

The Toxic Components and the Clinical Uses of Snake Venom: A Review

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Abstract

Background: The venom of different snake species has a distinctive composition. This composition can be also affected by other factors such as age, sex, geographical, and seasonal variations. Generally, snake venom is composed of small molecules such as inorganic cations as well as enzymatic and non-enzymatic peptides, and proteins. Although snake bite poisoning is highly associated with death after systemic absorption of the venom, some studies report on snake venom's composition, toxicodynamic, and potential therapeutic value.

Methods: Using electronic databases like ISI Web of Knowledge, PubMed, and Scopus, this review aims to point to some components of snake venom and how these components can be used for therapeutic and diagnostic purposes.

Results: Snake venom was used for the treatment of different pathophysiological conditions in ancient times and is now being used in both modern and folk medicine. These have created the opportunity for scientists to discover new drugs that are more targeted to the site of action and have fewer adverse effects.

Conclusion: Today, using special techniques of isolation and formulation, some purified snake venom components are being used for the treatment of acute and chronic conditions, while some others are under further clinical trials. This is due to their potential to produce antitumor, antimicrobial, analgesic, antiplatelet, hypotensive, and other activities.

Keywords: Snake venom, Platelet Aggregation Inhibitors, Analgesic, Tumors

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INTRODUCTION

Venom is a toxic substance produced by animals as a defense mechanism. Till now, a large number of venomous snake species have been identified [1]. Venomous snakes usually have one or more pairs of fangs in their upper jaw that pass the victim's tissue allowing the penetration of venom produced in the snake's venom gland [2].

Venomous snakebite is considered as a public health problem. However, epidemiological data reporting the occurrence of snakebites shows a global disparity due to the heterogeneity of ecological and economic conditions throughout the world. For instance, it was seen that agricultural activities especially in tropical and subtropical countries were highly associated with snakebite emergencies around the world. Snake venom is a unique composite mixture of enzymatic and non-enzymatic peptides and proteins as well as other small molecules whose absorption through the systemic circulation [3] can result in variable and progressive multisystem manifestations including local, inflammatory, necrotic, hematological, cytotoxic, neurotoxic, myotoxic, and cardiotoxic effects that may sometimes require intensive care [2].

Delayed first aid or access to appropriate medical facilities

and antivenom therapy may cause a high rate of morbidity and mortality [4]. Among the 3150 snake species, the amount of each component in the venom is variable. Studying this variation has an obvious importance allowing the selection of the most appropriate antivenom for the treatment of snakebite toxicity. This difference in composition is also seen within the same species and is found to be affected by age, sex, diet, geographic location, and seasonal variation [5].

Surprisingly, snake venom has been widely used for the treatment of some pathophysiological conditions in ancient times. This helped clinicians understand that snake venom does not necessarily cause harm and death to human being, but it also has therapeutic benefits that may open the path for drug developments with specific harmless systems that deliver the toxin directly to the site of action. Nowadays, snake venom components are used for their antimicrobial, antitumor, analgesic, anticoagulating, and many other activities [2].

Generally, different snake venoms are composed of varying ratios of hyaluronidase, cholinesterase, 5'-nucleotidases, L-amino acid oxidase (LAAO), phospholipase A2, serine protease, metalloproteases, disintegrins (DIS), cysteine-rich secretory proteins (CRISP), C-type lectins as well as some inorganic cations.

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This review investigates the toxicodynamic of different components of snake venom and how these toxic agents can be used as a therapy for many pathophysiological conditions.

METHODS

Electronic databases including ISI Web of Knowledge, PubMed, and Scopus in English language were searched from 2000 to 2021. The search strategy included a combination of the following Medical Subjects Headings (MeSH) terms: Toxic Components, Snake venom, clinical uses, antitumor, antimicrobial, analgesic, hypotensive, and antiplatelet.

A total of 103 articles were found via the electronic search. Finally, 47 articles fulfilled the eligibility criteria and were included in this review (Figure 1).

