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SNAKE VENOM: A BLESSED THERAPEUTIC TOOL IN SAVING LIFE

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ABSTRACT
Snake bite envenomation was previously considered to be a curse in life of human beings that causes painful and traumatic death. All over the world, snake venoms were considered to be a toxin that can be the only factor to cause a high rate of mortality. But along with time, gradually through many researches and lab-oriented studies, snake venoms have been found to open a new horizon in drug discovery field producing innumerable life saving drugs for cardiac diseases, nervous diseases, antimicrobial infections and diseases as well as cancer. Moreover, there have been lot of antivenoms prepared from venomous snake species that act as life saving injection after a snake bite. This review basically brings out the therapeutic uses of snake venoms in the field of research and medicine.

KEYWORDS: Snake bite envenomation, Toxin, Mortality, New horizon, Drug discovery, Cardiac diseases, Nervous diseases, Antimicrobial infections, Cancer, Antivenom.

INTRODUCTION
Snake venom, synthesized and stored in venomous gland of snakes are basically the modified parotid-salivary gland secretion containing zootoxins. These zootoxins get injected through tubular fangs of snakes, during bite as a mode of its self defense. Snake venom containing more than 20 different compounds, is mainly a combination of several proteins (90% protein by dry weight), polypeptides, enzymes (25 different enzymes found in various venoms and 10 of them occurring most commonly in venoms) show synergistic effects along with other various substances having toxic as well as lethal properties. A toxicological test that assess toxicity of snake venom is called median lethal dose (LD_{50}) that helps in determining the toxin concentration required to kill half the members of tested population of animals.[1-3]

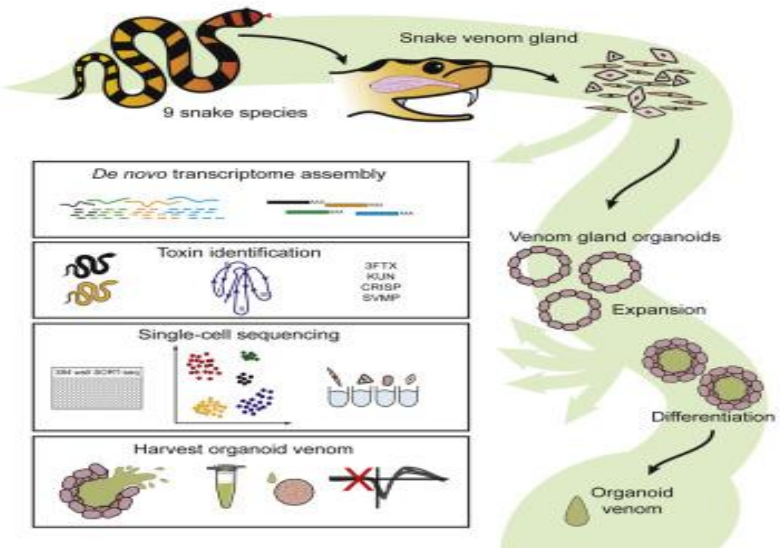


Figure-1: Snake venom organoid.

Snake venoms are complex mixtures of enzymes and proteins of various sizes, amines, lipids, nucleosides, and carbohydrates. Venoms also contain various metal ions that are presumed to act as cofactors and include sodium, calcium, potassium, magnesium, and zinc. Snake venoms are complex mixtures of enzymes and proteins of various sizes, amines, lipids, nucleosides, and carbohydrates. Venoms also contain various metal ions that are presumed to act as cofactors and include sodium, calcium, potassium, magnesium, and zinc. Snake venoms have been studied much more thoroughly in members of the families Elapidae, Hydrophiidae, and Viperidae, with considerably less knowledge regarding venoms from Atractaspididae and Colubridae. There is a large degree of variability in venom composition at all taxonomic levels. In addition, within the same species, venom components have been shown to vary considerably among populations and across geographical areas. Venoms act on a variety of cells and tissues with pronounced physiological responses. Some of the actions of venom components include the digestion of cells and cell membranes, disruption of procoagulant and anticoagulant activities of blood, production of oxidizing agents, breakdown of collagen and the intercellular matrix between cells, and the disruption of nerve tissue. Snake toxins with defined actions include neurotoxins, hemotoxins, cardiotoxins, cytotoxins, and myotoxins. Snake venom components can be grouped by their molecular weight. Low-molecular weight components (<1500 Da) are usually considered the least physiologically active and includes peptides, lipids, nucleosides, carbohydrates, amines, and metal ions. Larger venom components (mol. wt. 4500–10000 Da) include polypeptide toxins such as post-synaptically acting neurotoxins and myotoxins. The largest components, the enzymes (mol. wt. 13000–150000 Da), comprise a diverse group and produce marked physiological effects. The percentage of enzymes in snake venom can vary widely and can constitute as much as 90% or more in some of the viperid venoms and as little as 25% in some elapid venoms. There are over 30 enzymes that have been identified in snake venoms including some that are common to all venomous snake families. Snake venom is a heterogeneous and complex mixture of proteins, amino acids, lipids, carbohydrates, metal ions, and other compounds. Venom composition varies tremendously between different species, between different individual snakes of the same species, and even in the same snake depending on its age and time of the year. Though there are exceptions, the venom of the Elapidae family is primarily neurotoxic with some myotoxic effects. Conversely, the venom of the Viperidae family is generally hemotoxic and myotoxic with some (usually) minor neurotoxic effects. The study of venom and its composition falls under the field of toxicology and is an area of increasing interest. Multiple pharmaceutical agents have been developed from snake venom. Examples include tirofiban, which was derived from the saw-scaled viper (*Echis carinatus*) and angiotensin converting enzyme inhibitors from the Brazilian viper (*Bothrops jararaca*). Many more potential venom-derived agents are currently being investigated to treat various conditions ranging from chronic pain to multiple sclerosis. As the composition of snake venom varies between species, so too does its potency. Australian elapids and sea snakes are consistently reported to have among the most potent venom in the world. Venom is thought to have several functions including defense, prey neutralization, and pre-digestion. It is delivered into the prey or attackers from the venom gland via ducts through specialized teeth or fangs. Some snakes species, such as the vipers, have large hollow front fangs which are very effective in delivering large amounts of venom while others possess poorly developed relatively ineffective grooved rear fangs. Not all venomous snakebites result in envenomation. Twenty-five percent or more of snakebites are suspected to be 'dry' bites.[4]

