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Venoms classification and therapeutic uses: a narrative review

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Abstract. **The mere glimpse of venomous animals has always terrified humans because of the devastating effects of their venoms. However, researchers across the globe have isolated therapeutically active ingredients from these venoms and continue to explore them for drug leads. These efforts lead to the discovery of therapeutic molecules that the US-FDA has approved to treat different diseases, such as hypertension (Captopril), chronic pain (Ziconotide), and diabetes (Exenatide).**

The main active constituents of most venoms are proteins and peptides, which gained more attention because of advancements in biotechnology and drug delivery. The utilization of newer screening approaches improved our understanding of the pharmacological complexity of venom constituents and facilitated the development of novel therapeutics. Currently, with many venom-derived peptides undergoing different phases of clinical trials, more are in pre-clinical drug development phases. This review highlights the various sources of venoms, their pharmacological actions, and the current developments in venom-based therapeutics.

Key Words:
Snake venom, Spider venom, L-Amino acid oxidase, Proteolytic enzymes, Arginine ester hydrolase, Hyaluronidase, Phospholipase A2, Snake venom metalloproteinases, Disintegrins and C-type lectins, Drug discovery.

Introduction

Various species underwent random mutations during evolution in response to climatic changes and predation. These effects led to the formation of venom in phylogenetically distant species. Today, about 100,000 species of venomous vertebrates and invertebrates exist[1-3]. The venomous vertebrates include fish like catfish and stonefish, snakes like pit vipers, and platypus-like mammals. The invertebrates include mollusks like cone shells and cone snails, arachnids like funnel-web spiders and scorpions, and insects like bees and ants[4]. Depending on the habitat, venomous animals (Figure 1) are aquatic or terrestrial. Aquatic animals include cnidarians, sea snakes, and venomous fishes, whereas terrestrial animals include arthropods (scorpions, spiders, hymenopterans) and vertebrates (terrestrial venomous snakes). A more detailed classification of venomous animals and their venom-producing glands is illustrated (Table I).

Venoms are the concentrated, biologically active, complex secretions usually secreted from glands identified along with their stings, teeth, or spines for self-defense or immobilization of prey[5,6]. Chemically, they are heterogeneous mixtures of bioactive components, such as proteins, glycoproteins, peptides, and other chemical entities, such as lipids, nucleosides, free amino acids, and metallic ions. Proteins and peptides make up approximately 90-95% of the dry components of a venom. Besides, metal ions, such as sodium (as a major cation), zinc, and calcium, are found in different metalloproteinases isolated from snake venoms[7-10]. Furthermore, carbohydrates exist mainly conjugated as glycoproteins[11,12].

The historical interest in animal venoms has its roots deep in history, as far as humans recorded their civilization. The interest in the physiological activities of venoms from different sources (Table I) grew parallel to human fear of venomous ani-

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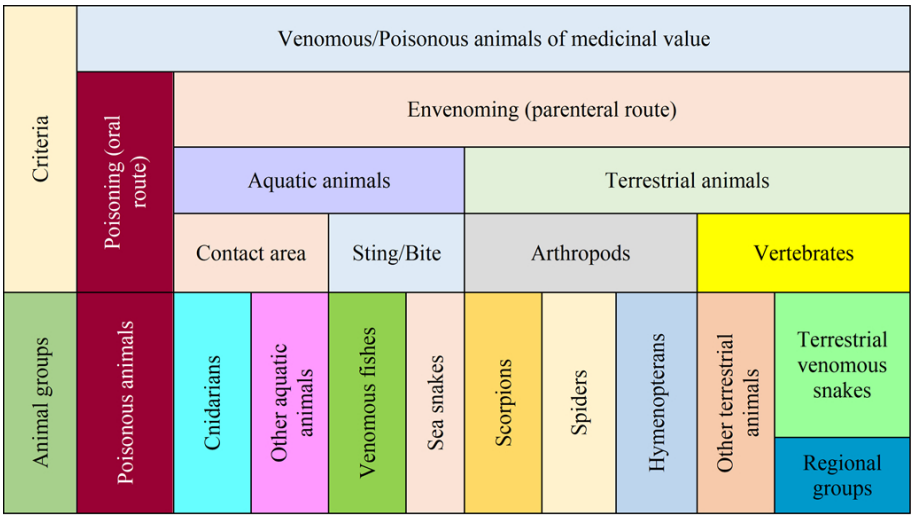

Figure 1. Grouping venomous and poisonous animals with an easy set of criteria.

mals[13]. Historical accounts, including the *Charaka Samhita*, Unani, and Chinese medical systems, acknowledged the therapeutic potential of venoms[14]. Thus, it is well-laid in history that despite the toxic nature of venom, it can be explored for various biological activities. The prime constituents of venom, such as peptides, enzymes, and glycoproteins, can be utilized in investigating/modulating various pathophysiological processes[15]. Previous studies[16] showed that exposure to bee and wasp venom extracts increased CD203c expression in blood basophils. Another study[17] showed that human basophils express CD16 in respiratory and insect venom allergy patients. Five allergens induced allergy by seven *Hymenoptera* species, which were assessed by different diagnostic setups[18,19]. Extensive research continues to extract and identify therapeutic molecules from venomous substances from different species. This article reviews the different biological activities and chemical constituents in venoms[20-22].