RESULTS

1. Toxicodynamic and Toxic Effect of Snake Venom

Neurotoxicity, one of the most important effects of snake venom, can occur as a result of presynaptic or postsynaptic inhibition. Neurotoxins producing antagonistic action at the

nicotinic acetylcholine receptors at the postsynaptic membrane result in paralysis of the smooth muscles of respiration. Additionally, neurotransmitter inhibition can occur by binding the neurotoxin to the presynaptic nerve membrane receptors that is followed by a phospholipase activity resulting in a phase of increased neurotransmitter release whose action is then blocked due to the increased release [6]. Cardiotoxicity can also occur in some cases of snake bite resulting in variable ECG changes including T wave abnormalities, ST segment depression, prolongation of QRS interval, and defects in AV conduction [7]. These effects finally lead to hypotension, cardiac arrest, circulatory shock, and internal hemorrhage that may increase the risk of mortality [6].

Moreover, vasculotoxins, also called hemorrhagins can result in spontaneous local as well as systemic bleeding (Table 1) especially in the vital organs such as brain, kidney, etc. [8]. One of the causes of bleeding is the damaging effect of hemorrhagins on the capillary endothelium [6]. There are also components that affect the blood coagulation and platelet function by their enzymatic or non-enzymatic effects on

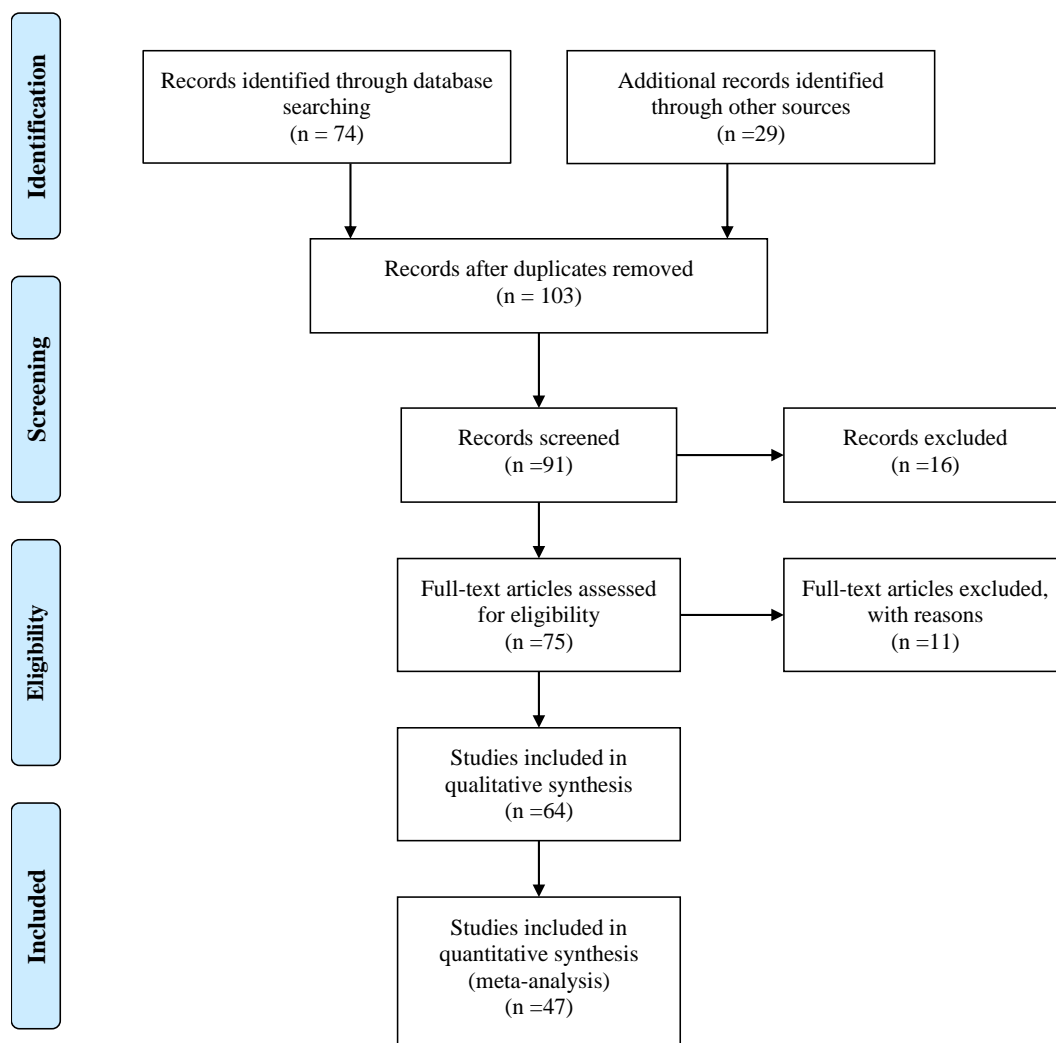


Figure 1. Schematic Representation of Selected Articles for the Accomplishment of This Review

platelet aggregation, release reactions, and clot retraction resulting in hematological abnormalities [6].

