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SNAKE VENOMS: TOXICITY, BIOLOGICAL EFFECTS, IMMUNE RESPONSES, THERAPEUTIC AND BIOTECHNOLOGICAL USE

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ABSTRACT

This review article discusses the composition of snake venom, detailing its biological effects, risks, and potential medical applications. Snake venom contains anticoagulants that can cause severe bleeding, as well as various toxic compounds that affect the nervous and cardiovascular systems. Snake venom contains several neurotoxic, cardiotoxic, cytotoxic, nerve growth factor, lectins, disintegrins, haemorrhaging, and many other enzymes. Snake venom toxins impose fibrinolytic, cardiotoxic, neurotoxic, immunomodulatory, inflammatory, antimicrobial, and anticancer effects. Snake venom very quickly imposes neuro/cardio toxicity, myonecrosis, and impairs respiration and imposes deep oxidative stress on the patient. The article emphasizes the need to study the venom's structure and reactivity to develop new drugs and expand therapeutic applications.

KEYWORDS: Snake toxins, tissue and cell damage, neurotoxic, cytotoxic, antitumor, antimicrobial, anticoagulating, and analgesic activities.

INTRODUCTION

Snakes are poisonous, limbless, carnivorous reptiles which possess fangs with a quick venom injector. Snake venom is generated inside specialized glands. Snake venom developed over a long evolutionary period, used for hunting prey, and for self-protection or defense against enemies.[2] Snake venom contains a complex mixture of biologically active molecules that are responsible for a broad spectrum of clinical manifestations, ranging from local tissue

injury to fatal complications. Anti-venoms remain the only specific treatment that can prevent or reverse most effects of snakebite envenoming when administered early at an adequate therapeutic dose. Early access to safe, affordable and effective antivenoms is critical for minimizing morbidity and mortality, and improving this access is a significant component of an emerging WHO strategy to control snakebite envenoming.

Snake envenomation is a severe health problem in rural areas, as millions of snakebite cases and deaths are reported worldwide every year. These fatalities occur every year due to snake venom poisoning and lack of antivenin and clinical care. Unintentional snake bites cause many fatalities in rural tropical, subtropical, and temperate countries. Coastal regions also have a high rate of snake envenomation.

Snake venom poisoning causes heavy pathogenesis and generates reactive oxygen species (ROS). Snake venom envenomation leads to severe pathogenesis and triggers the production of reactive oxygen species (ROS). Severe bleeding (haemorrhage) caused by snake venom occurs due to hypocoagulability, neurotoxicity, cardiotoxicity, and muscle tissue damage (myonecrosis). It harms local tissues and has adverse effects on the entire system. It also causes heavy oxidative stress and long-term complications of musculoskeletal disabilities.[3] Venom toxic effects are exhibited as neurotoxic and cardiotoxic symptoms, haemorrhage, acute kidney injury, renal failure, tissue necrosis and rhabdomyolysis with severe inflammation and discomfort at the bite site. Phospholipases A2 metalloproteinases, three-finger toxins, and L-amino acid oxidase are among the components of snake venom that are known to cause oxidative stress. Most snake venom toxins/proteins interact with components of the human hemostatic system, influencing the blood coagulation pathway, endothelial cells, and platelets.[4] Snakebite envenomation causes severe inflammation induced by platelet-activating snake venoms.[5,6]

There is a need for potential antivenins that can mitigate adverse biological effects.[1] A crucial issue hindering the treatment of snakebite envenoming is the limited availability of antivenoms. In the absence of antivenin, thousands of people die from venom poisoning from snake bites; consequently, new therapeutic approaches must be investigated using molecular and biotechnological tools to meet the need for antivenoms. Most bioactive toxins in snake venom can be exploited as sources of new antigens for antivenin production.

Snake venom is a natural depository of mini-drug libraries of pharmaceuticals and medicines. These can be used to develop new bioactive drugs, primarily analgesics.[7] In the past, these were also used for thousands of years as medical tools in India, China, Africa, Australia, and most Asian countries. Snake species exhibit extensive worldwide diversification and distribution, except in the northern hemisphere. Beyond species diversification, snake toxins also exhibit structural and functional diversification. But unfortunately, less than 0.01% of snake toxins have been identified and characterized.[8] Snake venom toxins can be used as valuable therapeutic tools.[8] Use of snake venom fractions in the coagulation laboratory. This review article discusses the composition of snake venom, detailing its biological effects, risks, and potential medical applications.[9] Various snake toxins also have potential uses in the development of medicinal drugs.

Source of information

For writing this comprehensive research review on *snake venom toxins*, various databases were searched. For the collection of relevant information, specific terms such as Medical Subject Headings (MeSH) and key text words, including “venom allergens”, “biological and pharmaceutical effects”, and "therapeutic uses”, published up to 2020, were used in MEDLINE. Most especially for retrieving all articles about the lethality and safety of snake venom, electronic bibliographic databases were searched, and abstracts of published studies with relevant information on snake envenomation, venoms, and biological effects were collected. Furthermore, additional references were included by searching for the references cited in studies on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about *a subject* and incorporation of recent knowledge, relevant research articles, books, conference proceedings, and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including Scopus, Web of Science, EMBASE, PubMed, and SwissProt, as well as Google searches. From this standard methodology, discoveries and findings were identified and summarized in this final review.

