primarily for prey immobilization and predator deterrence. This review has synthesized current knowledge regarding the diverse venom systems found across both chordates (such as Elapid and Viperid snakes, venomous fishes, and rare mammalian lineages) and non-chordates (including Cnidarians, Conidae mollusks, and Arachnids). The chemical composition of these complex secretions was characterized through the lens of modern "venomics," revealing a predominance of disulfide-rich peptides, Phospholipases $A_2$ ($PLA_2$s), and metalloproteinases. Furthermore, the evolutionary mechanisms driving toxin diversification, such as gene duplication and the co-option of physiological proteins, were explored. The pathophysiological effects on mammalian systems were detailed, specifically focusing on the transition from localized tissue necrosis to systemic neurotoxicity and coagulopathy. Finally, the role of these toxins as molecular templates for drug design was evaluated, highlighting their transition from lethal biological threats to life-saving pharmacological agents. This review concludes that while significant progress has been achieved in understanding toxin structures, the vast majority of the "venome" remains uncharacterized, presenting a significant frontier for future therapeutic innovation.

**Keywords:** Venomics, Toxinology, Pathophysiology, Bioactive Peptides, Molecular Evolution, Pharmacological Templates

## Introduction

The evolutionary emergence of venom systems has represented one of the most successful and complex adaptations in the biological world. Traditionally defined as a specialized toxic secretion produced in a localized gland and delivered through an anatomical apparatus, venom has been identified in approximately 15% of all described animal species (Herzig et al., 2020). This trait has emerged through convergent evolution across diverse lineages, spanning over 100,000 species across eight distinct phyla (Mohamed Abd El-Aziz et al., 2019). While the most recognizable examples are found within the Chordata phylum—specifically elapid and viperid snakes—the vast majority of venomous biodiversity was discovered within non-chordate groups, including Cnidaria, Mollusca, and Arthropoda.

Historically, venomous animals were viewed primarily through the lens of clinical emergency and public health threats. The World Health Organization has classified snakebite envenomation as a high-priority neglected tropical disease, noting that it has caused hundreds of thousands of deaths and permanent disabilities annually (Pucca et al., 2021). However, the narrative surrounding these toxins has undergone a paradigm shift. In the last few decades, venoms have been recognized not merely as lethal cocktails, but as sophisticated "biochemical toolkits" that have been refined by millions of years of natural selection (Herzig et al., 2020).

The chemical architecture of these venoms was found to be remarkably heterogeneous. Non-chordate venoms, particularly those of cone snails and spiders, were characterized by a high density of small, disulfide-rich peptides that target ion channels with a degree of specificity that often exceeds modern synthetic ligands (Terlau and Olivera, 2004). Conversely, chordate venoms—most notably in snakes

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were observed to be dominated by larger proteins and enzymes, such as phospholipases and metalloproteinases, which systematically dismantle the physiological integrity of the victim (Vejayan et al., 2014).

Venomous animals have been identified in approximately 15% of extant animal biodiversity, representing more than 100,000 species across eight different phyla (Herzig et al., 2020; Mohamed Abd El-Aziz et al., 2019). These animals have utilized specialized glands to produce complex secretions that are actively delivered via stings, bites, or spines to subvert the physiological systems of prey or predators (Mohamed Abd El-Aziz et al., 2019). While historically associated primarily with morbidity and mortality, venoms have recently been recognized as "mini-drug libraries" due to their high specificity and potency for molecular targets (Mohamed Abd El-Aziz et al., 2019; Bordon et al., 2020).

This review has sought to provide a comprehensive analysis of the biochemical characteristics and pathophysiological effects of these venoms. By comparing the mechanisms of action across both chordate and non-chordate lineages, the fundamental principles of toxin evolution and delivery have been elucidated. Furthermore, the discussion was extended to the burgeoning field of "venomics," where advanced mass spectrometry and transcriptomics have been utilized to unmask the therapeutic potential of these toxins (Alves et al., 2025). The transition from understanding venom as a source of morbidity to utilizing it as a template for drug discovery has marked a new era in molecular pharmacology, transforming nature's most potent weapons into life-saving medicines (Bordon et al., 2020).