2. Major Components of Snake Venom and Their Effects

3. Potential Clinical Application of Isolated Snake Venom Components

As shown in Figure 2, isolated snake venom components can have different therapeutic uses that are discussed below.

Table 1. Main components of snake venom with their toxic effects and suggested mechanism of toxicity

	Components	Mechanism of toxicity	Pathophysiological effect
Inorganic cations	Zinc	Enhance anti-cholinesterase activity [3]	
	Calcium	Activates Phospholipase A2 [3]	
Enzymatic components	Phospholipase A2	Bind to target protein only (due to reciprocity in hydrophilicity, charge and van der Waal's forces) → Calcium dependent hydrolysis of membrane phospholipids and glycerophospholipids producing fatty acid + lysophospholipids [2,3,9]	<ul style="list-style-type: none"> • Neurotoxicity -Presynaptic (block the release of Acetylcholine from axon terminus) -Postsynaptic • Myotoxicity • Cardiotoxicity • Hemolysis: Anticoagulant and antiplatelet activity • Hypotension • Edema
	Hyaluronidase	Decrease connective tissue's viscosity by hydrolyzing hyaluronan into oligosaccharides + N-acetylglucosamine [3,4]	<ul style="list-style-type: none"> • Facilitate the spread of the venom in victim's tissue [4]
	Proteolytic enzymes (Serine protease and metalloproteases)	<ul style="list-style-type: none"> • Breakdown structural proteins/peptides [3] • Activate prothrombin, clotting factors and protein C [2] • Thrombin like activities • Release bradykinin [1] 	<ul style="list-style-type: none"> • Hypotension • Bleeding [1,10]
	Cholinesterase	Hydrolyze Acetylcholine producing choline + acetate at the neuromuscular junction [3]	<ul style="list-style-type: none"> • Myotoxicity
	L-Amino acid oxidase (LAAO)	Oxidative deamidation of L- amino acids and hydroxy acids [3,11]	<ul style="list-style-type: none"> • Platelet dysfunction (by blocking the ADP-dependent platelet aggregation) • Hemorrhage • Edema • Induce apoptosis • Cytotoxicity [11]
	5'-nucleotidases	Hydrolysis of phosphate at position 5' of the sugar of DNA or RNA [12]	<ul style="list-style-type: none"> • Platelet dysfunction
Non-enzymatic components	Disintegrins (DIS)	Block platelet fibrinogen receptor Inhibit integrin αIIbβ3 [13]	<ul style="list-style-type: none"> • Platelet dysfunction • Antiangiogenic activity
	Cysteine-rich secretory proteins (CRISP)	Block CNG and Calcium channels [14]	<ul style="list-style-type: none"> • Cytotoxicity
	C-type lectins	Bind to GPIIb, GPVI or integrin α2b1 [15]	<ul style="list-style-type: none"> • Platelet dysfunction