The toxicity of venoms varies considerably according to the source; the variation is parallel to that of the broad range of animal species producing them. This broad spectrum of activity leads to the discovery of organ-specific components in animal venoms, e.g., cytotoxins, cardiotoxins, neurotoxins, and hemotoxins, especially with the current advancements in drug discovery techniques[2,23-27]. Many of the isolated peptides and proteins target the cardiovascular or nervous systems. Overall, the primary clinical indications for venom-based biologics in humans include neurological, oncological, cardiac, hematological, and renal applications[28]. Furthermore, many isolated non-lethal components modulate ion channel function[29-34] and can serve as future therapeutic agents. Other possible applications are in the field of cosmetics[20,35-37] and as potential pesticides[38-42].

Composition of Venom

Animal venoms consist of complex, natural, biologically active molecules with different cellular targets and pharmacological activities[43,44]. The main components are protein/peptides, with and without enzymatic activity, and other chemical entities[43,45,46]. These biologically active molecules have evolved extravagantly in context with enzymes, peptides, selectivity, and their potency.

Enzymes

The diverse proteinaceous macromolecules with enzymatic activities are major constituents of animal venoms. The commonly found enzymes are proteinases[47,48], phospholipases[9,49,50], arginine ester hydrolases[51,52], hyaluronidases[53], cholinesterases[54], collagenases[55], phosphodiesterases[56,57], DNase[58,59], and RNase[58,60,61]. The enzymatic variations of venoms of different species are listed in Table II. The venom enzymes of spiders, scorpions, bees, and snakes are primarily responsible for their hemolytic, proteolytic, lipolytic, oxidoreductive, and hydrolytic activities. The main clinicopathological manifestations of venom exposure in humans include cell/organ injury, neuromus-

Table I. List of sources of different venoms.

COELENTERATES (Cnidarians)	• Hydroides (direct body contact) • Jellyfish • Sea anemones • Corals (stinging cells, nematocysts)
ANNELIDS	• Blood-feeding leaches (polychaete worms) • Blood worms • Scale worms (possess strong jaws with channels and pores for venom release from underneath venom glands • Amphinomida or bristle worms (fragile spines or modified chaetae)
MOLLUSCS	• Squid • Cuttlefish • Octopuses • Snugs • Snails (harpoon-like radular tooth)
ARTHROPODS	• Crustacean (glands connected to muscles surrounding reservoirs, which are attached to the needle structure on front claws) • Scorpion (stinger tail) • Spider (chelicerae, a pair of jointed jaws having sharp fangs) • Millipedes • Centipedes (pinch using the first pair of walking legs) • Insects (piercing and sucking mouth parts)
ECHINODERMS	• Starfish (spines/stings) • Sea urchins (long, sharp, sometimes venom-coated spines) • Sea cucumbers (Cuvierian tubules)
CHORDATES	• Cartilaginous and bony fishes (spines, fangs, cleithral spines, and opercular or subopercular spines) • Sharks (spines-like process anterior to dorsal fins) • Amphibians (glands located in various skin sites) • Reptiles • Birds • Mammals

cular dysfunction, coagulopathy, inflammation, and disruption of homeostatic mechanisms, such as lowering blood pressure and stimulating pain sensation.

Cholinesterase

It is mainly extracted and purified from different species of snake venoms. Cholinesterases catalyze the hydrolysis of the neurotransmitter acetylcholine into choline and acetic acid[62-64]. This action directly disrupts the nervous system by interfering with cholinergic signaling, which leads to uncontrolled relaxation or paralysis of muscle tissues and contributes to venom toxicity[54,65].

L-Amino Acid Oxidase (LAAO)

The LAAOs are flavoproteins that constitute approximately one-tenth of total venom proteins. Venom LAAOs exist mainly as homodimers that give snake venoms the characteristic yellow color thanks to their flavin adenine dinucleotide content. In a stereospecific deamination reaction, they catalyze the conversion of L-amino acid substrates (mostly the hydrophobic ones such as L-isomers of methionine, leucine, isoleucine, phenylalanine, and tryptophan) to the corresponding α-keto acid liberating hydrogen peroxide[66]. Snake venom LAAOs have demonstrated cytotoxic (proapoptotic), antimicrobial, antiparasitic, and platelet-aggregating activities[67]. The toxic effects of these enzymes are attributed to their liberation of hydrogen peroxide and induction of oxidative stress[68]. On the other hand, a recent study reported the attenuation of neutrophil-mediated inflammation and oxidative stress by crude venom and the purified LAAO from a *Bothrops* snake[69].

