***Review Article***

**Venom's Edge: Balancing Peril and Promise in Snake Venom Biology**

 **Abstract:**

According to the WHO, an estimated 5.4 million individuals are bitten by snakes annually, leading to an estimated 1.8 to 2.7 million cases of envenomations. Snake venom comprises a sophisticated blend of proteins, peptides, enzymes, and bioactive molecules, showcasing a complex structural organization and diversity. Based on their composition and the mode of action, snake venoms are classified as neurotoxic, haematotoxic, cytotoxic, and myotoxic. The diversity of venoms across snake species is a result of evolutionary adaptations, leading to a wide range of toxic effects on prey and predators. In addition to their toxic properties, snake venom-derived compounds show medicinal activities such as anticancer, antimicrobial, analgesic, and anticoagulant activities. This paper explores the multifaceted nature of snake venoms, highlighting their diverse composition, the intricate modes of action of their components, and potential therapeutic applications of the venoms.

**Keywords:** Snake Venom; Enzyme; Medicine; Drug Discovery

1. **Introduction:**

Toxic chemicals are produced by a wide diversity of living taxa, including but not limited to microorganisms, fungi, plants, and animals. Snake venom comprises a sophisticated blend of biologically active substances with both enzymatic and non-enzymatic features. They are target-specific and serve roles in both self-defence and predatory behaviours. Venom is primarily used by snakes to immobilize prey. Due to habitat loss, agricultural expansion, and human settlements in their territories, human-snake conflicts have surged significantly in the last few decades[1]. According to the WHO, an estimated 5.4 million individuals are bitten by snakes annually, leading to an estimated 1.8 to 2.7 million cases of envenomations[2]. Snakebite envenomation represents a potentially fatal condition triggered by the toxins injected through the bite of a venomous snake. Each year, approximately 81,410 to 137,880 fatalities result from snakebites, with nearly three times as many instances of amputations and other lasting disabilities attributed to these incidents[3][4]. The majority of these incidents happen across Africa, Asia, and Latin America[5]. Vulnerable populations include rural agricultural labourers, herders, fishermen, hunters, individuals residing in inadequately built dwellings, and those with restricted access to education and healthcare[2].

Snake venom is produced and secreted by specialized glands in the heads of venomous snakes, called venom glands, injected through specialized fangs[6]. The venom gland is a modified salivary gland which can store 1 – 850 mg of venom depending on the size and species of the snake. The venom is a sophisticated blend of proteins, peptides, and other bioactive molecules, that show a complex and varied structural association. The composition of the blend varies among species as well as their native location and habitat. The composition of the venom also plays a key role in determining their mode of action when injected into the victim’s body. Snakebite envenomation may cause haemorrhage, tissue necrosis, and/or kidney failure[7]. Although they pose a great health hazard when injected through a snakebite, these marvels of nature are proven to have numerous health benefits against several human diseases. In this chapter, we discussed to composition, diversity, mode of action, and mechanism of action of snake venom, intending to compare both the hazardous and promising sides of nature’s marvel.

1. **The Intricate Composition of Snake Venoms:**

Snake venom comprises a diverse mix of proteins (enzymes), polypeptides, metal ions, carbohydrates, nucleosides, amines and traces of lipids, showcasing a complex and diverse composition[8]. Venom typically contains various toxins, such as neurotoxins, hemotoxins, cytotoxins, and enzymes, each with distinct molecular architectures and biological effects, targeting specific physiological systems in prey or predators. Its structural intricacy results from the elaborate folding of constituent proteins and peptides, aided by disulphide bonds and secondary structures like alpha helices and beta sheets, forming a tightly compact tertiary conformation. This structural complexity is essential for venom's effectiveness, enabling it to disrupt vital biological processes in victims, leading to immobilization, paralysis, or death. Variations in venom composition and structure among snake species reflect evolutionary adaptations to ecological niches, prey preferences, and defensive strategies, underscoring nature's diverse and sophisticated biochemical weaponry.

Snake venom are intricately structured globular proteins, usually composed of one or more polypeptide chains arranged in a compact tertiary form; with specific segments accountable for receptor or molecular target binding. The tertiary structure is pivotal, governing their ability to interact with different biological or cellular targets in the victims. About 90% of the venoms are protein by dry weight and most of the proteins are enzymes. Sanke venom is a bioactive cocktail of about 25 different enzymes, out of which 10 are present in almost all of them[9]. For instance, the venom of the snake family *Elapidae* contains peptides and proteins majorly from six families including secreted phospholipases A2 (PLA2s), three-finger toxins (3FTxs), snake venom metalloproteinases (SVMPs), snake venom serine proteases (SVSPs), L-amino acid oxidases (LAAOs), and Kunitz-type peptides[9]. The venoms of the *Viperidae* family are mainly composed of PLA2s, SVMPs, SVSPs, LAAOs, C-type lectins, C-type lectin-like proteins, and natriuretic peptides. However, there are countless exceptions and substantial diversity of venoms at the species level as their abundance and proportions vary from species to species. In the next section, we have discussed the structural diversity of these venom-making proteins.