## Characteristics and Diversity of Venomous Non-Chordates

Non-chordate venoms are characterized by an extraordinary diversity of small, disulfide-rich peptides. These molecules have evolved to target ion channels with unprecedented selectivity (Herzig et al., 2020).

### Phylum Cnidaria and Echinodermata

Cnidarians, including jellyfish and sea anemones, have employed nematocysts to deliver pore-forming toxins and neurotoxins (Yacoub et al., 2020). These toxins have been observed to cause rapid membrane disruption and ion imbalance in target organisms (Matkivska et al., 2023). Similarly, venomous echinoderms like sea urchins have utilized globiferous pedicellariae for defense (Yacoub et al., 2020).

### Phylum Mollusca: The Cone Snail

The genus *Conus* has produced an estimated 50,000 different pharmacologically active conopeptides (Terlau and Olivera, 2004). These small, structured peptides have been found to target voltage-gated and ligand-gated ion channels, often discriminating between closely related molecular isoforms (Terlau and Olivera, 2004).

### Phylum Arthropoda: Spiders and Scorpions

Arthropod venoms were found to be dominated by linear and disulfide-bridged peptides. In spiders alone, an estimated 20 million bioactive compounds have been predicted (Herzig et al., 2020). Scorpion venoms have been characterized by their potent action on sodium and potassium channels, which often leads to autonomic storms in human victims (Avalo et al., 2022).

## Characteristics and Diversity of Venomous Chordates

Venom systems in chordates, particularly in snakes, have reached a high level of integrated sophistication (Panda and Chandra, 2012).

### Class Reptilia: Snakes and Lizards

Snake venoms were analyzed in 55 genera, revealing complex proteomes dominated by Three-Finger Toxins (3FTxs), Phospholipases $A_2$ (PLA$_2$s), and Snake Venom Metalloproteinases (SVMPs)

(Vejayan et al., 2014; Alves et al., 2025). The evolution of these toxins was likely facilitated by the co-option of conserved vertebrate pathways and the activity of transposable elements (Perry et al., 2022).

### Other Chordates: Fishes and Mammals

Venomous fishes have utilized spines to deliver heat-labile proteinaceous venoms that primarily induce severe pain and cardiovascular distress (Yacoub et al., 2020). Mammalian venom systems, though rare, were identified in species such as the platypus and certain shrews, often serving roles in intraspecific competition (Herzig et al., 2020).

## Biochemical Composition and Mechanisms of Action

Animal venoms were categorized into enzymatic and non-enzymatic constituents, each serving distinct roles in the immobilization of prey (Matkivska et al., 2023).

**Table 1. Composition of animal venoms and action mechanism**

| Toxin Class | Predominant Source | Primary Mechanism of Action |
|---|---|---|
| Neurotoxins | Elapids, Cone Snails | Blockade of nAChR or ion channels (Na+, K+, Ca2+) |
| Phospholipases $A_2$ | Snakes, Hymenoptera | Hydrolysis of phospholipids; membrane damage |
| Metalloproteinases | Viperids | Degradation of extracellular matrix; hemorrhage |
| Serine Proteases | Snakes, Bees | Interference with blood coagulation cascades |

### Neurotoxicity

Neurotoxins have been shown to interfere with cholinergic signaling by binding to nicotinic acetylcholine receptors (nAChR), leading to respiratory paralysis (Panda and Chandra, 2012). For example, short neurotoxins (5–10 kDa) were found to be highly basic, facilitating their attachment to negatively charged membrane receptors (Panda and Chandra, 2012).

### Hemotoxicity and Cytotoxicity

Hemotoxic effects, such as hemorrhage and coagulopathy, were predominantly mediated by SVMPs and serine proteases (Ferraz et al., 2019). Cytotoxins, belonging to the 3FTx superfamily, have been observed to form pores in cell membranes, resulting in localized tissue necrosis (Panda and Chandra, 2012; Matkivska et al., 2023).