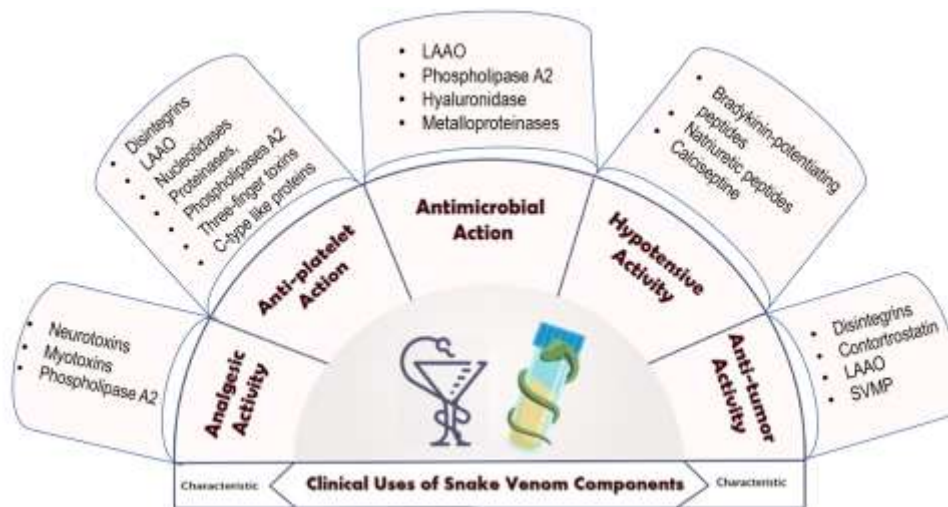


Figure 2. Major Clinical Uses of Isolated Snake Venom Components

3.1 Antitumor Activity

Despite the efforts on development of anticancer medications, cancer is considered one of the deadliest diseases around the world. Numerous cancer treatment strategies have been developed including surgery, chemotherapy, and radiotherapy. However, the recurrence risk and the side effects of these methods encouraged the development of other anticancer treatment strategies such as the use of natural sources including plants or animals [2,16]. Therefore, modern medicine scientists started isolating and characterizing the components of snake venom for targeted cancer therapy. It was shown that isolated snake venom components have two major mechanisms for their antitumor activity including the inhibition of angiogenesis or the induction of apoptosis. Angiogenesis is a process enhancing tumor metastasis. Integrins are one of the factors that result in cancer and its progression [17]. Many disintegrins isolated from the venom of variable snake species were shown to have an anti-angiogenic activity [18]. For instance, Salmosin; a disintegrin isolated from *Agkistrodon halys brevicaudus* blocks $\alpha\beta_3$ integrin preventing tumor growth in lung cancer patients. Also, contortrostatin isolated from *Agkistrodon contortrix* was shown to have an effect in treating breast cancer [19]. Defects in apoptosis also known as cellular suicide, may induce an unrestrained cell growth that results in cancer. Therefore, the induction of apoptosis is a mechanism that treats cancer by killing tumors. Among the components in snake venom, apoptosis induction was observed with some of the isolated LAAO, disintegrins, and snake venom metalloproteinases (SVMP) [19,20].

3.2 Antimicrobial Activity

The resistance of pathogens to the available medications has been an important issue in recent years. Therefore, studies for developing more efficient antimicrobial agents are needed. Snake venom components have also shown inhibitory effects on pathogenic microorganisms such as bacteria, fungi, virus, parasite, etc. that can sometimes be deadly [21,22]. It was seen that LAAO, phospholipase A2, hyaluronidase, and metalloproteinases can destabilize bacterial cell surface of both gram-negative and gram-positive bacteria due to their ability to hydrolyze phospholipids. However, the efficacy of these isolated components varies among the different classes of bacteria [23]. The antiviral activity of snake venom is suggested to be due to the non-cytotoxic, crotoxin, and phospholipase A2 components. Their effects were seen against measles, yellow fever, and dengue viruses [24]. Also, phospholipases A2 exerts anti-HIV activity by inhibiting the viral entry into the host cell before virion uncoating [25]. This component also inhibits entry and replication of hepatitis C virus depending on the stage of viral life cycle [26]. Cytotoxic effect of snake toxins may also result in anti-yeast and candidal effect. The suggested mechanism of antifungal activity is modulating cell viability, formation of biofilm, and redox homeostasis [27].

3.3 Analgesic and Antinociceptive Activity

Pain control with the most effective and appropriate agents has been a challenge in health care systems [28]. Isolated

snake's neurotoxin, phospholipase A2 and myotoxin can be used as therapeutic agents for the treatment of pain due to their analgesic activity with a series of unique mechanism of action [2]. These peptides produce potent painkilling effect by rapidly and reversibly blocking the subtypes of neuronal acid sensing ion channels (ASICs) that are expressed in CNS [29] and normally get activated by protons resulting in pain sensation. The inhibition of these channels produces an analgesic effect in both acute and chronic inflammatory pain [30]. Other mechanisms were also suggested such as increasing the plasma concentration of IL-1ra that is an endogenous IL-1 receptor antagonist or the involvement of central muscarinic acetylcholine receptors whose activity is mediated by serotonin receptors and alpha-adrenoceptors [31].