1. **Snake venom diversity and their modes of action:**

Snake venoms are toxins, which are a complex mixture of proteins and enzymes as well as anticoagulants and other substances. They can be categorised into several types based on their composition and the mode of action. The major types are discussed below:

* 1. **Neurotoxic Venom:**

Neurotoxic venom is predominately ejected by elapid snakes, which is mainly responsible for affecting the nervous system and causing paralysis or respiratory failure. Neurotoxic envenomation is responsible for more than 70% of victims of snake bite deaths. Most neurotoxins derived from snake venom either function on the nicotinic acetylcholine receptor on the motor end-plate (postsynaptic) or the motor nerve terminals (presynaptic)[10]. Toxin exposure to the presynaptic neuron causes a reduction in synaptic vesicles, which in turn damages the motor nerve terminals structurally[11]. Postsynaptic neurotoxins derived from snake venom exhibit a strong and non-reversible affinity for the agonist-binding sites of nicotinic acetylcholine receptors on the motor endplate, hence obstructing neuromuscular transmission[12]. In addition, various toxins found in snake venom influence acetylcholinesterase activity in the neuromuscular junction or act on particular ion channels. These venoms interfere with or impede the production of the neurotransmitter acetylcholine, which specifically prevents the transmission of electrical impulses in the neuromuscular junctions, resulting in paralysis of the skeletal muscles. Lastly, these venoms can also overstimulate neurotransmitters, which can lead to rapid muscle twitching or convulsions. Regardless of the mode of action, all of these neurotoxins have the same clinical symptoms that include muscle weakness, respiratory failure and even death if not treated properly. This venom occurs in cobras, kraits, mambas and coral snakes.

* 1. **Haemotoxic Venom:**

Haemotoxic venom affects the blood, blood vessels and its components, and coagulation factors. It disrupts blood clotting, thereby impacting the cardiovascular system. The venom attacks the endothelial cells of the inner surface of the blood vessels, the blood leaks out from the vessel into its surrounding tissues resulting in hemorrhage. Additionally, the venom also targets blood clotting components like platelets and clotting proteins like fibrinogen and thrombin, which can lead to either reduced or accelerated coagulation[13][14]. This results in widespread tissue injury, circulatory collapse, and organ degeneration if treatment is delayed. Even though hemotoxins have different mechanisms based on their constituents, they all eventually cause haemorrhage. Crotalid venom is a complex mixture of proteins, including metalloproteinases, collagenase, hyaluronidase, and phospholipase. The enzyme metalloproteinases or Snake venom metalloproteinases (SVMPs), for instance, can induce haemorrhage, impede platelet aggregation, and cause fibrinogen and fibrin to be broken down by proteases[15][16]. The symptoms of haemotoxic envenomation include lethargy, headache, nausea, and vomiting. This venom occurs in species from the *Viperidae* family and the *Crotalinae* subfamily[17].

* 1. **Cytotoxic Venom:**

Cells are referred to as cytos, and cytotoxicity is the general term for the harmful effect on cell activity. These venoms target cells/tissues and cause severe pain by impairing the tissues at the molecular level. Cytotoxins are roughly 6.5 kDa β-sheet proteins that affect vital membrane-binding proteins such as integrins, Na+/K+-ATPase, and protein kinase C. It is commonly acknowledged that the majority of cytotoxins' pathogenic effects initiate from their capacity to bind to cell membranes and disrupt the structure and functionality of lipid bilayers[18]. The cytotoxin-mediated toxicity pathways involve modifying the activity of membrane enzymes, depolarizing excitable membranes of neurons and heart cells, preventing platelet aggregation, causing hemolysis and cytotoxicity, triggering cardiac arrest, cytological alternations and apoptosis[18][19]. Victims who get bitten by snakes with cytotoxic venom begin to experience symptoms like severe pain, swelling of the area surrounding, and necrosis. This venom occurs in rattlesnakes, some species of pit vipers, and black mambas. The venom of the Indian Cobra (*Naja naja*) is recognized for its high abundance of cytotoxins[16].

* 1. **Myotoxic Venom:**

Myotoxins are components found in certain venoms that specifically target muscle tissue. The first myotoxin to be identified and isolated was *cromatine* by the Brazilian Scientist Jose Moura Goncalves venom of *Crotalus durissus terrificus*, a tropical South American Rattlesnake, in the 1950s. A few more snake venom myotoxins to name are phospholipases A notexin, taipoxin, and crotoxin. These are proteins that can induce localised or widespread skeletal muscle deterioration or necrosis. The specific modes of action of myotoxins are still up for debate, however, the order of collapse of muscle cells is well-explored. Following the binding of the protein to the muscle cell membrane in the first hour, generally, a restricted oedema occurs in the extravascular area. The first three hours see the degeneration and hypercontraction of myofibres as well as the accumulation of phagocytic cells. The resting potential drops, the plasma membrane is damaged, and phagocytes infiltrate necrotic myofibres in a span of three to six hours. After six to twenty-four hours, individual muscle fibres fully degenerate, while the basal lamina and surrounding support structures remain unaffected[20][14].