Types of Venoms and their effects on human body: Depending on the nature of classification of venom, venomous (poisonous) snakes belong to three main categories:

1. **ELAPIDAE:** They mainly secrete neurotoxic venoms that affects the nervous system, along with high amount of cytotoxin that can cause cellular necrosis in human. Systemic absorption of Elapidae venom is dependent on lymphatic transport following subcutaneous envenomation. The onset of neurotoxic symptoms usually occurs within 4 h but

can be delayed up to 10 h following a bite. The metabolism of venom components is not well understood. It is likely that venom components are inactivated by enzymes within tissues where the venom is ultimately distributed. The distribution of venom is variable and complex and possibly reaches different tissue sites unevenly. The biological half-life of Elapidae venom has not been determined. It is likely that metabolized venom fractions are eliminated primarily by the kidneys.[5]

2.Their bite is accompanied with certain local features like

(i) Fang marks

(ii) King cobra *(Naja bangarus)*

(iii) Krait [Common krait *(Bangarus caeruleus)*]

(ii) Burning and pain
(iii) Swelling and discoloration
(iv) Serosanguinous discharge

The systemic features of Elapidae bite exhibit two stages

1. Pre-paralytic Stage (Vomiting, headache, giddiness, weakness, lethargy)
2. Paralytic Stage (Convulsion, ptosis, drowsiness, opthalmoplegia, death)

Examples of Elapidae

(i) Common cobra *(Naja naja)*

2.VIPERIDAE: They secrete vasculotoxic/hemotoxic venom that effects the cardiovascular and circulatory system along with certain amount of cytotoxin that initiates cellular necrosis in human being. More than 90% of the snake venoms produced by mambas, cobras and tiger snakes (which all belong to the family Elapidae), contain small protein molecules that are responsible for a wide range of toxicological and pharmacological activities. The complex mixtures of polypeptides that are present in most snake venoms can be generally divided into neurotoxins and cardiotoxins (6000–10 000 amu), together with phospholipases A2 (c. 13,000 amu) and larger enzymes. Often, the toxic effects of these peptides result from a synergistic effect of the polypeptides rather than from a high intrinsic toxicity of individual compounds, and they have attracted interest

for their potential therapeutic applications.[6] The analysis of snake venoms has traditionally relied on chromatographic separations using gel filtration and ion exchange phases, with protein size determined using methods such as sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). Subsequent sequencing of the amino acids in the isolated proteins can be carried out by automated Edman degradation with a gas phase micro-sequencer. Using these techniques, the isolation of 28 peptides from the venom of the black mamba snake has been reported, most of which are structurally related cationic peptides, called dendrodotoxins, with similar activities. However, the application of capillary electrophoresis–electrospray ionization–mass spectrometry (CE-ESI-MS) has been shown to be a particularly effective technique for the separation and analysis of such complex mixtures of small proteins as are found in these venoms. A problem that is often encountered when separating basic peptides is the retention of a net positive charge that leads to peak broadening due to the sorption of analytes to the negatively charged column wall. Several column wall derivatizing reagents have been reported to minimize this problem and it has been shown by Tomer and co-workers that when CE is carried out using a fused silica column derivatized with 3-aminopropyltrimethoxysilane (APS), the charge on the capillary wall becomes positive. Excess negative ions in solution drive the electroosmotic flow from a high negative potential to ground, and positively charged analyte ions are repelled by the column wall. ESI-MS is particularly useful for the analysis of large protein analytes, as these become multiply charged. The m/z ratio (determined by the mass spectrometer) is consequently reduced, which permits the determination of higher charged large molecules using spectrometers with significantly lower mass ranges. For example, the CE-ESI-MS analysis of the black mamba snake venom showed two dominant ions in the spectrum at m/z 1020 and 1090 which were related to the [M+7H]7+ and [M+6H]6+ ions of toxin 1 (7133.5 amu), previously shown to be the predominant dendrodotoxin.[7]

Their bite develops local features like:
(i) Bleeding from biting site
(ii) Discoloration
(iii) Blister formation with intense pain
(iv) Rapid swelling of biting site

Systemic features of viperidae bite shows:
(i) General bleeding (Hemoptysis, hematuria, bleeding gums, haemorrhage on skin)
(ii) Shock syndrome
(iii) Renal failure

Examples of Viperidae:
(A) Pitless vipers:
(i) Russell's viper (*Daboia russelli*)

(ii) Saw-scaled viper (*Echis carinatus*).

(B) Pit vipers.