Composition

Snake venoms are complex mixtures of many different biologically active proteins and peptides. Venom possesses complex mixtures of enzymatic and non-enzymatic components with specific pathophysiological functions. Metalloproteases with disintegrin domains are

among the most abundant toxins in many Viperidae snake venoms.[10] Snake venoms also contain proteins/ enzymes: Zn^{2+}- metalloproteinases, serine proteinases, L-amino acid oxidase, 5'-nucleotidase, phosphodiesterase, phosphomonoesterase, nucleases, hyaluronidase, phospholipase A2, C-type lectin-like protein, disintegrin, DC-fragment, cysteine-rich secretory protein, proteinase inhibitors, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), low molecular weight peptides[11] (Table 1). Many of these components can be utilized in new drug design.

Bothrops moojeni snake venom possesses fibrinogenolytic metalloproteinase (Bmoo FIBMP-I), a low molecular weight peptide 22.8 kDa. Bmoo FIBMP-I showed pH-dependent proteolytic activity on azocasein, but was devoid of coagulant, defibrillating, or hemorrhagic activities.[12] The disintegrins are an interesting group of peptides that contain the cell adhesion recognition motif Arg-Gly-Asp (RGD) in the carboxy-terminal half of their sequences. These agents act as antagonists of the fibrinogen receptor (integrin GPIIb/IIIa). In contrast, integrin is believed to mediate platelet-platelet bridge formation and platelet aggregation, as well as platelet aggregation and platelet aggregation. Platelet GPIIb/IIIa blockade is an effective therapy for thrombotic events (Table 1). Snake venom probes from both families selectively target platelet adhesion receptors, including glycoproteins (GPs) Ib-IX-V, GP VI, alpha2beta1, and alphaIIbbeta3 (GP IIb-IIIa). These receptors act together to mediate platelet adhesion, activation and aggregation (thrombus formation) under hydrodynamic shear stress in flowing blood.[13] The receptors are members of the leucine-rich repeat family (GP Ib-IX-V), the immunoglobulin superfamily (GP VI), or integrins (alpha2beta1, alphaIIbbeta3).[14] These proteins modulate platelet adhesive interactions (Table 1).

Non-enzymatic proteins from snake venoms play important roles in prey immobilisation and include large, well-recognised families of toxins.[15] Most non-enzymatically active snake venom toxins exhibit therapeutic potential, including antitumor, antimicrobial, anticoagulant, and analgesic activities. Snake venom enzymes are clinically used as anticoagulants. These promote fibrinogen coagulation and fibrinogen degradation. It also contains plasminogen activators, prothrombin activators, factor V activators, factor X activators, enzymes with haemorrhagic activity, platelet aggregation inducers, and platelet aggregation inhibitors. However, many snake venoms contain several hemostatically active components.

Table 1: presents the essential enzyme categories found in snake venom.

Snake family	Name of factor	Name of enzymes and their action
Viperidae	Clot fibrinogen	Thrombin converts soluble fibrinogen into insoluble fibrin monomers.
Viperidae, *Elapidae* and *Crotalidae*	Enzymes degrade fibrin(ogen);	Plasmin, is generated from its precursor plasminogen
Viperidae	prothrombin activators	a complex of a dozen blood coagulation factors that functions in catalyzing prothrombin into thrombin
Viperidae	factor V activators	primarily mediated by thrombin and activated factor X (Xa), which cleave specific peptide bonds in factor V, releasing activation fragments and creating the active cofactor.
Viperidae	factor X activators	It is a serine endopeptidase (protease group S1, PA clan). Factor X is synthesized in the liver and requires vitamin K for its synthesis.
Viperidae	anticoagulant activities	prothrombinase complex formation, inhibitors of thrombin, phospholipases, and protein C activators
Viperidae	enzymes with hemorrhagic activity	metalloproteinases
Viperidae	enzymes that degrade plasma serine proteinase inhibitors	Metalloproteinases and serine proteases
Viperidae	platelet aggregation inducers	alpha-fibrinogenases, 5'-nucleotidases, phospholipases, and disintegrins.
Trimeresurus stejnegeri venom plasminogen activator	plasminogen activators (TSV-PA),	Tissue-type plasminogen activator and urokinase
	Lachesis muta muta venom plasminogen activator (LV-PA), and Agkistrodon halys venom plasminogen activator (Haly-PA).	

Group I activators	These efficiently convert prothrombin into meizothrombin, and their activity is not influenced by the non-enzymatic cofactors of the prothrombinase complex ($CaCl_2$, factor V_a and phospholipid).
Group II and III activators	These activators can cleave both peptide bonds in prothrombin necessary to convert prothrombin into thrombin. Phospholipids and factor Va strongly stimulate the prothrombin-converting activity of Group II activators in the presence of $CaCl_2$, whereas the activity of group III activators is only stimulated by $CaCl_2$ and phospholipid.
Group IV	It consists of snake venom proteases that do not convert prothrombin into enzymatically active products but cleave peptide bonds in prothrombin, forming inactive precursor forms of thrombin.