Proteolytic Enzymes (Proteases)

The molecular weight of these enzymes ranges from 20 kDa to 95 kDa. Proteases catalyze the hydrolysis of tissue proteins into smaller peptides and simple amino acids[70-72]. Sometimes, metal ions are required to activate these enzymes, whereas reducing agents are used to deactivate them[72-74]. Akin to the pathophysiological functions of endogenous proteases such as thrombin, trypsin, elastase, and matriptase[75,76], the venom content of proteolytic enzymes might modulate cellular and tissue function by their protease activity[77,78]. Importantly, these enzymes can activate, disarm, or modulate the function of protease-activated receptors[75,76]. Since their discovery in the 1990s, accumulating evidence illustrates the role of protease-activated receptors in regulating inflammation[75,79], cellular proliferation[80], and vascular function[81-83], to mention a few of their functions[84]. Venom proteases offer valuable research opportunities in drug discovery based on their ability to act like endogenous proteases.

Table II. Description of enzymes and peptides in various types of venoms.

	Snake venom	Spider venom	Scorpion venom	Bee venom
Enzymes	Phospholipase A_2 L-Amino acid oxidase Hyaluronidases Acetylcholine esterase	Phospholipase A_2 L-Amino acid oxidase Antithrombins Hyaluronidases	Hyaluronidases Phospholipase A_2 Metalloproteinases L-Amino acid oxidase	Phospholipase A_2 Phospholipase B Hyaluronidases Acid phosphatase α-Glucosidase
Peptides/ polypeptides	Sarafotoxins Lipopolysaccharide Bradykinin potentiating or angiotensin-converting enzyme inhibitors Neurotensin Phyllolitorin Litorin Tryptophyllin	Antimicrobial peptides (cytolytic or cationic peptides) Cysteine-rich peptides Cystine knot inhibitor Psalmopeotoxin I, II Huwentoxin I	Ion channel (Na+, Ca2+, K+, and Cl-) toxins Non-disulfide-bridged peptides (NDBPs)	Melittin Apamin Peptide 401 Tertiapin Secapin

Arginine Ester Hydrolase

Arginine ester hydrolase, also known as arginine esterase, is extracted from highly venomous species of snakes like *Crotalus scutulatus,* and it induces the hydrolysis of substrate proteins containing arginine residues[85]. The processing of kininogens by arginine ester hydrolases causes the release of bradykinin[86]. Agkihpin is an arginine ester hydrolase from snake venom that showed anti-metastatic potential in liver cancer model systems[87]. The anti-migratory effect of agkihpin was attributed to its reversal of epithelial-to-mesenchymal transition and attenuation of Wnt/β-catenin signaling, possibly *via* degradation of frizzled-7, a vital component of the Wnt receptors associated with cancer development and metastasis[87,88]. Thus, this enzyme carries the potential for the development of novel anti-cancer biotherapeutics.

Thrombin and Thrombin-Like Enzymes

Thrombin is a serine protease that cleaves fibrinopeptides to convert fibrinogen to fibrin[89]. Besides its vital role in blood coagulation, thrombin is essential to cellular homeostasis in vascular and non-vascular tissues[79,90]. Thrombin-like enzymes are also serine proteases with 29 kDa to 35 kDa molecular weight, extracted and purified from the venom of snakes (primarily pit vipers)[91,92]. They also play an active part in the blood coagulation pathway and the released unstable blood clots[93]. These effects are achieved either directly by the thrombin or thrombin-like constituents of the venom or indirectly by activating the endogenous coagulation cascade[94]. On the other hand, fibrinogen depletion caused by envenomation precipitates fatal hemorrhagic disorders, such as venom-induced consumption coagulopathies and subsequent thrombotic microangiopathies[95-97].

Collagenase

Collagenases are metalloproteinases that, as the name implies, break down collagen molecules and other matrix proteins[74]. These enzymes are critical to tissue remodeling and activation of signaling pathways during development and pathogenesis[98-100]. Enzymes with collagenolytic activity are ubiquitous in living organisms ranging from bacteria to higher mammals and can serve as modular therapeutic targets[99,100]. Notably, the venoms of many species contain collagenases that contribute to their biological effects[101,102].

Hyaluronidase

Degradation of the extracellular matrix hyaluronan (hyaluronic acid) by the hyaluronidase activity of the venom enhances the spreading of the toxic venom into the tissues and leads to a more pronounced biological effect. Hyaluronidases act mainly by hydrolysis of glycoside bonds in mucopolysaccharides of connective tissue and thus decrease their viscosity. Therefore, they facilitate the penetration of other active high molecular weight components of venoms inside the tissues[2,59,78]. Moreover, the exact mechanism can be exploited for therapeutic and cosmetic applications[103].

Phospholipase A_2 (PLA_2)

Snake and bee venoms are sources of PLA_2, which primarily promotes the calcium-dependent hydrolysis of phospholipids (especially membranous) to produce fatty acids like arachidonic acid and lysophospholipids like lysophosphatidic

acid[2,78,104]. Thus, venom PLA_2 can trigger various signaling pathways responsible for pain sensation[105] and cellular proliferation[106].