(i) Common Green Pit viper (*Trimeresurus gramineus*)

3. HYDROPHIDAE: They secrete myotoxic venoms causing muscular necrosis in human. Snake venom was another well-known arrow poison. Since snake venom is digestible, it could be safely used for hunting because the venom did not make game harmful to eat, but the venom in the bloodstream of an enemy brought a painful death or a never-healing wound. Numerous poisonous snakes exist around the Mediterranean and in Africa and Asia. Snake venoms are complex mixtures of several different components or 'fractions' that can vary considerably within Crotalinae members. A complete review of venom components is beyond the scope of this review. Depending on the content of the venom, multiple organ systems may be affected. Historically, Crotalinae venom was classified as neurotoxic, hemotoxic, cardiotoxic, or myotoxic, depending on the species of snake involved in the envenomation. This oversimplifies the complex nature of Crotalinae venom. Clinically, a patient may develop such multisystem disorders as platelet destruction, internal bleeding, hypotension, paresthesias, and rhabdomyolysis. Snake venoms include toxins showing high selectivity for subtypes of muscarinic acetylcholine receptors, which control a variety of processes including the modulation of the heart rate, control of motor systems, and the modulation of learning and memory, as well as toxins that block particular subtypes of voltage-dependent sodium or potassium channels in neurons.[8]

Detection of snake toxins and toxin antibodies in body fluids remains very important for the identification of the biting species and the correct management of envenomation. As snake venoms consist of a complex mixture of pharmacologically active peptides and proteins, detection is usually approached by immunological techniques. Radioimmunoassay (RIA) using specific monoclonal antibodies has proved to be highly reliable and sensitive. However, the difficulty of handling radioisotopes and the need of elaborate equipment limit its application in routine diagnosis in the field. In contrast, agglutination tests using purified rabbit antivenom IgG are inexpensive, rapid, and simple to perform, making them appropriate for use in rural health centers of developing countries, but because of low level sensitivity and instability of the coupling agents, these tests have received only limited attention. In terms of specificity, sensitivity, rapidity, and simplicity, ELISA methods appear to be the ideal systems for detecting venom and venom antibodies. Approaches to achieve species specificity have included the use of a single venom component as the immunogen and the use of mixtures of monoclonal antibodies or affinity purified venom-specific antibodies as immunoreagents. The incorporation of avidin–biotin system and fluorogenic substrates significantly increased the sensitivity of these techniques allowing the detection of venom concentrations at picogram levels. Since snakebite is a medical emergency, immediate identification of the species is needed in order to administer the specific antivenom. In this respect, optimization of ELISA with unprocessed and undiluted blood and other biological samples reduced the assay time considerably. Optimization of the incubation steps at ambient temperature and visual discrimination of the optical density of test samples compared to controls are the two main approaches followed to achieve simplicity. Only a few commercial detection kits have been developed. Among them, a highly sensitive species-specific avidin–biotin microtiter ELISA (AB-microELISA) kit for the detection of venoms from four common Indian snakes has demonstrated efficacy to detect venom levels up to 10 ng ml−1 without ambiguity. The assay can be performed using 600 µl of blood collected with an anticoagulant without further manipulation and can be completed in 30 min. Recently, an ion-sensitive field effect transistor based immunosensor has been developed for the detection and quantification of the potent neurotoxin β-bungarotoxin. For analysis, separation, or structural studies of these toxins at the basic research level, a variety of methods have been used including LC, LC–MS, CE, MS, and NMR. A number of snake venoms affect the neuromuscular junction. Predatory arthropods and reptiles have highly developed envenomation systems designed for both defense and predation. The actions of these venom toxins can be broadly divided into those with presynaptic and postsynaptic loci. The postsynaptically acting toxins characterized by the snake alpha toxins (α-bungarotoxin) will be considered later in this chapter. These latter toxins have proven to be vital

tools in characterizing, identifying, and isolating the nicotinic AChR.

Neurotoxins that block neuromuscular transmission by presynaptic actions are found in the venom of many of the same species of snakes that contain postsynaptic toxins. The best known of these, and the first to be described, was β-bungarotoxin, from the snake *Bungarus multicinctus*. Bungarotoxins are a group of closely related neurotoxic proteins of the three-finger toxin superfamily found in the venom of kraits including *Bungarus multicinctus*. α-Bungarotoxin inhibits the binding of acetylcholine (ACh) to nicotinic acetylcholine receptors; β- and γ-bungarotoxins act presynaptically causing excessive acetylcholine release and subsequent depletion. Both α and β forms have been characterized, the α being similar to the long or Type II neurotoxins from other elapid venoms.

There are four types: α-Bungarotoxin, β-Bungarotoxin (not a three-finger toxin), γ-Bungarotoxin (Q9YGJ0) & k-Bungarotoxin. This toxin blocks neuromuscular transmission irreversibly by reducing ACh release. Other neurotoxins with similar presynaptic actions are notexin from the Australian tiger snake, *Notechis scutatus*, taipoxin from the Australian taipan, Oxyuranus scutellatus, and a myotoxin from the Asian sea snake, *Enhyodrina schistosa*. β-Bungarotoxin has a triphasic pattern of effects on ACh release. Initially, release is decreased; this is followed by a transient increase in release, with a subsequent progressive inhibition to block. Actions of β-bungarotoxin have also been demonstrated in the CNS. However, much higher concentrations of the toxin are needed to alter transmitter release in the brain. Its actions in the peripheral nervous system are proposed to be specific for cholinergic neurons; peripheral noradrenergic terminals are unaffected by β-bungarotoxin.