Group I, Group II, and Group III activators can cleave both peptide bonds in prothrombin required for its conversion into thrombin. Phospholipids and factor Va strongly stimulate the prothrombin-converting activity of Group II activators in the presence of $CaCl_2$, whereas the activity of group III activators is only stimulated by $CaCl_2$ and phospholipid. Group IV consists of snake venom proteases, which do not convert prothrombin into enzymatically active products but cleave peptide bonds in prothrombin, resulting in the formation of inactive precursor forms of thrombin.[16]

Biological effects

Snakes utilise venom to immobilise their prey. Venom's enzymes are essential for the digestion of prey, which serves as a protective mechanism. Venoms influence many cells, cellular structures, and tissues, including the skin, nervous, haematological, digestive, excretory, and immunological systems, as well as the heart. The biological repercussions of venom envenomation are incredibly deadly. Most snake venoms exhibit specific bioactivities and are complex mixtures of small molecules and peptides/proteins. Venom from venomous snakes has a variety of pharmacological and biological effects. Both local tissue damage and systemic consequences, including neurotoxicity, cardiotoxicity, haemorrhage, renal damage, and rhabdomyolysis, can be brought on by snake venom. Reactive oxygen species primarily cause inflammation and damage. The venom contains a variety of toxins, including those that harm nerve cells, general cells, the heart, and muscles, as well as enzymes that disrupt bodily processes. These venom components can affect various parts of the body, including the skin, nervous system, blood, digestive and excretory systems, and immune system, as well as the heart and kidneys. Specifically, the venom from *Vipera berus berus* has a significant toxic and immunological impact on people[17](Table 1).

Neurotoxic Effects

Snake toxins are neurotoxic venom, and severely affect physiology of the nervous system, especially where nerves meet muscles, eventually causing paralysis. These toxins really mess up how charged atoms move in and out of nerve cells and mess with acetylcholine receptors called nAChRs. Many of these toxins are small protein fragments that act as kininogenases, kininases, and related peptides. Researchers have found these in the venoms of snakes from Central Asia, including *V. lebetina turanica* and *E. multisquamatus* (from the Vipera and Echis families), *Ag. halys halys* (from the Agkistrodon family), and *N. oxiana* (from the Naja family). Snake venom toxins also disrupt muscle contraction and cause breathing problems.

Viper snakes, particularly those in the Daboia, Macrovipera, and Vipera groups, latch onto specific neuronal nicotinic acetylcholine receptors (nAChRs).[18] Cobra venom has been observed to produce contractions mimicking kinin-induced contractions. All these substances are small and have a particular ability to enhance bradykinin's effects while blocking the enzyme that breaks down kinins, known as kininase II (or angiotensin I-converting enzyme, ACE).[18] They can also interfere with how ion channels work, tighten blood vessels, affect the body's defense system, cause blood platelets to clump together, disrupt blood clotting, interfere with cell communication, and mess with blood pressure control. Snakes in the Elapidae family are known for their neurotoxic effects(Table 1) (Figure 1).

Fasciculins are mostly found in the venom of mambas (*Dendroaspis* spp.) and some rattlesnakes (*Crotalus* spp.) These toxins disrupt cholinergic neurotransmission by inhibiting acetylcholinesterase activity. Therefore, ACh cannot be broken down and remains in the receptor. This causes tetany (involuntary muscle contraction), which can lead to death. Fasciculins cause severe, generalized and long-lasting muscle contractions. Dendrotoxins inhibit nerve transmission by blocking the exchange of positive and negative ions across the neuronal membrane, preventing nerve impulses and thereby paralysing the nerves. α-neurotoxins from mambas attack the nicotinic acetylcholine receptors of cholinergic neurons. They mimic the shape of the acetylcholine molecule and bind to receptors, blocking the flow of ACh and leading to numbness and paralysis. A few examples of alpha neurotoxins are α-Bungarotoxin, α-toxin, erabutoxin, and cobratoxins isolated from sea snakes, banded krait and cobras.[20]

Thrombin-like enzymes

Russell's viper (*Daboia russelli*) venom (RVV) is a rich source of prothrombin activators. These have been used to assay blood clotting factors V, VII, and X, platelet factor 3, and, importantly, lupus anticoagulants (LA).[21] Snake venom contains thrombin-like enzymes (SVTLE) used in fibrinogen/fibrinogen breakdown product assays and for detecting fibrinogen dysfunction and dysfibrinogenemias. These (Ancrod and Defibrase) are also used for therapeutic anticoagulation and to detect individual haemostatic factors (protein C, prothrombin, factor X, and lupus anticoagulant). Naturally, these agents facilitate the spread of venom toxins throughout the body and initiate hemolysis and blood clotting.[22] The fibrinogenases as thrombolytic agents.[23] Thrombotic enzymes have been isolated from Southern copperhead snake venom as Protac. and STA-Staclot from *Crotalus viridis helleri*.

and botrocetin (*Bothrops jararaca*). Finally, snake venom C-type lectins and metalloproteinase-disintegrins, a large family of Arg-Gly-Asp (RGD)-containing snake venom proteins. These are used to study platelet glycoprotein receptors and show great potential for use in routine coagulation laboratories.[24] Prothrombin activators are found in the venoms of many snakes. The disintegrins are also used as an anticoagulant to achieve 'therapeutic defibrillation'. Other snake venom proteins show promise in the treatment of a range of haemostatic disorders.[26] Snake venom toxins affect haemostasis (Malayan pit viper, *Calloselasma rhodostoma*)(Table 1).