The clinical patterns of venom-induced myotoxicity are of two types―local myotoxicity, which is characteristic of viperid bites and affects predominantly the muscles surrounding the site of the snake bite; and systematic myotoxicity, which is characteristic of the envenomation by Sea Snakes, terrestrial elapids, and some viperid species. Systemic myotoxicity occurs when the venom components spread through the bloodstream and affect muscle tissues throughout the body[21]. The breakdown of muscle tissue releases myoglobin and other cellular contents into the bloodstream. High levels of myoglobin can cause kidney damage (myoglobinuria), leading to acute kidney injury[22]. The destruction of muscle cells releases large amounts of potassium into the bloodstream, potentially causing hyperkalemia. This can disrupt normal cardiac function and lead to arrhythmias[23]. Systemic distribution of myotoxins can cause widespread muscle pain, weakness, and paralysis, potentially affecting respiratory muscles and leading to respiratory failure.

1. **Medicinal applications of snake venoms:**

The fangs of a snake act as a bunker for one of the dangerous yet medicinally marvellous venom. The uses of snake venom have already been demonstrated in ancient ayurvedic practices with methods like intake with dried meat, claiming that once the venom is dried the poisonous activity reduces and it becomes rather medicinal[24]. Some contemporary medicinal applications of snake venom are discussed below:

* 1. **Anticancer activity:**

The venom-derived toxins seem to act only on certain types of cells and have shown differential lytic activity against various cell lines and subcellular organelles. The different lytic activity makes it efficient to be used as a cure for cancer. The fibrinolytic enzymes in snake venom have been used in attempts to inhibit tumour growth by interfering with fibrin deposition and platelet aggregation to stop the growth of cancer cells. Induction of cytotoxicity (PLA2), free radical generation (LAAOs), apoptosis induction (PLA2s, MP, and LAAOs), and antiangiogenesis (disintegrins and lectins) are some of the anticancer properties of snake venom[25][26][27]. The cytotoxin, cytotoxin 1 (CTX1), found in cobra venom can cause tumor cells to undergo both necrosis and apoptosis[28]. Another cytotoxic venom, cytotoxin NN-32, from Naja naja was reported to have suppressing effects on the growth and progression of human leukemic cells[28]. To our knowledge, there isn't yet an approved anticancer medication based on snake venom toxin, though.

* 1. **Antimicrobial activity:**

Numerous components of snake venom have been investigated for their antibacterial properties through damaging bacterial cell membrane[26]. They include the enzymes such as metalloproteinases, L-amino acid oxidases, and phospholipase A2. The other family of peptides is called antimicrobial peptides, and it contains secretory proteins rich in cysteines, crotamine, and cardiotoxins, also known as cytotoxins[29][30]. Cardiotoxin 3 from Taiwan cobra (*N. naja atra*) permeabilizes bacterial cell membranes and showed strong antibacterial activity against *Staphylococcus aureus*. With regard to fungi, such as *Trichosporon sp.*, *Cryptococcus neoformans*, and *Candida albicans*, crotamine had a strong inhibitory effect that resulted in notable morphological alterations. In addition, *in-vitro* antileishmanial activity of crotamine isolated from *C. durissus terrificus* was also manifested[31].

* 1. **Analgesic activity:**

Numerous research have been published on the usage of neurotoxins and myotoxins found in the venoms of elapids and viperids to manage pain. This included the analgesic effects of hannalgesin from *Ophiophagus hannah*, mambalgins from *Dendroaspis polylepis polylepis*, crotamine from *C. durissus terrificus*, and cobrotoxin from *N. naja atra*. The opioid and nitric oxide systems (hannalgesin) in the antinociceptive pathway, the central cholinergic neurons (cobratoxin), and the central and peripheral nervous systems (crotamine and mambalgin) were probably responsible for the analgesic responses[31][32].

* 1. **Anticoagulating activity:**

A few substances found in snake venom have anticoagulant properties; they are primarily fibrinolytic enzymes or disintegrins. The integrin-inhibitory protein extracted from the venoms of vipers includes disintegrins, which inhibits platelet aggregation. Other platelet aggregation inhibitors found in snake venom include Mambin (*Dendroaspis jamesoni*), γ-bungarotoxin (*Bungarus multicinctus*), and angustatin (*Dendroaspis angusticeps*)[26][31].

1. **Conclusion:**

In conclusion, the study of snake venom continues to unveil a captivating world of biological complexity and therapeutic potential. Through meticulous investigation, researchers have unravelled the intricate structure and diverse composition of these venoms, shedding light on their evolutionary significance and ecological roles. Perhaps most importantly, the medicinal applications of snake venom-derived compounds offer promising avenues for drug discovery and development. From antivenom production to the treatment of various diseases, including cancer and neurological disorders, the pharmacological properties of snake venom components hold immense therapeutic promise. As research in this field continues to advance, further discoveries are poised to revolutionize both our understanding of venom biology and our ability to harness these potent biochemical cocktails for the betterment of human health.

**Conflict of Interest Statement:**

The authors have no conflict of interests related to this publication.

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