The precise mechanisms underlying the various actions of β-bungarotoxin are not yet completely understood. Several snake venoms contain toxins with phospholipase A2 (PLA2) activity. These include notexin, β-bungarotoxin, and taipoxin. There is considerable sequence homology among amino acids for β-bungarotoxin and other snake venom PLA2 enzymes. Snake venom PLA2 neurotoxins are thought to hydrolyze membrane phospholipids. However, several studies suggest that the PLA2 activity, in and of itself, does not explain the toxin's effects. For example, a potassium channel blocking action has also been reported for β-bungarotoxin. This effect occurs independently of the phospholipase activity and has been proposed to be responsible for the transient increase in ACh release. However, it is unclear how this action could be specific for peripheral cholinergic terminals since potassium channels would be found on other terminals as well. The cause of the ultimate block of release of ACh by β-bungarotoxin and other PLA2-type neurotoxins is unknown. Suggested mechanisms include inhibition of oxidative phosphorylation, inhibition of cytoskeletal phosphorylation, and cytoskeleton disruption. β-Bungarotoxin also inhibits phosphorylation of synapsin I in rat brain synaptosomes. Synapsin I is a neuronal phosphoprotein associated with synaptic vesicles that have been implicated in moving vesicles from a reserve to a releasable pool near the active zones. Ammodytoxin A, the principal toxin in the venom of the long-nosed viper (Vipera ammodytes ammodytes), is reported to block neuromuscular transmission by de-energization of the nerve terminal, resulting from mitochondrial degeneration and subsequent impairment of coupling between the action-potential-induced depolarization of the nerve terminal and the evoked transmitter release.[9]

Local feature of Hydrophidae bite is accompanied with local pain and swelling of biting site.
Systemic feature consists of:

(i) Muscle stiffness
(ii) Muscular necrosis
(iii) Myaglia
(iv) Renal failure
(v) Myoglobinuria

Examples of Hydrophidae

(i) Coral snake (*Micrurus fulvis*)

(ii) Beaked sea snake (*Enhydrina schistose*)

Constituents and composition of snake venom:

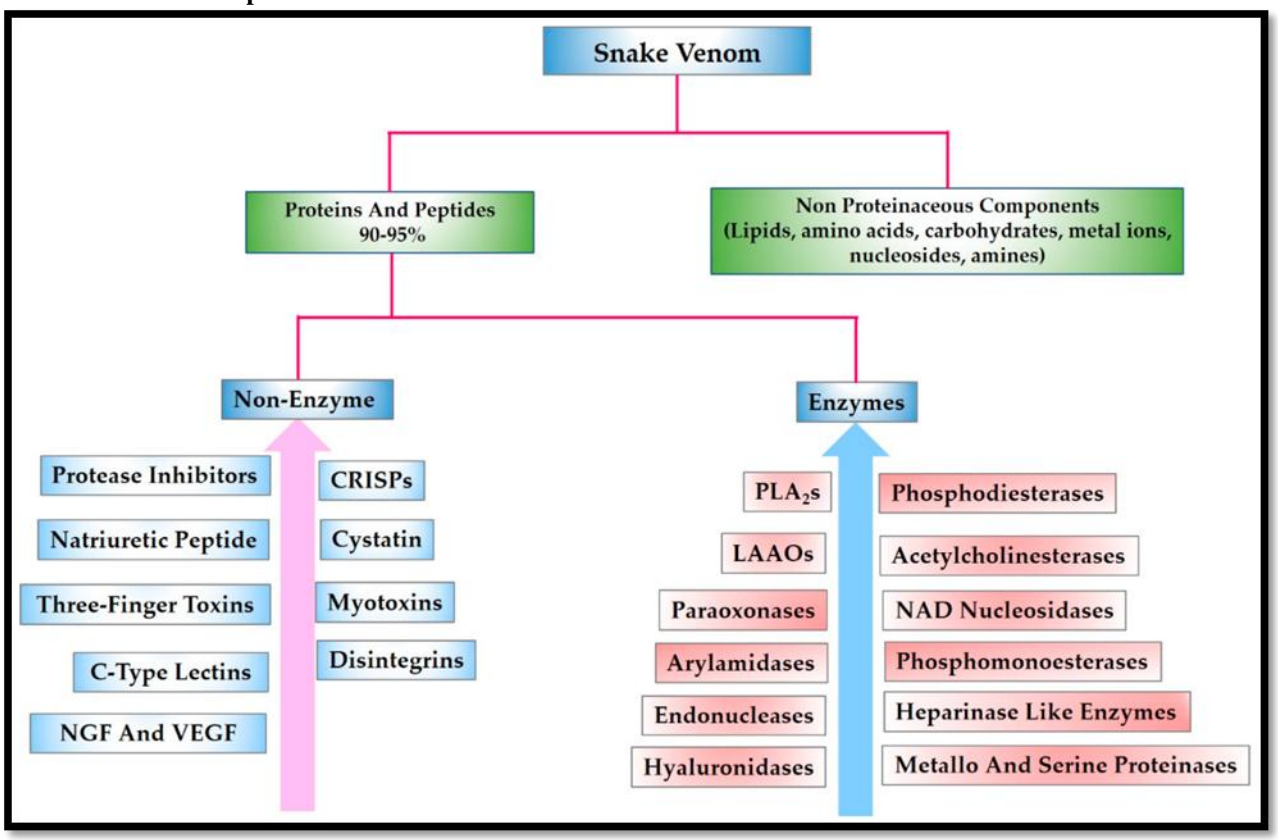


Figure-2: Components of snake venom.

Table-A

List of enzymatic venom components found in Elapidae and Viperidae family along with their sizes and activities.