Thromboinflammation

Envenomation by viperid snakes causes systemic thrombotic syndrome and local inflammation. Research shows that the thrombo-inflammation and blood clotting triggered by Viperidae venoms involve overlapping mechanisms in the immune and hemostatic systems. Bothrops snake venom exhibits inflammatory effects, particularly activating platelet function and inflammation. Venom components (metalloproteases and C-type lectins), which both stimulate platelet function and exhibit pro-inflammatory activity, play important roles in thromboinflammation during viper envenomation(Table 1).

Snake venom proteins, C-type lectin-like family members, or metalloproteinase-disintegrins modulate platelet adhesive interactions. These metalloproteinases activate/inhibit clotting factors, affect blood vessels, interfere with platelet function, and induce haemorrhage.[26] Snake venom probes from different families target specific platelet adhesion receptors, including GP Ib-IX-V, GP VI, alpha2beta1, and alphaIIbbeta3. These receptors help platelets adhere, activate, and aggregate in flowing blood. They belong to various protein families, including the leucine-rich repeat family, the immunoglobulin superfamily, and the integrin family. Additionally, snake venom proteins target adhesive glycoproteins, including von Willebrand factor, collagen, and fibrinogen. Regulation of interactions between these proteins may target similar receptors on other vascular cells.[27] Envenomation by viperid snakes is characterized by systemic thrombotic syndrome and prominent local inflammation[28] (Table 1) (Figure 1).

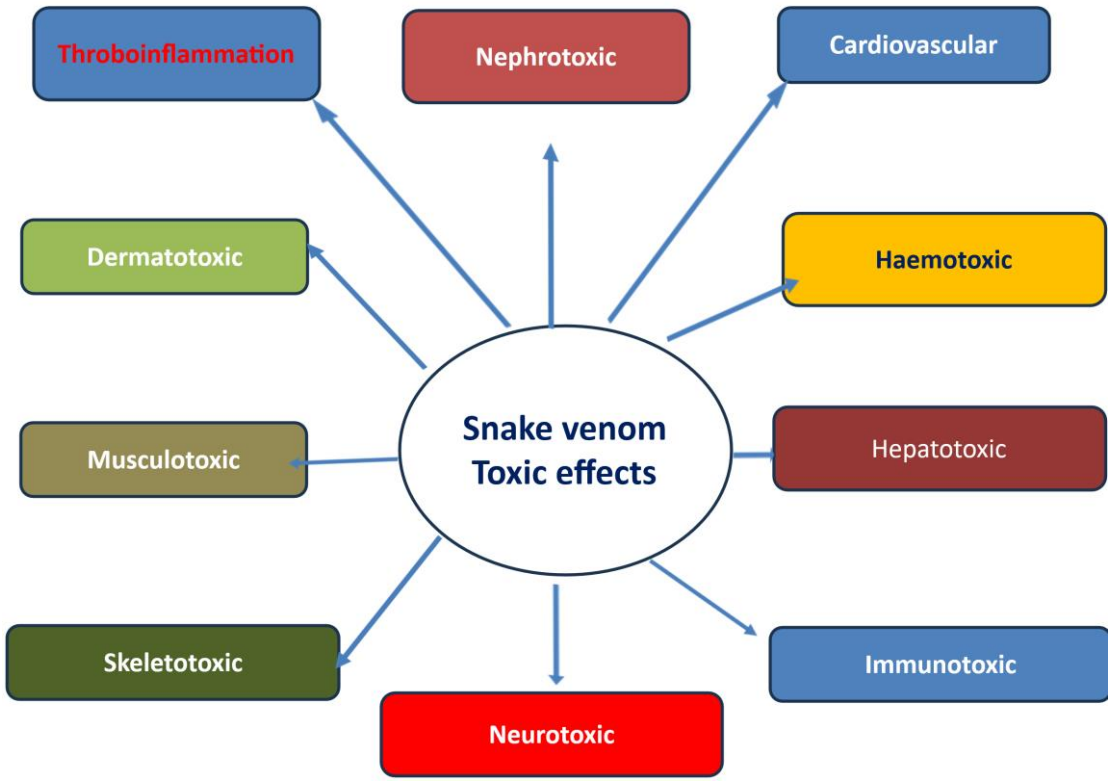

Figure 1: Effects of snake venom on the human body.