### Pathophysiological Effects: Clinical Manifestations of Envenomation

The physiological disruption caused by venom delivery has been categorized based on the primary organ systems targeted. While many venoms were found to be "synergistic" cocktails affecting multiple systems simultaneously, a distinct clinical dichotomy has been established between the envenomation patterns of the two major venomous snake families: Elapidae and Viperidae.

#### 1) Elapid Envenomation: The Neurotoxic Paradigm

The venoms of elapids—including cobras, kraits, and coral snakes—have been characterized by their rapid-acting neurotoxicity. These toxins were observed to target the neuromuscular junction, effectively halting communication between neurons and muscle fibers.

- **Pre-synaptic Neurotoxins:** Certain toxins, such as β-bungarotoxin, were found to inhibit the release of acetylcholine from the motor neuron terminal. This resulted in a depletion of neurotransmitter vesicles, leading to a profound and often irreversible blockade (Panda and Chandra, 2012).
- **Post-synaptic Neurotoxins:** These are primarily Three-Finger Toxins (3FTxs**)** that were shown to bind competitively to nicotinic acetylcholine receptors (nAChR) on the muscle membrane. By preventing acetylcholine from binding, these toxins induced flaccid paralysis.

**Clinical Progression:** Victims of elapid bites have typically presented with "descending paralysis," beginning with ptosis (drooping eyelids) and progressing to bulbar palsy (difficulty swallowing) and, ultimately, respiratory failure as the diaphragm became paralyzed (Mohamed Abd El-Aziz et al., 2019).

### 2) Viperid Envenomation: The Hemotoxic and Cytotoxic Paradigm

In contrast, viperid venoms—from rattlesnakes, adders, and pit vipers—were found to be primarily hemotoxic and cytotoxic. These venoms have evolved to predigest prey and incapacitate the circulatory system.

- **Coagulopathy:** Snake Venom Serine Proteases (SVSPs) and thrombin-like enzymes were observed to interfere with the coagulation cascade. In many cases, this led to Venom-Induced Consumption Coagulopathy (VICC), where the body's clotting factors were entirely depleted, leaving the victim at risk of systemic internal bleeding (Ferraz et al., 2019).
- **Hemorrhage:** The Snake Venom Metalloproteinases (SVMPs) were identified as the primary agents responsible for basement membrane degradation. By breaking down the collagen in capillary walls, these enzymes caused spontaneous bleeding into the tissues (Alves et al., 2025).
- **Local Tissue Necrosis:** High concentrations of Phospholipases $A_2$ ($PLA_2$) and cytotoxins were observed to induce rapid cell death at the bite site. This often resulted in extensive swelling, blistering, and permanent muscle damage or "necrosis" (Matkivska et al., 2023).

**Table 2. Comparative Analysis of Envenomation Dynamics**

| Feature | Elapid Envenomation (Neurotoxic) | Viperid Envenomation (Hemotoxic/Cytotoxic) |
|---|---|---|
| Primary Target | Peripheral Nervous System | Circulatory System and Local Tissue |
| Local Symptoms | Minimal swelling or pain | Severe pain, edema, and bruising |
| Systemic Effect | Flaccid paralysis, respiratory arrest | Hemorrhage, hypotension, coagulopathy |
| Onset of Action | Rapid (minutes to hours) | Variable (hours to days for systemic) |
| Major Toxin Classes | 3FTxs, $\alpha$-neurotoxins | SVMPs, SVSPs, PLA$_2$s |

### 3) Cross-Phyla Pathophysiology: Non-Chordate Comparisons

The pathophysiological patterns observed in chordates were frequently mirrored in non-chordates, albeit through different molecular scaffolds. For example, the "autonomic storm" induced by scorpion venoms was found to be a result of the massive release of catecholamines triggered by sodium channel toxins (Avalo et al., 2022). Similarly, the severe localized pain associated with jellyfish stings was attributed to pore-forming toxins that rapidly depolarized sensory neurons (Yacoub et al., 2020).