Sl.no	Components of enzyme	Molecular Mass (kDa)	Mechanism of Action	Biological effects	Families of snakes
1.	Phospholipase A2 (PLA2)	12-14	Hydrolysis occurs at SN^2 position of ester bond in phospholipids that produces free fatty acids along with lysophospholipid. This enzyme action can result in toxic effects.	Presynaptic neurotoxicity, Myotoxicity, Anti-coagulation effect, Oedema formation, hypotension	Elapidae (type I PLA2) Viperidae (type II PLA2)
2.	Snake venom metalloproteases (SVMP)	P-I: 20-30 P-II: 30-60	Degradation of protein structures due to	Local and systemic bleeding,	Mainly present in venoms of viperidae

		P-III: 60-100 [Classification has been done on the basis of domain organization]	proteolytic activities. Haemorrhagic effects are caused due to disintigrin-like domain of SVMP	Haemostasis due to anti-coagulant property, Cytotoxic effect causing tissue necrosis	family
3.	Serine proteases (SVSP) Eg: Thrombin-like enzyme	26-27	In the pro-enzyme coagulation cascade, the hydrolysis of peptide bonds causes pro-coagulation, fibrinolytic/ fibrinogenolytic activities. In some cases, SVSP releases bradykinin due to kallikrein – like activity.	Haemostasis, Hypotension	Viperidae and Elapidae venoms (Except: Australian Elapidae snakes)
4.	L-amino acid oxidase (LAAO)	Gel filtration method: 110-150 SDS/PAGE method: 50-70 (under reducing and non-reducing conditions)	Stereospecific oxidative deamination of L-amino acid is catalyzed that results in producing alpha-keto acid, NH_3 and H_2O_2	Effect's platelet aggregation, induces cell apoptosis and anti-microbial activities	Both elapidae and viperidae
5.	5'-Nucleotidases	53-60	Phosphate monoester at 5'-position of DNA and RNA is hydrolyzed	Inhibition in aggregation of platelets	Both elapidae and viperidae family
6.	Acetyl-cholinesterase	55-60	Acetylcholine is hydrolyzed to choline and acetate group	Acetylcholine terminates neuro-transmission	Elapidae (except: Dendroaspis genus)
7.	Hyaluronidases	33-110	Oligosaccharides N-acetylglucosamine are formed by hydrolysis of hyaluronan	The structural, rheological and chemical properties of extracellular matrix are altered by this 'Spreading factor'	Both elapidae and viperidae

Table-B

List of non-enzymatic venom components in snakes of Elapidae and Viperidae families, their sizes and activities.

Sl.no	Components of Non-enzyme	Molecular Mass (kDa)	Mechanism of action	Biological effects	Families of snakes
1.	Three-finger toxins (3FTx) Eg: alpha- neurotoxins	6-9	Interference with neuromuscular transmission is occurred due to inhibition in postsynaptic nicotinic acetylcholine receptors in neuromuscular junction	Post synaptic effect	Elapidae and very rare in Viperidae
2.	Kunitz peptides (KUN)	7	Interferes blood coagulation and fibrinolysis by inhibiting serine protease. Other activities include inflammation and ion channel blockade	Haemostasias disruption	Elapidae and Viperidae
3.	Cystine-rich secretory proteins (CRiSP)	20-30	Cyclic nucleotide- gated (CNG) channel blockade and L-type calcium channel blockade	Smooth muscle contraction is inhibited	Common in Viperidae
4.	C-type lectins (CTL)	Comprises of two units: Alpha (A	Blood oagulation factors or specific platelet membrane receptors are either activated	Anti-coagulation is promoted along with inhibition or promotion of	Mostly found in Viperidae

		chain): 14-15 Beta (B chain): 13-14	or inhibited by this component in venom	platelet aggregation	
5.	Disintigrins (DIS)	5-10	On binding to glycoprotein IIb/IIIa it gets expressed on activated platelet that prevents fibrogen interaction	Aggregation of platelet is inhibited	Present in Viperidae but absent in elapidae
6.	Natriuretic peptides (NP)	3.5-4	cGMP level is increased along with subsequent cascade signaling due to an interaction between NPs and guanylyl cyclase receptors. Inhibition of angiotensin-converting enzyme is caused as an effect on rennin-angiotensin by NPs	Vasodilation results in hypotension. Diuresis and natriuresis promotes sodium and water excretion	Both in Viperidae (found abundantly) and also in elapidae

Snake venom collection from snakes: The process of collecting venom from snakes in order to prepare anti-venom for medical or research purposes is called snake milking process. Depending on species, snakes can be milked within a range from 2-3weeks to every 3 months. In case of dangerous species use of short-acting general anesthesia or moderate cooling (15^0C approx) at the time of milking can help reduce accidents for snakes as well as handlers.

Process of collecting venom: The head of the snake is gasped between the thumb and the index finger of the handler. The jaws are opened by gentle pressure to expose the fangs, which are then penetrated through plastic or parafilm membrane, over the lip of the glass vessel and hence the venom is squeezed out.

Figure-3: Snake milking.

Precautionary measures during venom collection

1. Blood contaminated sample should be rejected.
2. Withdrawal of fangs after venom collection to prevent damage to mouth and the dentilation of the snake should be done very carefully.
3. All materials required during milking should be sterilized over flame after each milking and should be cooled properly by air before next milking.
4. Mask, vinyl gloves and protective clothing is mandatory for handler to fervent infection or sudden accidents.