Cardiovascular Effects

Many snake venoms contain toxins that significantly affect the heart and blood vessels. These toxins act on cardiac and vascular muscles and can increase vascular permeability. Some venoms contain peptides that inhibit angiotensin-converting enzyme and enhance bradykinin activity, while others contain peptides that act as natriuretic peptides. Sarafotoxins in certain snake venoms can strongly constrict blood vessels. Snake toxins have also been shown to block specific calcium currents. Proteins such as the increasing capillary permeability protein (ICPP) have been identified and have potential therapeutic use for understanding and treating cardiovascular diseases(Table 1).

Snake venom toxins that impact blood clotting. Snake venom proteins can increase vascular permeability. Increasing capillary permeability protein (ICPP) from *Vipera lebetina* is highly potent and closely resembles vascular endothelial growth factor. These proteins may help treat cardiovascular diseases.[29] Many snake vessels contain toxins that significantly affect the heart and blood vessels (Figure 1). These toxins act on the heart muscle, blood vessel walls, and small blood vessels. Some venoms contain peptides that inhibit angiotensin-converting enzyme and enhance bradykinin's effects. Other venoms contain peptides similar

to those found in mammals—sarafotoxins, for instance, cause strong blood vessel constriction. Certain toxins also block calcium currents. These diverse toxins help in studying physiology and developing new treatments.

Snake venom components known to induce oxidative stress include phospholipases A_2, metalloproteinases, three-finger toxins, and L-amino acid oxidase. The study examines the content of kininogenases, kininases, and related peptides in the venoms of several Central Asian snakes, including *V. lebetina turanica*, *E. multisquamatus*, *Ag. halys halys*, and *N. oxiana*. All venoms cause muscle contractions in isolated preparations. Cobra venom exhibits prolonged contractile activity and inactivates the rat uterus due to its cytotoxic components. A specific effect related to bradykinin was linked to the inhibition of kininase II. Two peptide inhibitors were isolated from the venom. NNAV and its active components may have therapeutic value in the treatment of inflammatory chronic pain and autoimmune disease. However, several fatal snake venom toxins have found potential uses as diagnostic tools, therapeutic agents, or drug leads. *Naja naja atra* venom (NNAV) exerts potent analgesic effects on various animal models of pain[30] (Table 1).

Anticancer activity

Snake toxins exhibited cytotoxicity against multiple cancer types. *C. albolabris* and *C. rhodostoma* venom inhibit the proliferation and growth of cancer cells, against KATO-III and BT474 cells, more than standard cancer drugs.[31] drCT-1 from *Daboia russelli russelli* venom, caused apoptosis in EAC and leukaemia cells. *Lapemis curtus* venom shows anti-tumour effects against EAC in mice and cell cultures, reducing tumour size and cell counts.[32] *C. albolabris* venom toxins showed strong effect on Hep-G2 and BT474, while *C. Rhodostoma* worked well on SW620 and KATO-III.[33] Snake venom affects the growth of breast cancer cell lines, specifically T470 and MRDMB-468, even at low doses.[33] These also cause cell death, primarily through reactive oxygen species and apoptosis based on caspase 3 and 9-dependent activity. *Naja kaouthia* venom showed cytotoxic effects on leukaemia cells, U937 and K562 cells. It significantly inhibited cell proliferation in a dose and time-dependent manner. Salmosin, a disintegrin from Korean snake venom, could suppress tumour growth, and Contortrostatin from Southern Copperhead venom blocked tumour cell invasion. Similarly, crude Cobra snake venom significantly reduces RNA and DNA production in breast cancer tissue, suggesting it may serve as an alternative anti-tumour drug for treatment[34-35] (Table 1).

Antimicrobial effect

Most proteins and polypeptides in snake venom exist as single units, but some form complexes. These complexes have more potent effects and play a big role in envenomation. Many of these peptides act as antibiotics against drug-resistant bacteria. Toxins such as phospholipases A2 can harm bacterial cell surfaces, while other compounds, such as metalloproteinases and L-amino acid oxidases, also exhibit antimicrobial effects. Antimicrobial peptides offer different approaches for developing new drugs.[36] Venom toxins could serve as templates for the development of broad-spectrum, effective antibiotics and may be part of complementary and alternative medicine.[37] are created through various interactions. These target molecules are cell surface receptors on microbial cells. They form through covalent and/or non-covalent interactions, creating holes in microbial cells.[38] These could easily replace harmful antibiotic drugs(Table 1).

Diagnostic Uses Of Snake Venom

Snake venom toxins are also used as diagnostic tools to test blood coagulation factors and to study the overall haemostasis process. These proteins contribute to research tools, diagnostic methods, and drugs in life science and medicine. For example, when Poecilobdella manillensis attacks, it causes significant bleeding but little pain due to anticoagulant molecules in its saliva. Peptide poeciguamerin inhibits elastase activity and has potential as a pain-relief and antithrombotic treatment.[39] Snake venom also contains an elastase inhibitor with potent analgesic and antithrombotic properties.[40] C-type lectins, CTL-like proteins, and snake venom metalloproteinases are found in colubrid snake venom.[41] Australian elapid venom contains peptides phospholipase A2 and L-amino acid oxidase.[42]