3.4 Hypotensive Activity

Persistent rise in blood pressure is a sign of hypertension that when complicated, may result in multi-organ damage [32]. To date, many antihypertensive medications with different mechanisms of action have been developed. But there is always a need for safer and more targeted medications. One of the clinical manifestations in case of snake venom toxicity is hypotension. The isolation of the direct hypotensive agents can help us develop a new class of antihypertensive medications [2,33]. One of these agents is bradykinin-potentiating peptides that decrease blood pressure by enhancing the action of the endogenous bradykinin causing vasodilation and the inhibition of angiotensin converting enzyme (ACE) [34,35]. The first success story of developing drug from snake venom was producing Captopril from the Brazilian pit viper *Bothrops jararaca*. Snake venom also contains natriuretic peptides that decrease blood pressure by inducing diuresis, natriuresis, vasodilation, and inhibiting renin and aldosterone [34,36]. Additionally, due to the presence of L-type calcium channel blockers such as calciseptine, snake venom is shown to block calcium channels thus preventing muscle contraction and eventually causing vasodilation and decrease in blood pressure [34,37].

3.5 Antiplatelet Activity

After atherosclerotic plaque formation, there is a possibility of rupture of the formed plaques resulting in platelet aggregation, thrombosis, and increase the risk of acute coronary syndromes (ACS) [38]. The final major pathway in platelet aggregation happens due to the activation of α IIB β 3 integrin; also known as fibrinogen receptor or glycoprotein IIb/IIIa receptors. Thus, antiplatelet medications targeting this receptor can be indicated in case of ACS and in percutaneous coronary procedures [39,40]. Snake venom contains disintegrins that have RGD motif that helps them bind to integrin and prevent the binding of fibrinogen to this receptor, eventually inhibit platelet aggregation as well as integrin receptor-dependent cell adhesion [41,42]. Some other components in snake venom such as LAAO, nucleotidases, proteinases, phospholipases A2, three-finger toxins, and C-type lectin-like proteins also produce anti platelet activity and can be used to prevent platelet aggregation while preventing the risk of unwanted bleeding [39,43].

DISCUSSION

The composition of different species of snake venom has been frequently studied by scientists. These studies have contributed to an advanced field of drug discovery and disease treatment. It was seen that isolated components of snake venom can have different therapeutic uses [44]. In today's pharmaceutical market, some of the approved products contain snake venom components that can be readily synthesized via different technologies [45]. For instance, the first agent approved was captopril, an ACE inhibitor that enhances the action of endogenous bradykinin, that is used as a blood pressure reducing agent in hypertension or cardiac failure. This agent is derived from the venom of the snake *Bothrops jararaca* [2]. After those two other agents; Tirofiban and Eptifibatide derived from snake venom disintegrins of *Echis carinatus* and *Sistrurus miliaris barbouri*, respectively were approved as antiplatelet medications. The development of these agents was associated with a reduced risk of thrombotic cardiovascular events such as acute coronary syndromes (ACS) due to their inhibitory activity on platelet glycoprotein (GP) IIb/IIIa [24]. In addition to the therapeutic value of these toxic components, they also can be used in diagnostic procedures. For example, the diagnosis of protein C (PC) deficiency in human beings is facilitated by measuring the serum level of protein C and S using a serine proteinase named Protac[®]. This agent is isolated from *Akistrodon contortix* venom and works by activating plasma protein C and S [24]. Despite the efforts on the isolation and formulation of snake venom components such as peptides, very few of them have been approved for evaluation in clinical trials and even fewer got the approval to be marketed. This may be due to the low bioavailability, low stability, and special storage conditions of the synthesized peptides. Therefore, further studies are required to find the most appropriate formulation to deliver these agents to the target site of action, prevent the occurrence of side effects, maintain the stability of the peptide, and prevent peptide degradation [46]. In recent years, scientists developed different technologies and techniques for the development and formulation of detoxified snake venom peptides. This includes conjugating the toxin with polymers, such as liposomes, microspheres, hydrogels, or nanoparticles [2,47].

CONCLUSION

It may be concluded that only a small fraction of snake venom components has been identified, isolated, and formulated for their diagnostic or therapeutic uses. Because the isolation of toxins from crude venom is very expensive and involves all kinds of regulatory authorities. However, improvements in techniques for the development of such products continues and this may pave the way for new achievements in research and drug discovery.

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