Therapeutic uses of snake venom

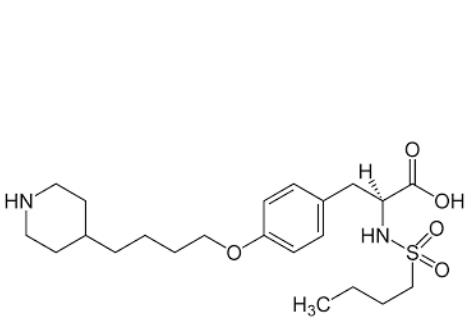
Snake venom having fatal nature possess several toxin peptides that have significant therapeutic uses.[10]

Table-C

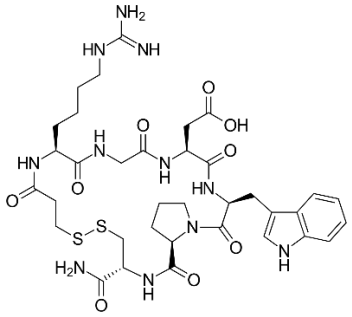
(A) Drugs

Sl.no.	Name of drug	Type of drug / Symptoms treated	Venom obtaining species
1.	(a) Tirofiban (b) Eptifibatide	Anti-platelet drugs (FDA approved)	*(a) Echis carinatus* *(b) Sistrurus miliarus barbouri*
2.	Captopril (derivative of bradykinin potentiating peptide)	Anti-hypertensive drug (FDA approved)	*Bothrops jaracusa*
3.	(a) Hemocoagulase (thrombin and thrmboplastin- like enzyme) (b) Batroxobin (serine protease)	(a) Treats hemorrhage (b) De-fibrogenating agent effective for patients undergoing anti-coagulant therapy	*(a) Bothrops moojeni* *(b)Bothrops atrox*
4.	Dendroaspis-NP (Natriuretic peptide)	Congestive cardiac failure	*Dendroaspis angusticeps*

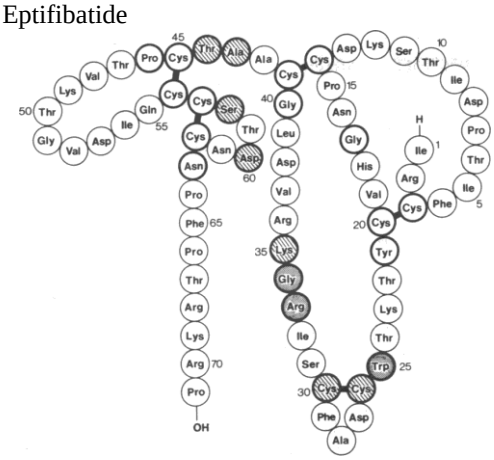
	[Phase II clinical study is ongoing]		
5.	(a) α-Cobratoxin (b) α-Cobrotoxin (Undergoing human trials)	Used as analgesics	*(a) Naja knouthia* *(b) Naja nivea*
6.	Ancrod (Undergoing phase III clinical trials)	De-fibrinogenating agent	*Agkistrodan rhodostoma*
7.	Contortrostatin/ Eristrostatin	Used for treating cancer	Asian sand snakes
8.	Hannalgesin (oral drug)	Analgesic drug	*Ophiophagus hannah*



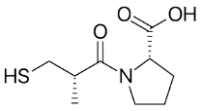
Tirofiban



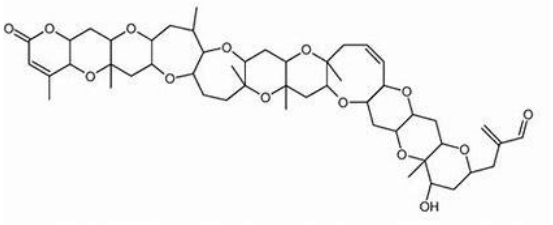
Eptifibatide



Cobrotoxin



Captopril



Bungarotoxin

(B) Antivenom: The term 'antivenom' has been derived from the word 'antivenin' and the term 'venom' from the Latin word 'venemum' which means 'poison'. Antivenom (antivenin, venom antiserum and antivenom immunoglobulin) composed of antibodies remains the only specific treatment of certain venomous bites and stings, if given in proper quantity and at right time, in cases of significant toxicity. The antivenom injections are specific and determined by the species involved during bites.

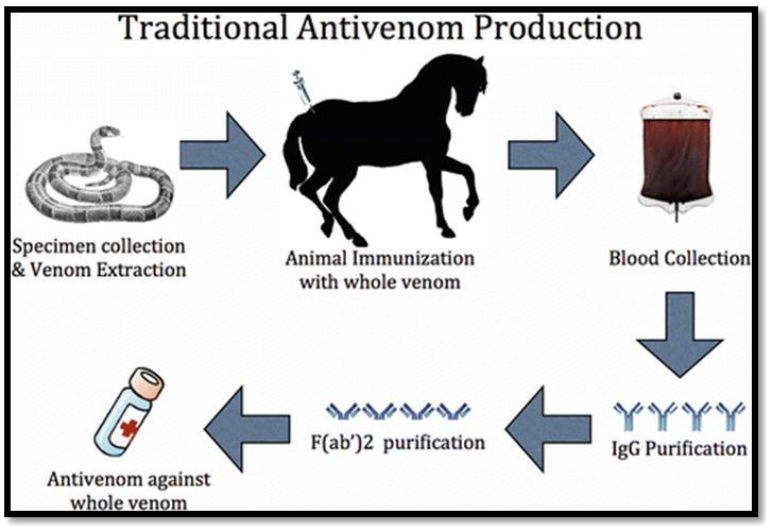


Figure-4: Antivenom Production.

Types of antivenom

1. **Monospecific antivenom:** Administered in a limited way to any specific and single species of venomous snake or to very few closely related species whose venoms show clinically effective cross- neutralization.