Phosphodiesterase

Phosphodiesterases are enzymes that break the phosphodiester bonds in a polynucleotide sequence to release 5-mononucleotide[1,107,108]. Although the term usually refers to cyclic nucleotide phosphodiesterases that convert cyclic nucleotide monophosphates into acyclic forms[109], this class also includes other exonucleases and endonucleases, which cleave a nucleotide sequence either at the terminal or middle positions, respectively[110]. These enzymes are isolated from various species of snake venoms. Based on their target specificity, phosphodiesterases can significantly affect cell signaling, modulate the biological response to toxic venom, and serve as novel platforms for drug development[111,112].

RNase

The RNase enzymes, also known as ribonucleases, facilitate the point-cleavage of the RNA molecules into smaller units, hence its inactivation. Interestingly, most snake venoms contain ribonucleases[60,61,113]. Although not fully understood, the suggested function of venom RNase is the generation of purines (e.g., adenosine) that are important in regulating vascular and immune function and cell survival[114,115].

DNase

DNases are endonucleases that specifically cleave the DNA structure into small components. Like RNases, they can be extracted from different species of snake venoms[61]. Beyond their known digestive effects on DNA (and sometimes RNA), little is known about their function as venom components. However, they might be involved in purine generation[58,113,115].

5'-Nucleotidase

These enzymes are active phosphatases extracted and purified from snake venoms and known for their nucleotide cleavage activity, mainly the conversion of adenosine monophosphate to adenosine[116,117]. Noteworthy, the combined actions of phosphodiesterases, RNases, and DNases degrade cellular genetic precursors to form purine and pyrimidine 5'-nucleotides, which are the substrates of 5'-nucleotidase and non-specific phosphatases for the generation of nucleotides. The generation of adenosine is crucial because it accounts for many of the venom-related effects[58,113,118].

Lactate Dehydrogenase (LDH)

This oxidoreductase is an intracellular enzyme found in the tissues of all animal species. It is mainly responsible for the reversible conversion of lactic acid to pyruvic acid and NAD^+ to NADH in equilibrium[119-121]. Under hypoxic conditions, when oxidative phosphorylation fails to produce ATP for energy, the levels of LDH (cytoplasmic enzyme) consequently increase and affect the metabolic pathway of glucose for energy production[120,122]. The massive activation of the LDH enzyme reflects a loss of cytoplasm, transient damage to the tissue integrity, and cell death[120,123]. Notably, envenomation induces hemotoxicity and cytotoxicity due to local tissue injury resulting in multiple organ dysfunction. Thus, the immoderate release of LDH from the damaged cells into the bloodstream is associated with marked toxicity induced by snake venom. In a previous study, Bahadorani and Mirakabadi[124] showed that exposing human endothelial kidney cells to the venom of *Echis carintus* dose-dependently upregulated the LDH content and consequent cellular damage[124].

Similarly, the concentration of LDH increased in the rats injected with three different venoms of *Bitis gabonica, Dendroaspis polylepis, and Naja nigricollis*[125]. Moreover, intraperitoneal injection of Bothrops asper venom in mice significantly increased LDH levels[126]. In line with the above data, victims of snake bite envenomation represented an early rise in LDH content[127,128]. Conclusively, all the above findings uncover the importance of LDH as a potential biochemical marker in venom-induced tissue damage.

Peptides

Venoms of poisonous animals are complex mixtures of low molecular weight peptides that could significantly threaten human life. These small peptides are the dominant components in most venoms[2,92]. The peptides from snake venom affect endothelial cell proliferation, migration, and response to growth factors, notably the vascular endothelial type[2,129,130]. Similarly, spider venoms also have different peptides, which target ion channels/receptors to modulate cellular function and proliferation[131,132]. Scorpion venom is a significant source of therapeutical actives, especially ion channel blockers[133]. Moreover, the polypeptides in bee venom activate specific signaling pathways that modulate the effects of pro-inflammatory cytokines and mitigate oxidative stress in different disease models[134-136]. The peptides/polypeptides variations in the venoms of snakes, scorpions, spiders, and bees are listed in Table II.

Types of Venoms

Snake Venoms

There are approximately 3,400 species of snakes worldwide. The snakes fall in the suborder Serpentes, order Squamata, reptilian, and infra-orders like blind snakes and non-blind snakes[137]. Different venomous snake families, such as Viperidae, Atractaspididae, and Colubridae, live on land, at high altitudes, and in the deep sea. Moreover, the venoms of these snakes contain various therapeutic/non-therapeutic moieties, including enzymes, such as LAAO, PLA_2, serine proteases, and 5'-nucleotidase[7,8,117,138,139] and non-enzymatic components, such as peptides, cysteine-rich secretory proteins, waprins, disintegrins, and sarafotoxins[140-144]. In addition, different peptide molecules isolated from venoms of various species of snakes have already been identified as neurotoxins (K^+ channel-binding, presynaptic and postsynaptic types), cardiotoxins, myotoxins, and cytotoxins[7,8,137,139,145,146].