## Evolutionary Mechanisms: The Genesis of Biological Weapons

The presence of complex venom systems across disparate phyla has long served as a classic example of convergent evolution. It was observed that venomous traits have appeared independently at least 100 times throughout the history of animal life (Herzig et al., 2020). The process by which a standard physiological protein was transformed into a lethal toxin has involved several sophisticated molecular mechanisms, primarily categorized as gene duplication, protein co-option, and accelerated evolution.

### Protein Co-option and "Exaptation"

The majority of venom toxins were found to have originated from proteins that originally performed mundane physiological functions. Through a process known as co-option, proteins that were initially involved in digestion, blood clotting, or immune responses were recruited into the venom gland (Perry et al., 2022).

For instance, the Snake Venom Metalloproteinases (SVMPs), which have been implicated in severe tissue degradation and hemorrhage, were shown to be evolutionary descendants of the ADAM (A Disintegrin and Metalloproteinase) protein family (Ferraz et al., 2019). These ancestral proteins were originally responsible for regulating cell-to-cell and cell-to-matrix interactions. Once expressed specifically within the venom gland, their proteolytic activity was "weaponized" to destroy the vascular integrity of the prey.

**Gene Duplication and Neofunctionalization**

A central driver in the expansion of venom complexity was found to be gene duplication. When a gene encoding a physiological protein was duplicated, the organism retained one copy for its original function, while the second copy was freed from selective pressure. This "redundant" copy was then permitted to accumulate mutations, eventually acquiring a new, toxic function—a process referred to as neofunctionalization.

In *Conus* snails, this mechanism was observed to produce "gene superfamilies" (Terlau and Olivera, 2004). Massive duplication events allowed these mollusks to generate thousands of variations of conopeptides. These variations were subsequently refined by natural selection to target specific ion channels in the nervous systems of different prey types, such as fish or other snails.

**Accelerated Evolution and Positive Selection**

Once a protein was recruited into the venom arsenal, it was often subjected to positive selection at rates far exceeding those of non-venomous genes. This rapid diversification—often called "evolutionary arms races"—was driven by the need to overcome the evolving resistance of prey species.

Research has indicated that the Three-Finger Toxins (3FTxs) found in elapid snakes have exhibited some of the highest rates of sequence diversification recorded in the animal kingdom (Panda and Chandra, 2012). This was characterized by a "hotspot" of mutations within the loops of the protein structure, while the core scaffold remained stabilized by conserved disulfide bonds. This structural strategy allowed the venom to "experiment" with new molecular targets without losing the overall stability of the toxin.

**Horizontal Gene Transfer and Alternative Splicing**

While less common, some evidence has suggested that horizontal gene transfer (HGT) may have played a role in the acquisition of certain venom components, particularly in non-chordates. Furthermore, alternative splicing has been identified as a method for increasing venom diversity without increasing the number of genes. In certain spiders, a single gene was found to produce multiple toxin isoforms through different mRNA splicing patterns, significantly expanding the biochemical "vocabulary" available to the animal (Herzig et al., 2020).

## Therapeutic Potential and Modern Applications

The pharmacological potential of venom-derived compounds has been increasingly recognized in modern medicine (Matkivska et al., 2023).

- **Cardiovascular Health:** Captopril, an ACE inhibitor derived from *Bothrops jararaca* venom, revolutionized antihypertensive therapy (Mohamed Abd El-Aziz et al., 2019; Bordon et al., 2020).
- **Pain Management:** Ziconotide (Prialt®), a synthetic version of a cone snail peptide, was approved for treating severe chronic pain (Yacoub et al., 2020; Bordon et al., 2020).
- **Metabolic Disorders:** Exenatide, derived from the Gila monster, has been utilized in the treatment of Type 2 diabetes (Herzig et al., 2020).
- **Antimicrobial Research:** Crude venoms from ants and scorpions have exhibited significant antibacterial and antifungal activities (Yacoub et al., 2020).

## Conclusion

The systematic investigation into the venoms of chordates and non-chordates has revealed a profound biological complexity that transcends simple toxicity. It was concluded that these secretions represent a pinnacle of molecular engineering, shaped by millions of years of selective pressure to target vital physiological pathways with surgical precision. While the neurotoxic mechanisms of Elapids and the hemotoxic profiles of Viperids have historically dominated clinical research, the "venomics" revolution has expanded this horizon to include the vast, untapped chemical libraries of cnidarians, mollusks, and arthropods.