2. **Polyspecific antivenom:** A venom mixture obtained from various species of snakes are administered to animals to make them immune. Hence, the resulting antivenom will be containing different antibodies against venom components of different species of snakes. In this way, polyspecific antivenoms are generated and it is thus seen in some cases that the titre of neutralizing antibodies in polyspecific antivenom is higher than the monospecific ones.[11]

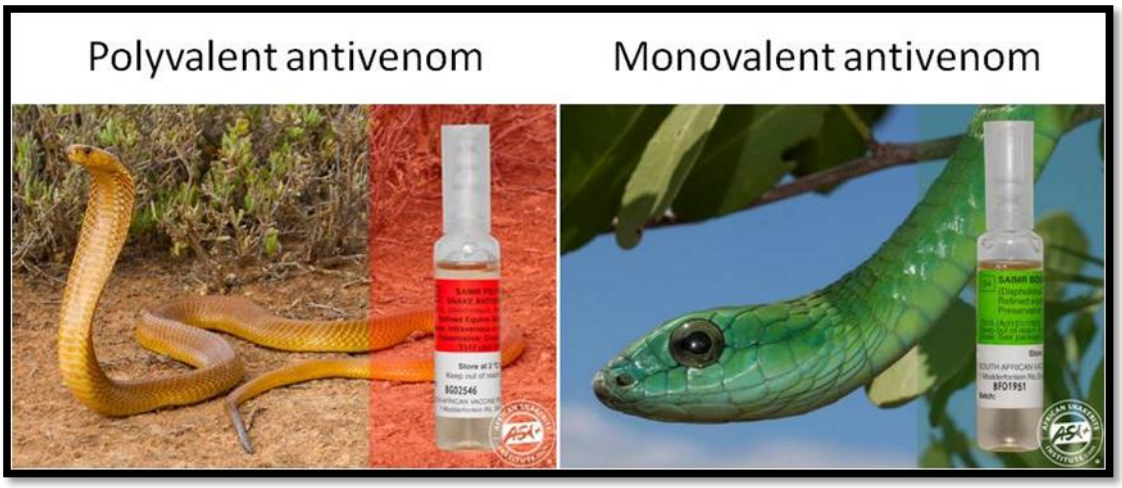


Figure-5: Polyspecific and monospecific antivenom.

Table-D: List of some available antivenoms, the species names and countries to which the species belong.

Sl. No.	Antivenom	Name of species	Country/ Region
1.	(a) PANAF PREMIUM [Purified lyophilized enzyme refined Equine Immunoglobulins] (b) Snake venom antivenom [Purified lyophilized enzyme refined Equine Immunoglobulins]	(a) (i) *Echis ocellatus* (ii) *Bitis arietans* (iii) *Dendroaspis viridis* (iv) *Naja nigricolis* (b) (i) *Naja naja* (ii) *Vipera russelli* (iii) *Echis carinatus*	India
2.	INOSERP MENA	(i) *Bitis arietans* (ii) *Ceratus ceratus* (iii) *Daboia deserti* (iv) *Echis coloratus* (v) *Macrovipera labetina obtusa* (vi) *Naje haje* (vii) *Vipera latastei*	(Middle East and North Africa), Spain
3.	INOSERP PAN- AFRICA	(i) *Echis ocellatus* (ii) *Bitis arientans* (iii) *Dendroaspis polylepis* (iv) *Naja nignicollis*	Spain (Sub- Sahara Africa)
4.	Echi TAbG	(i) *Echis ocellatus* (ii) *Echis pyramidum*	UK (Sub- Sahara Africa)
5.	ANAVIP (Polyvalent snake antivenom)	(i) South American rattlesnake (*Crotalus durissus*) (ii) Fer-de-lance (Bothrops asper)	(i)Mexico (ii)South America
6.	Polyvalent snake antivenom	(i) Saw-scaled viper (*Echis carinatus*) (ii) Russell's viper (*Daboia russelli*) (iii) Spectacled cobra (*Naja naja*) (iv) Common krait (*Bungarus caeruleus*)	India
7.	(a) Death adder antivenom (b) Taipan antivenom (c) Black snake antivenom	(a) Death adder (b) Taipan (c) Pseudechis spp.	Australia

	(d) Tiger snake antivenom (e) Sea snake antivenom	(d) Australian copperheads, Tiger snakes, Rough scaled snakes (e) Sea snake	
8.	Vipera tab	Vipera spp.	UK
9.	(a) Polyvalent crotalid antivenom (Crofab) (b) Polyvalent Immune fab (Ovine)	(a) Pit vipers (b) Copperheads	North America
10.	(a) Soro antibotropicocrotalico (b) Antielapidico	(a) (i) Pit vipers (ii) Rattle snake (b) Coral snakes	Brazil
11.	(a) SAIMR polyvalent antivenom (b) SAIMR echis antivenom (c) SAIMR boomslang antivenom	(a) (i) Mambas (ii) Cobras (iii) Rinkhalses (iv) Puff adders (b) Saw-scaled vipers (c) Boomslang	South Africa
12.	(a) PanAmerican Serum (b) Anticoral (c) Anti-mipartitus antivenom (d) Anti- coral monovalent (e) Antimicrurus (f) Coralmyn (g) Anti-micruricoscorales	Coral snakes	(a) Costa Rica (b) Costa Rica (c) Costa Rica (d) Costa Rica (e) Argentina (f) Mexico (g) Columbia
13.	Anavip [Crotalidae immune F(ab')2 equine]	Crotalinae	North America, US