Because of the heterogeneous complex composition, we are far from understanding the exact mechanisms by which snake venoms exert their effect. Venoms of the snakes possess various active constituents that show different pathological/physiological outcomes like bleeding, edema, and muscle cell necrosis[147,148]. Snake envenomation induces pathological changes, like damaging local tissues, because of blistering, hemorrhage, and inflammation[2,96,149]. Further, this response to inflammation triggers the release of endogenous mediators, such as histamine, prostaglandins, and bradykinins. Thus, envenomations of snake biting lead to a complex pathogenic process with local and systemic effects. The toxic manifestations of snake envenomation result mainly from their effects on the nervous, cardiovascular and respiratory systems[50,96,150]. The severity and outcomes depend on many factors, such as the site of envenomation, venom volume and concentration, age, weight, and genomic variations in the victim[151-155]. Moreover, snake bites may induce vital organ failure (e.g., heart and kidney) and even death, which were corroborated in clinical reports[151,156].

The hemotoxic effects of venoms from the Viperidae family are caused by venom proteins, which disrupt the coagulation cascade to affect bleeding and tissue necrosis[95,151,157]. In contrast, neurotoxic venoms from the Elapidae family interfere with the function of the peripheral nervous system, primarily the myoneural junction, by disrupting ion transport and membrane homeostasis[78,105,158]. On the neuromuscular junction, neurotoxins act on either presynaptic or postsynaptic membranes to prevent the release of acetylcholine or its interaction with its nicotinic receptors[78,158,159]. Although many snake envenomation symptoms are neurotoxic effects related to the blockade of the peripheral nervous system and neuromuscular junction, central nervous system toxicity symptoms, such as drowsiness, are observed as a result of central nervous system depressant effects of venom ingredients[160,161]. Different venom neurotoxins, such as bungarotoxins, dendrotoxins, and fasciculins induce paralysis-like symptoms by blocking the nicotinic acetylcholine receptors[162]. Thus, emergency management protocols for snake envenomation should synonymously consider a suitable identification procedure for the source of envenomation, e.g., by immunological assays, followed by appropriate antivenom therapy[153,163,164]. The therapeutic procedure should be carefully monitored to take care of any fatal anaphylaxis reactions induced by antivenom therapy[165,166]. Thus, studying the pharmacological actions of different venom components, either alone or combined with other active moieties, is essential to understand the adverse effects observed in snake envenomation fully and to exploit this knowledge in the management and drug discovery.

Proteinases

The heterogeneous proteinases extracted and purified from viper venoms, with molecular weights of 15-100 kDa, are primarily implicated in tissue necrosis, hemorrhage, and bleeding[167-174]. The proteinases extracted from snakes are primarily categorized as snake venom serine proteases (SVSPs) and snake venom metalloproteinases (SVMPs). Both categories are structurally stabilized by disulfide bonds (bridges) and are capable of hydrolyzing various natural (e.g., casein and hemoglobin) and synthetic substrates (Olaoba et al[175], Larreche et al[96]). Few of these proteolytic enzymes affect the hemostatic system either by activation (pro-coagulant) or inhibition (anti-coagulant).

The SVSPs (20-100 kDa) are extracted from different species of snakes (Pit viper, Gaboon viper from Viperdiae, and Boomslang from Colubridae)[2,112,170]. They have been widely utilized for their active role in hemostasis[171] by induction of platelet aggregation[169,172]. Broadly, these enzymes are known for their thrombin-like actions. They all have a common active site structure that comprises three basic amino acids: serine, histidine, and aspartic acid, each of which plays a role in the catalytic activity of the enzyme. Afaacytin extracted from the venom of the desert horned

viper *Cerastes cerastes* is an example of SVSPs that exhibits α- and β-fibrinogenase activity[172,173].

The initial classification of SVMPs into four classes relied on their molecular weight and chemical structure[174]. Later, scientists classified SVMPs into three main types according to the complexity of their domain structures. The simplest SVMPs (P-I SVMPs) contain only metalloproteinase domains. Members of the second class of SVMPs (P-II SVMPs) contain metalloproteinase and disintegrin domains. The third and the most complex members are the P-III SVMPs that contain metalloproteinase, disintegrin, and cysteine-rich domains[175]. The SVMPs are usually proenzymes of three major domains: a catalytic domain (binding site for zinc and lectin), a pro-domain, and a signal peptide[175,176], and have the unique motif sequence HEXXHXXGXXH, which is essential for their pharmacological activity[177,178]. Moreover, they have a conserved histidyl system mainly responsible for Zn^{2+} binding[179,180].

Several SVMPs (primarily the Zn^{2+}-type) were isolated from snake venoms with molecular weights ranging from 22 to 100 kDa[9,10,175]. Several SVMPs display preferential affinity and specificity to endothelial cells[130,181,182]. These enzymes have also been evaluated pharmacologically for their hemostatic function[183,184]. Additionally, metalloproteinases are involved in the pathophysiology of inflammation[77], heart failure[185,186], and inhibition of platelet aggregation, which initiate bleeding[96,175,187]. These proteins induce blood extravasation via the degradation of extracellular matrix proteins, such as fibronectin and collagen; hence they are called hemorrhagins[188-190]. Pathological effects, such as tissue necrosis, blistering, and swelling in major organs, occur as a result of local or systemic bleeding[96,191,192] or by direct stimulation of inflammatory and apoptotic pathways in such tissues[130,192,193].