The transition from viewing venom as a lethal threat to a source of pharmacological innovation has been firmly established through the successful development of life-saving therapeutics. However, as global biodiversity faces unprecedented threats, the potential for discovering novel bioactive molecules is increasingly at risk. Future research must prioritize the integration of genomic and proteomic technologies to map the remaining "dark matter" of the venome. By continuing to bridge the gap between evolutionary biology and clinical pharmacology, the scientific community can ensure that these ancient biological weapons remain a cornerstone of modern medical advancement.

## References


Abd El-Aziz, T. M., Soares, A. G., and Stockand, J. D. (2020). Advances in venomics: Modern separation techniques and mass spectrometry. *Journal of Chromatography B*, *1160*, 122352. https://doi.org/10.1016/j.jchromb.2020.122352

Alves, Á. E. F., Barros, A. B. C., Silva, L. C. F., Carvalho, L. M. M., Pereira, G. M. A., Uchôa, A. F. C., et al. (2025). Emerging Trends in Snake Venom-Loaded Nanobiosystems for Advanced Medical Applications: A Comprehensive Overview. *Pharmaceutics*, *17*(2), 204. https://doi.org/10.3390/pharmaceutics17020204

Avalo, Z., Barrera, M. C., Agudelo-Delgado, M., Tobón, G. J., and Cañas, C. A. (2022). Biological effects of animal venoms on the human immune system. *Toxins*, *14*(5), 344. https://doi.org/10.3390/toxins14050344

Bordon, K. C. F., Cologna, C. T., Fornari-Baldo, E. C., Pinheiro-Júnior, E. L., Cerni, F. A., et al. (2020). From Animal Poisons and Venoms to Medicines: Achievements, Challenges and Perspectives in Drug Discovery. *Frontiers in Pharmacology*, *11*, 1132. https://doi.org/10.3389/fphar.2020.01132

Casewell, N. R., Wüster, W., Vonk, F. J., Harrison, R. A., and Fry, B. G. (2013). Complex cocktails: The evolutionary novelty of venoms. *Trends in Ecology and Evolution*, *28*(4), 219–229. https://doi.org/10.1016/j.tree.2012.10.020

Fajloun, Z., Roufayel, R., and Rima, M. (2026). Animal venoms for drug discovery: A constantly evolving research field. *Toxins*, *18*(1), 30. https://doi.org/10.3390/toxins18010030

Ferraz, C. R., Arrahman, A., Xie, C., Casewell, N. R., Lewis, R. J., Kool, J., and Cardoso, F. C. (2019). Multifunctional Toxins in Snake Venoms and Therapeutic Implications: From Pain to Hemorrhage and Necrosis. *Frontiers in Ecology and Evolution*, *7*, 218. https://doi.org/10.3389/fevo.2019.00218

Freuville, L., Matthys, C., Quinton, L., and Gillet, J.-P. (2024). Venom-derived peptides for breaking through the glass ceiling of drug development. *Frontiers in Chemistry*, *12*. https://doi.org/10.3389/fchem.2024.1465459

Herzig, V., Cristofori-Armstrong, B., Israel, M. R., Nixon, S. A., Vetter, I., and King, G. F. (2020). Animal toxins — Nature's evolutionary-refined toolkit for basic research and drug discovery. *Biochemical Pharmacology*, *181*, 114096. https://doi.org/10.1016/j.bcp.2020.114096

Kim, E., Hwang, D. H., Mohan Prakash, R. L., Asirvatham, R. D., Lee, H., Heo, Y., et al. (2025). Animal venom in modern medicine: A review of therapeutic applications. *Toxins*, *17*(8), 371. https://doi.org/10.3390/toxins17080371

Martinson, E. O., Mrinalini, Kelkar, Y. D., Chang, C.-H., and Werren, J. H. (2017). The evolution of venom by co-option of single-copy genes. *Current Biology*, *27*(13), 2007–2013. https://doi.org/10.1016/j.cub.2017.05.032