Thrombin-like enzymes (SVTLE) from snake venom are used in assays for fibrinogen and its breakdown products. These are also used to detect dysfibrinogenemias without being affected by heparin. Various snake venoms are used to assay different clotting factors and to measure resistance. Snake venom contains novel toxins that exhibit curative activity against microbial diseases, arthritis, and cancer. For neutralisation of venom effects of the most poisonous snakes. Single-chain fragment variable scFv antibodies are used. These are also used in diagnostic assays to confirm their effectiveness against venom.[43]

Snake venom thrombin-like enzymes (SVTLE) help test fibrinogen levels and detect fibrinogen issues, and they work in samples containing heparin. Venoms also serve as prothrombin activators for prothrombin assays and for the study of blood clotting

disorders. Russell's viper venom is effective for assessing various blood-clotting factors and lupus anticoagulants.

Snake venom-induced immune responses

Snake venoms are mixtures of chemical compounds, including proteins, peptides, amines, salts, polypeptides, and enzymes, among others, that produce their toxic effects. Snakebite envenoming involves a mixture of proteins/toxins that display potent bioactivity, capable of affecting various aspects of envenomation. These initiated cascades of immune responses, driven by the immune cells, molecules, mediators and pathways, contribute both systemic and local inflammatory effects. The initial line of defence against envenomation is the innate immune response, as signals for the complex reaction are initiated by specialised cells. These act as immunostimulators, immunosuppressants, and include molecules involved in autoimmune disorders, anticancer, and anti-pathogenic activities. To understand the snake-induced immune response, deeper knowledge of venom components is needed to develop more effective novel immunotherapies.[44]

Snake antivenins

Snakebite envenomation has a significant impact on public health globally, predominantly affecting impoverished individuals engaged in agricultural work across Africa, Asia, Latin America, and Oceania. Snake envenomation is a severe health problem in rural areas, with millions of cases reported annually. Poisoning represents the most significant cause of preventable death globally. Most fatalities associated with poisoning are attributed to inadequate management, often due to a lack of facilities or insufficient resources. The delay in receiving treatment for snakebites, along with the unavailability of such treatment, can be fatal; moreover, it is expensive and may lead to serious side effects. The effects of snake venom include severe swelling and haemorrhaging that can extend from the affected limb to the trunk, potentially leading to long-term disabilities. Administering antivenom within 1 hour can halt the venom's systemic effects and mitigate adverse reactions. Both antivenom treatment and hospital care are essential for ensuring patient safety (Table 2).

Snake venom contains numerous biologically active toxic substances, the majority of which are enzymes. Among the various types of snakes, desert and sea snakes are the most venomous. Vipers. To neutralise the toxic effects of snake venom, antivenom is administered to ensure the patient's safety. Use of antivenom is an effective treatment for snakebite envenoming. This is safe, effective, affordable, accessible, and administered appropriately.

Although several phyto-antidotes have been developed for snake poisoning.[45] These antidotes are utilised in the management of poisoning, primarily to neutralize the toxic effects of venoms.[45] Another approach is the para-specific neutralization targeting species-specific toxins.[46] These phytoantidotes can help address the scarcity of antivenoms in many regions worldwide, especially in Sub-Saharan Africa and certain areas of Asia.

Vipers and cobras strike rapidly, and without appropriate treatment within one hour, they can result in death. Antivenoms are developed against eight species of vipers: European *Vipera* spp. *V. berus* or *V. ammodytes*; *V. ammodytes*, *V. aspis*, and *V. berus*, *Macrovipera lebetina*, and *Montivipera xanthina*. venom. These are Zagreb, ViperFAV, and ViperaTAb, which are administered intravenously, not intramuscularly.[47]

Currently, polyclonal antivenom antibodies are used to treat snakebites. These are sourced from animals, such as horses, and are utilised; however, they may occasionally induce anaphylactic shock and serum sickness. For therapeutic applications, single-chain fragment variable (scFv) antibodies are generated against venom from highly poisonous snake species. Besides this, phage display antibody technology is employed to neutralize the neurotoxic venom proteins of the banded krait (*Bungarus multicinctus*).[48] Both IgY and scFv antibodies are used as alternative treatments for snakebite envenomation. Purified yolk IgY antibodies showed specific anti-NNA binding activity is an effective antivenin.[49] In addition, a combination of scFv antibodies was found to be highly effective in snake bites.[50] The enzyme inhibitor prinomastat efficiently neutralized the metalloprotease-driven Factor X activation of the procoagulant venoms.