Disintegrins and C-Type Lectins

Proteins with disintegrins and C-type lectins are extracted from snake venoms and are found in envenomation sites after snake bites. They gained popularity in biomedical research for developing new therapeutics and diagnostics[2,11,112,194]. These disintegrins and C-type lectins modulate platelet aggregation (Table III) due to their affinity toward different platelet receptors, such as α2β1, αIIbβ3, GPIb, and GPIIb/IIIa[195-197]. Moreover, these proteins have promising anti-cancer and anti-angiogenic potential[2,116,198-201]. They have also been explored clinically for treating coronary artery diseases and stroke[202,203]. Notable examples include eptifibatide and tirofiban; both are synthetic derivatives of disintegrins isolated from the dusky pygmy rattlesnake *Sistrurus barbourin* and *Echis carinatus*, respectively[194,204,205]. Other examples, such as lebectin and lebecetin, are promising candidates in the field of heart and cancer diseases[206-208].

Table III. List of non-enzymatic components found in snakes' venoms.

Non-enzymatic components	Molecular mass (kDa)	Mechanism of action	Pharmacological action	Type of snake family
Three-finger toxins e.g., α-neurotoxins	6-9	Blocks neuromuscular transmission by inhibiting acetylcholine receptors (postsynaptic nicotinic type), a blocker of calcium channel (L-type)	Neurotoxicity (postsynaptic)	Elapidae and Viperidae
Kunitz peptides	7	Interference with the blood coagulation cascade and ion channel	Interference with hemostasis	Elapidae and Viperidae
Cysteine-rich secretory proteins	20-30	A blocker of calcium channel (L-type) and cyclic nucleotide-gated channel	Inhibit smooth muscle contraction	Viperidae
C-type lectins	Composed of two subunits; α (A chain): β (B chain)	Interference with the blood coagulation cascade	Interference with hemostasis	Viperidae
Disintegrins	5-10	Interference with the blood coagulation cascade	Interference with hemostasis	Viperidae
Natriuretic peptides	3.5-4	Binding with guanylyl cyclase receptors triggers an increase in the level of cGMP and further signaling. Inhibitor of angiotensin-converting enzyme	Shows hypotension due to vasodilation, diuresis, and natriuresis	Elapidae and Viperidae

PLA_2

Many phospholipase isoenzymes have been identified in snake venoms, such as *Trimeresurus flavoviridis* and *Vipera russelli*[91,92,116,191,209]. Based on their primary structure and disulfide bonds, most PLA_2 enzymes are categorized as Group I and II[182,210], with more or less similar amino acids (~125 residues), and are stabilized by seven S-S bonds. However, small, even subtle, changes in amino acid sequence or the secondary structure greatly affect the substrate specificity[211,212]. Group I PLA_2 enzymes were isolated from Hydrophidae and Elapidae, whereas Group II PLA_2 enzymes were extracted from other sources[213-215]. PLA_2 enzymes show different pharmacological actions, such as inflammatory, cardiotoxic, myotoxic, neurotoxic, and anti-coagulant[49,50,57,78,105,216].

Scorpion Venoms

Approximately 3% of scorpion species are very poisonous. The Buthidae family is widely acknowledged for its fatality, poisonous, and medical importance[217,218]. Scorpion venom comprises multiple peptides and proteins. Significant enzymatic activities include phospholipases, hyaluronidases, alkaline phosphatases, acetylcholinesterase, and sphingomyelinases[25,154,218-220]. Other notable ingredients include amino acids and neurotransmitters[221]. Some of the peptides isolated from scorpion venoms are cysteine-rich. They show high specificity towards sodium, potassium, and calcium channels[133,222], which makes them beneficial as research tools and discovery platforms[223,224].

Bee Venom

Bee venom is a transparent, odorless liquid secreted from a gland in the abdominal cavity of honeybees, containing 88% water and only 0.1 µg dry venom[225,226]. The therapeutic application of bee venom finds its roots in ancient civilizations thousands of years ago[227]. Envenomation of various stinging insects like the honeybee releases many proteins, peptides, and enzymes, in addition to activating mast cell release of peptides and other chemicals (e.g., serotonin, acetylcholine, and histamine). These venoms also have hyaluronidase and other enzymatic activities, which diversifies their potential applications[43,49,134]. The role of bioactive mediators derived from bee venom and its isolated components have been extensively implicated in immunotherapy, arthritis, neurodegenerative diseases, cancer, and viral infections.

Spider Venoms

Venoms isolated from spiders, like snake venoms, are heterogeneous and complex mixtures that contain therapeutically active and inactive components in the form of proteins, polypeptides, enzymes, nucleic acids, amino acids, and inorganic salts[133,223,228-232]. Although most spider bites do not need much medical attention, venomous spider bites show neurotoxicity, necrotic effects, and sometimes organ damage[233,234]. Moreover, toxicity may vary with species and site of envenomation. Neurotoxins, like latrotoxins and atracotoxins, are the major component of venoms from Widow spiders and Australia funnel-web spiders, respectively. The latrotoxins induce the release of neurotransmitters, which further cause muscle contractions, painful abdominal cramps, gooseflesh, and sweating[235,236]. The atracotoxins show toxicity by modulating blood pressure, excessive neural activity by opening Na^+ channels, and muscle contractions[237,238]. They also cause fatal conditions like pulmonary edema. Similar pathological effects were noted with toxic envenomation of Brazilian wandering spiders. Moreover, the venom of this species also contains serotonin that stimulates pain[239-241].