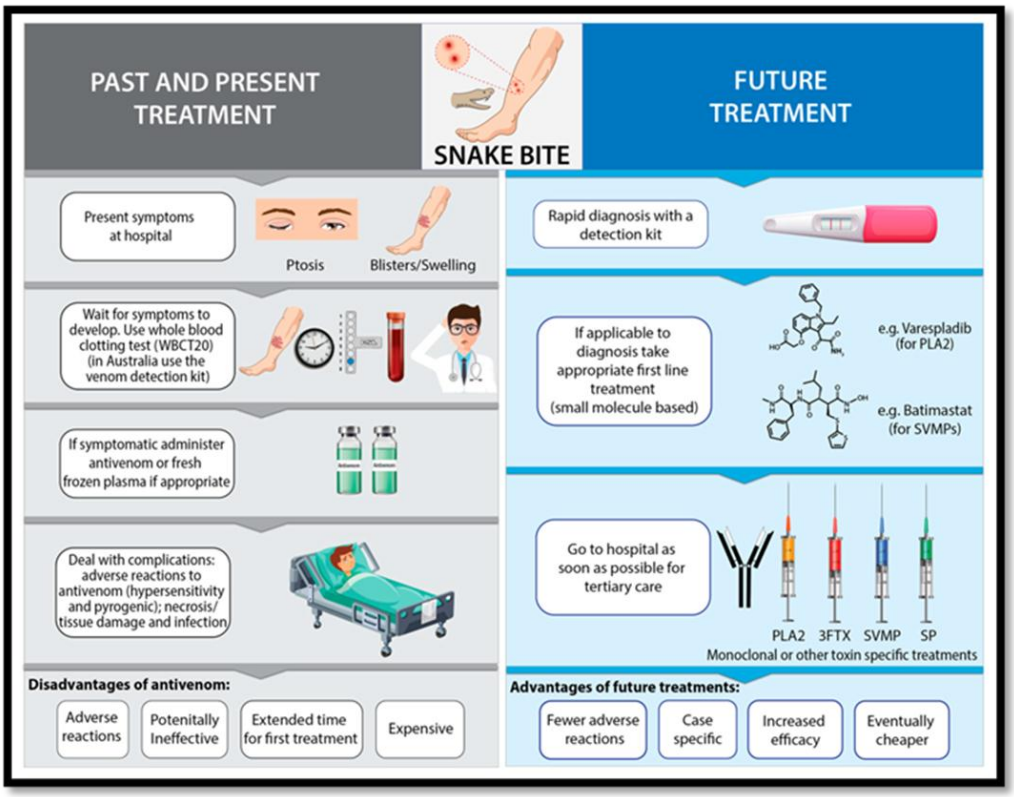


Figure-6: Further changes in treatments in future compared to present days.

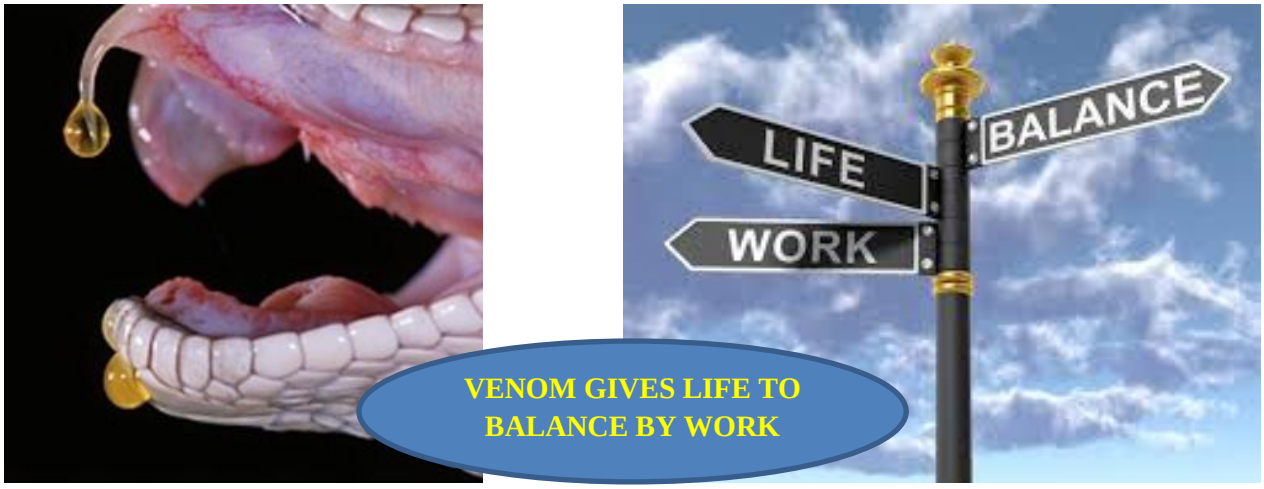
Limitations in use of antivenoms

Though antivenom acts as a life savior, but still is application can have some side effects on individuals like:

1. Breathing difficulty, reddening of eyes and skins, swelling of face and lips, sudden chills and fever which are mainly caused due to anaphylactic reaction of the antivenoms.
2. Inflammation of joints
3. Enlargement in some lymph nodes is also observed in some patients.

4. Due to high concentration of non-immunoglobulin proteins several pyrogenic reactions also occur.
5. Antivenom cannot reverse the effects caused on snake bite envenomation.

Snake venom has also been found to exhibit anti-microbial activities like antibacterial, antiviral, antifungal and antiparasitic properties that helps in treating several diseases like measles, yellow fever, HIV, hepatitis C as well as fungal species like *Candida parapsilosis*, parasites of Leishmania sp. and helps in converting gram- positive bacteria to gram-negative bacteria.



CONCLUSION

Halāhala (Sanskrit हलाहल) or kālakūṭa (Sanskrit कालकूटं, literally: 'black mass' or 'time puzzle') is the name of a poison (as per Hindu History) created from the sea when Devas and Asuras churned it in order to obtain Amrita, the nectar of immortality. Snake venoms previously have been known to have only toxic properties that can harm human beings causing painful and traumatic deaths. But later on, with gradual progress in scientific research and medical studies, snake venoms are considered to be the most valuable therapeutic tool that acts as a "blessing" in curing many diseases and along with the discoveries of antivenom it has opened a new horizon in curing victims of snake bites. Though a very small fraction of snake venom components has been identified, but still further more researches and studies are going on worldwide to give it a new and broader scope in the future of drug discovery field and to further uncover many more therapeutic leads from snake venom.

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