Anti-snake venom (ASV) can mitigate the toxicities induced by Zinc (Zn++) dependent snake venom metalloproteases (SVMPs). The promising protective efficacy of TTD may be applied to treat severe tissue necrosis.[51] It requires antivenom therapy to neutralise the toxic effects of snake venom.[52] Antivenom therapy is essential for counteracting the toxic effects of snake venom due its due to its effectiveness. Still, anti-venoms against several known species are still lacking against many snake species. This is the main reason of casualties occurring more in rural areas and forests.[52] Hence, a mixed approach is to be followed to save the patient and reduce the fatalities.[52]

Species-specific antivenom found to be effective in managing carpet viper envenomation. These led to rapid restoration of blood coagulability and the resolution of spontaneous

haemorrhage.[52] Monoclonal antibodies against snake venoms (*Vipera lebetina*, *Vipera russellii*, *Vipera berus berus*, *Vipera ursini*, *Echis carinatus*, *Agkistrodon halys*, *Bungarus caeruleus*, *Naja naja* oxiana, *Naja naja*, *Naja naja* atra) nerve growth factor have been developed. These have shown much better results.[53] Antivenoms have been developed against East: *Montivipera bornmuelleri*, *Macrovipera lebetina*, *Vipera (Daboia) palaestinae*.[54]

Vipera aspis aspis, *Vipera berus berus* and *Vipera ammodytes*, *Montivipera xanthina* and *Macrovipera lebetina* obtuse.[55] Venoms of Vipera lebetina (*Macrovipera lebetina*) subspecies *Macrovipera lebetina cernovi*, *Macrovipera lebetin*a *lebetina*, *Macrovipera lebetina obtusa*, *Macrovipera lebet*ina transmediterranea, *Macrovipera lebetina turanica*, the snake species causing the majority of human envenomings in Central Asia (Middle East) and North Africa.[56] Venoms of Vipera lebetina (*Macrovipera lebetina*) subspecies *Macrovipera lebetina cernovi*. Envenomation by the carpet viper (Echis ocellatus) leads to haemorrhage and coagulopathies. The immunization with a suitable vaccine may provide paraspecific protection within each genus of vipers.

Inoserp neutralised additional species compared to VIPERFAV, indicating its more complex antivenom immunisation formulation. Conversely, ViperaTAb was highly effective in neutralizing V. berus, yet, as a monovalent antivenom, it did not work against other Vipera species. The enzyme inhibitor prinomastat effectively neutralized the metalloprotease-driven activation of Factor X by procoagulant venoms. To assess efficacy, serum kinetics of venom antigen/antivenom levels should also be confirmed. Antivenomics analysis is employed to verify the suitability of antivenom effectiveness. Furthermore, quality assurance, standardisation, and efficacy depend on the antigen used; however, characterisation of toxin is highly essential.

Use of snake venoms in drug development

Drugs derived from snake venom possess significant curative capabilities. As suggested by[56], numerous new pharmaceuticals could be developed from snake venom. The unique biodiversity of snake venoms and toxins provides a valuable source of leads and structural templates for the creation of innovative therapeutic agents. Each minidrug library, constructed from the natural toxin templates present in snake venoms, contains pharmacologically active molecules. The structure of snake venom toxins may act as a framework for designing therapeutic tools that can modulate the immune system and address

various autoimmune diseases. Additionally, several distinct primary components of snake venoms can be used to identify new, highly effective therapeutic compounds. Medications such as Aggrastat (Tirofiban), Integrilin (Eptifibatide), and Captopril (Enalapril) are derived from snake venom and have been approved by the FDA. Furthermore, snake venom molecules can be commercially harnessed to develop antibiotic drugs resistant to microbial strains, particularly as antibiotic prototypes[57] (Table 2).

Snake venoms and their constituents can be converted into innovative immunotherapies.[58] These can facilitate the development of immunomodulatory pharmaceuticals. To achieve this, the molecular architecture, chemical reactivity, and target recognition of the most bioactive toxins are analyzed, from which bioactive drugs may be formulated. Many of these components also serve as intriguing models for drug design. It is feasible to develop potent new immunotherapies from snake venoms and their components (C Minutti-Zanella et al, 2020).[58] Snake venom-derived medications hold significant therapeutic potential. They may serve as valuable tools for elucidating cellular and molecular mechanisms. To formulate bioactive medications, the molecular structures, chemical reactivities, and target recognition properties of the most bioactive toxins are assessed. Many of these elements also serve as captivating models for drug design.[57] Snake venom molecules can be commercially harnessed to develop antibiotics resistant to microbial strains, primarily as prototypes (Table 2).

CONCLUSION

Snake venoms and toxins have been recognized for their potential as both a bioresource and therapeutic tool for centuries. Snake venoms contain various active proteins and peptides that serve specific functions. Venoms from several snake species, along with their active components (including protein and non-protein toxins, peptides, and enzymes), have shown toxic effects. Venom components can impact various body systems, including the nervous and immune systems. These show therapeutic potential for cancer, pain, and inflammation. Some venom enzymes are used as anticoagulants. Non-enzymatic toxins exhibit therapeutic properties, such as anticancer, antitumor, antimicrobial, and analgesic effects. They can also damage cholinergic neurons by hindering acetylcholinesterase. Snake venom components are being explored for their therapeutic applications, particularly in cancer treatment. Venom components can inspire drug design and lead to the development of new immunotherapies. Their immunomodulatory properties help in the development of effective

drugs. Snake venom toxins serve as templates for the development of active mini-drug libraries. These are natural sources of new drugs of multiple therapeutic uses.

Table 2: Snake venom toxin peptides, anti-venoms, therapeutic and biotechnological use.