The Sicariidae family includes the recluse spiders (genus: *Sicarius* and *Loxosceles*, species: *Sicarius ornatus* and *Loxosceles intermedia, Loxosceles gaucho*) and the six-eyed sand spiders (genus: *Hexophthalma*), known for their necrotic effects[242,243]. Furthermore, other spiders, including the white-tailed spider, sac spider, and hobo spider, can induce necrotic effects[243-247]. These pathogenic spider venom possesses sphingomyelinase D, a well-known dermo-necrotic agent responsible for necrotic effects and causes a range of local to systemic effects[244,245,248]. Mostly, no pain was found post-envenomation of these spiders, but the wound grows broader and deeper with time, and the site might become gangrenous and very painful. Along with localized effects, envenomation of these spiders also showed systemic effects like hemolysis, kidney damage, and muscle cramps[234,249].

Pharmacological Activity

Neurotoxicity

The venoms of venomous animals usually contain neurotoxins that attack the nervous system. The clinical manifestations of intoxication with neurotoxic venom are the blockage of

nerve impulses to the muscles, muscle cramps, and rigidity, which ultimately disrupts many of the body's functions, notably respiration[151,217]. Some neurotoxins, including atracotoxins of the funnel-web spider venom, directly stimulate the profound release of endogenous neurotransmitters, such as acetylcholine and norepinephrine, causing paralysis of the entire nervous system[237,238]. Neurotoxins from snake venoms (coral snake, tiger snake, rattlesnake, and Russell's viper snake) can induce acute neuromuscular paralysis[78,161,242,250]. These neurotoxins act in two ways to inhibit neuromuscular transmission; α-neurotoxins inhibit postsynaptic transmission of the neuromuscular junction, whereas β-neurotoxins inhibit presynaptic transmission[159,162]. One example of β-neurotoxins is β-bungarotoxins extracted from the many-banded krait snakes, which have PLA_2 enzymatic activity[251,252]. On the other hand, α-bungarotoxins are α-neurotoxins that inhibit the postsynaptic nicotinic acetylcholine receptors at the motor-end plate[146,253].

Hemotoxicity

Venoms from different sources have demonstrated activities, such as coagulant, anti-coagulant, and fibrotic properties, interacting with the blood coagulation system[95,96,185,187]. For example, venoms of the Levantine viper (*Vipera lebetina*) and *Bothrops atrox* can activate factor X and initiate blood coagulation[254,255]. However, venoms and their toxins might demonstrate pro-coagulant and anti-coagulant activities[67,173,256]. They show anti-coagulant effects by inhibiting the clotting factors and protein C activators[257]. Venom from *Bothrops jararaca* was isolated and characterized as Bothrojaracin, which acts as a thrombin inhibitor[258].

Cytotoxicity

Many cytotoxins have been isolated from venoms of various animals and showed targeted affinity towards several cellular sites/components[116,200,259,260]. Several studies[131,260,261] showed the potential application of cytotoxic venom constituents as cancer therapeutics. Constituents from Elapid venoms illustrated significant cytotoxic potential with neuroblastoma and leukemia models[262,263].

Myotoxicity

A very important invalidating effect of envenomation is the irreversible damage to muscle tissues. Venoms extracted from the Elapidae and Viperidae snakes have demonstrated high levels of PLA_2, one of the most abundant myotoxins[118,162,262]. Other myotoxins, like crotamine obtained from the Prairie rattlesnake (*Crotalus viridis*) showed affinity to bind with Na^+ channels and polypeptides cardiotoxins extracted from different snake venoms, which further induce the depolarization of skeletal muscle cell membrane[264-266].

Inflammation

The inflammation process initiated by envenomation was reported several years ago, and a complete understanding of the process is yet to be explored. Several components of snake venoms