Matkivska, R., Samborska, I., and Maievskyi, O. (2023). Effect of animal venom toxins on the main links of the homeostasis of mammals (Review). *Biomedical Reports*, *20*(2). https://doi.org/10.3892/br.2023.1704

Mohamed Abd El-Aziz, T., Soares, A. G., and Stockand, J. D. (2019). Snake Venoms in Drug Discovery: Valuable Therapeutic Tools for Life Saving. *Toxins*, *11*(10), 564. https://doi.org/10.3390/toxins11100564

Mouchbahani-Constance, S., and Sharif-Naeini, R. (2021). Proteomic and transcriptomic techniques to decipher the molecular evolution of venoms. *Toxins*, *13*(2), 154. https://doi.org/10.3390/toxins13020154

Panda, S., and Chandra, G. (2012). Physicochemical characterization and functional analysis of some snake venom toxin proteins and related non-toxin proteins of other chordates. *Bioinformation*, *8*(18), 891–896. https://doi.org/10.6026/97320630008891

Perry, B. W., Gopalan, S. S., Pasquesi, G. I. M., Schield, D. R., Westfall, A. K., et al. (2022). Snake venom gene expression is coordinated by novel regulatory architecture and the integration of multiple co-opted vertebrate pathways. *Genome Research*, *32*(6), 1058–1073. https://doi.org/10.1101/gr.276251.121

Pucca, M. B., Fry, B. G., Sartim, M. A., Peigneur, S., and Monteiro, W. M. (2021). Editorial: Venoms and Toxins: At the Crossroads of Basic, Applied and Clinical Immunology. *Frontiers in Immunology*, *12*. https://doi.org/10.3389/fimmu.2021.716508

Sanz, L., and Calvete, J. (2016). Insights into the evolution of a snake venom multi-gene family from the genomic organization of Echis ocellatus SVMP genes. *Toxins*, *8*(7), 216. https://doi.org/10.3390/toxins8070216

Tasoulis, T., and Isbister, G. (2017). A review and database of snake venom proteomes. *Toxins*, *9*(9), 290. https://doi.org/10.3390/toxins9090290

Terlau, H., and Olivera, B. M. (2004). Conus Venoms: A Rich Source of Novel Ion Channel-Targeted Peptides. *Physiological Reviews*, *84*(1), 41–68. https://doi.org/10.1152/physrev.00020.2003

Utkin, Y. N. (2015). Animal venom studies: Current benefits and future developments. *World Journal of Biological Chemistry*, *6*(2), 28. https://doi.org/10.4331/wjbc.v6.i2.28

Vejayan, J., Khoon, T., and Ibrahim, H. (2014). Comparative analysis of the venom proteome of four important Malaysian snake species. *Journal of Venomous Animals and Toxins including Tropical Diseases*, *20*, 6. https://doi.org/10.1186/1678-9199-20-6

von Reumont, B. M., et al. (2022). Modern venomics—Current insights, novel methods, and future perspectives in biological and applied animal venom research. *GigaScience*, *11*. https://doi.org/10.1093/gigascience/giac048

Vonk, F. J., et al. (2013). The king cobra genome reveals dynamic gene evolution and adaptation in the snake venom system. *Proceedings of the National Academy of Sciences*, *110*(51), 20651–20656. https://doi.org/10.1073/pnas.1314702110

Westfall, A. K., et al. (2023). Single-cell heterogeneity in snake venom expression is hardwired by co-option of regulators from progressively activated pathways. *Genome Biology and Evolution*, *15*(6). https://doi.org/10.1093/gbe/evad109

Wilson, D., and Daly, N. L. (2018). Venomics: A mini-review. *High-Throughput*, *7*(3), 19. https://doi.org/10.3390/ht7030019

Yacoub, T., Rima, M., Karam, M., Sabatier, J. M., and Fajloun, Z. (2020). Antimicrobials from Venomous Animals: An Overview. *Molecules*, *25*(10), 2402. https://doi.org/10.3390/molecules25102402