Snake species	Toxin type	Biological effects	References
Snake venom toxins/ proteins	Hemotoxic, cytotoxic, cardiotoxic	haemorrhagic activity; platelet aggregation inducers: and platelet aggregation inhibitors	(F S Markland Jr 1997).
Viperid venoms	bleed (haemorrhage), mostly due to hypocoagulability, neuro/cardio toxicity, and myonecrosis	musculoskeletal disabilities	(Dabor Resiere Hossein Mehdaoui , Remi Neviere 2022
Crotalid and Viperid venoms	Zn^{2+}-metalloproteinases, serine proteinases, L-amino acid oxidase, hyaluronidase, phospholipase A2, C-type lectin-like protein, disintegrin	Local and systemic haemorrhage, tissue damage, and inflammation	Jüri Siigu et al, 2019).
viperid venoms	Fibrinolytic metalloproteinases	provoke haemorrhage and affect hemostasis and thrombosis	F S Torres et al, 2012
Sanke venom	C-type lectin-like family, or the metalloproteinase-disintegrins	activate platelets by binding to specific receptors such as GPIb, alpha2beta1 and GPVI	Lakshmi C Wijeyewickrema et al, 2005).
Snake venom toxins/ proteins	Phospholipases A2	Affect the musculoskeletal and immune system of the body, heart, among other structures	Zharick Avalo 2022.
	metalloproteinases and L-amino acid oxidases	antibiotics and complementary and alternative medicine (CAM)	(Deivy Clementino de Lima et al, 2005).
Snake venom toxins/ proteins	Metalloproteinases	Induce hemorrhages	(Aura S Kamiguti 2005).
viper envenomation		thromboinflammation inflammation and hemostatic alterations	Catarina Teixeira et al, 2019
Snake venoms	Protein complexes	Cytotoxicity, haemotoxic	(R Doley [1], R M Kini 2009).
Daboia siamensis and Macrovipera	Cytotoxicity	inhibits cell growth of human prostate cancer	Abhinandan Chowdhury et al,

lebetina		cells by inducing apoptosis.	2022
V. lebetina turanica	ribonuclease H1-like enzyme	bradykinin-potentiating effect and block kininase II (angiotensin I converting enzyme, ACE).	(Yukelson LYa et al, 1992).
Snake venom	Non-enzymatic proteins	Inhibition of ion channel function, vasoconstriction, complement system activity, platelet aggregation, blood coagulation,	Ryan J R McCleary , R Manjunatha Kini 2013
Russell's viper (*Daboia russelli*) venom (RVV)	Metallo- and serine proteinases	Prothrombin activators	Neville Marsh , Vaughan Williams 2005
Sanke venom	thrombin-like enzymes, disintegrins, a family of Arg-Gly-Asp (RGD)-containing proteins	Bind to platelet glycoprotein receptors GPIIb/IIIa and Ib	(Marsh 1998)
fibrinogenolytic metalloproteinase (Bmoo FIBMP-I)	fibrinogenolytic metalloproteinase (Bmoo FIBMP-I)	fibrinogenolysis	(F S Torres et al, 2012).
Bothrops genus	inflammation and blood coagulation		Catarina Teixeira et al, 2019
Sanke venom	metalloproteinase-disintegrins	mediate platelet adhesion, activation and aggregation (thrombus formation)	Lakshmi C Wijeyewickrema et al, 2005
Malayan pit viper, *Calloselasma rhodostoma*	thrombin-like enzymes	haemostatic disorders	Neville Marsh [1], Vaughan Williams 2015
Atractaspis spp	Sarafotoxins peptide toxins	cardiovascular diseases	(Roy Joseph et al, 2004).
E. multisquamatus	kininase II (angiotensin I converting enzyme, ACE)		Yukelson LYa . 1992
Vipera lebetina venom	Neurotoxin		J Siigur et al, 1987. Neville Marsh [1], Vaughan Williams 2015
sea snake venom (*Lapemis curtus*)	antitumor activity	Inhibit Ehrlich's ascites carcinoma (EAC) in Swiss albino mice and HeLa and Hep2 tumor cell cultures	Karthikeyan *et al*
Bothrops jararacussu venom	Bjcul, a lectin	Cytotoxic effect on gastric carcinoma cells MKN45 and AGS.	Nolte *et al*

Snake venoms	Non-enzymatic proteins Sarafotoxins waprins; (xii) vespryns; and (xiii) veficolins.	Lethal effects	Ryan J R McCleary [1], R Manjunatha Kini.
Viperidae venoms	**elastase**-like activities	The inhibition of pain and thrombosis	(Chaoming Wang et al, 2023).

(i) three-finger toxins; (ii) proteinase inhibitors; (iii) snaclecs (C-type lectins and related proteins); (iv) nerve growth factors; (v) bradykinin-potentiating peptides; (vi) natriuretic peptides; (vii) cysteine-rich secretory proteins (CRISPs) or helveprins; (viii) sarafotoxins; (ix) cobra venom factors; (x) vascular endothelial growth factors; (xi) waprins; (xii) vespryns; and (xiii) veficolins.

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