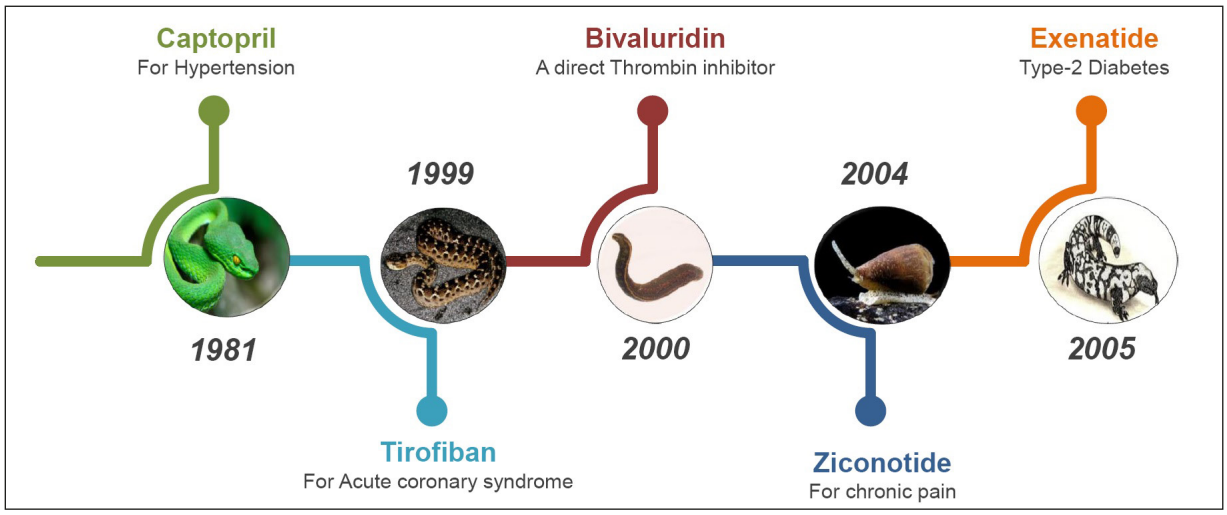

Figure 2. Important timelines of venom-based therapeutics.

Table IV. Venom-based approved therapeutics.

Protein & derivative	Source of venom protein	Molecular target	Mode of delivery	Indication	Company	Reference
Batroxobin (Baquting®)	Lancehead snake *(Bothrops moojeni & Bothrops atrox)*	Defibrino-genating agent	Parenteral (i.v. infusion)	Perioperative Bleeding	Nuokang Biopharma	Zhang et al[255]
Bivalirudin (Angiomax®)	Medicinal leech *(Hirudo medicinalis)*	Direct thrombin inhibitor	Parenteral (i.v. infusion)	Anticoagulant during surgery	The Medicines Co.	Warkentin et al[256]
Captopril (Capoten®)	Brazilian pit viper *(Bothrops jararaca)*	Angiotensin converting enzyme (ACE) inhibitor	Oral	Hypertension	Bristol-Myers Squibb	King[257]
Enalapril (Vasotec®)	Brazilian pit viper *(Bothrops jararaca)*	ACE inhibitor	Oral	Hypertension	Bausch Health (Formerly Valeant Pharm)	Bordon et al[26]
Eptifibatide (Integrilin®)	Pygmy rattlesnake *(Sistrurus miliariusbarbouri)*	Glycoprotein IIb/ IIIa inhibitor	Parenteral (i.v. infusion)	Antiplatelet	Merck	Tcheng & O'Shea[258]
Exenatide (Byetta®) and Lixisenatide (LyxumiaTM)	Gila Monster lizard *(Heloderma suspectum)*	Binds to glucagon-like peptide-1 (GLP-1) receptor	Parenteral (s.c. infusion)	Type 2 diabetes	Amylin and Eli Lilly; Sanofi	Barnett[259]
Tirofiban (Aggrastat®)	Saw-scaled viper *(Echiscarinatus)*	Glycoprotein IIb/ IIIa inhibitor	Parenteral (i.v. infusion)	Antiplatelet	Iroko Cardio and Merck (USA only)	Menozzi et al[260]
Zinconitide (Prialt®)	Cone snail *(Conus magus)*	Ca^{2+} channel antagonist	Intrathecal	Chronic pain	Azur Pharma and Eisai (Europe)	Miljanich[261]

Source: http://clinicaltrials.gov

(e.g., PLA_2 and proteinases) are responsible for initiating inflammation response induced by increased vesicular permeability[77,193]. The *Bothrops asper* venom induces muscular and other tissue inflammation synchronous with a high concentration of interleukin-6, interleukin-1β, and other inflammatory mediators[267-276].

Venom-Derived Approved Therapeutic

Although many animal bites and stings usually have serious implications on the vital organs, such as the heart, brain, liver, and intestine, careful isolation, purification, chemical analysis, synthesis, or synthetic modification of venom ingredients led to the discovery of beneficial therapeutics[20,22,24,132,164,176,261]. Venoms are now well-recognized as the biggest natural source of drugs after plants. Figure 2 shows a few important landmarks of venom-based therapeutics. Several successful examples (Table IV) highlight the commercial importance of venom-based therapeutics. Famous clinically successful cardiovascular preparations include Aggrastat (tirofiban), Capoten (captopril), and Integrilin (eptifibatide), which were designed based on model molecules from snake venoms. Many venom components from different sources of animals have shown their potential in treating various disease states and in different clinical phases.

Conclusions

From toxin to drug development, this overview highlights the categorization of several venom-derived enzyme and peptide products that are clinically available. Furthermore, as the efficiency and affordability of commercial peptide synthesis and recombinant expression of peptides improve,

more of these complex peptides will be generated. The application of high throughput screening after advanced purification techniques and structure-activity relationship studies is essential for discovering new venom-derived therapeutics and diagnostics.

Conflicts of Interest

The authors declare no conflict of interest.

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Authors' Contributions

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