**Snake Venom Therapeutic Potential against Cardiovascular Diseases**

**Abstract**

Snakes, belonging to the Phylum *Chordata* and Class *Reptilia*, are among the most evolutionarily adaptable and biologically diverse vertebrates. Venomous snakes possess specialized salivary glands that produce and store venom, a complex mixture of biologically active proteins, polypeptides, and non-protein components. These venom components exhibit dominant bioactivities such as neurotoxicity, haemotoxicity, and cytotoxicity, which disrupt fundamental physiological systems in envenomed victims. If left untreated, snake envenomation can lead to severe morbidity or death. Snake envenomation is a significant global health challenge, with an estimated 4.5–5.4 million bites annually, resulting in tens of thousands of fatalities and numerous cases of chronic disabilities due to tissue damage and systemic complications. Despite this, snake venoms have garnered increasing attention for their therapeutic potential. Their biologically active toxin mixtures exhibit diverse pharmacological properties, making them valuable in drug discovery and development. The success of captopril, the first drug derived from the bradykinin-potentiating peptide of *Bothrops jararaca* venom, highlights the potential of snake venom components as lead compounds for novel therapeutic agents. Significant progress has been made in developing drugs targeting cardiovascular diseases, including treatments for coagulopathies, hemostasis, and stroke prevention. This review explores the therapeutic potential of snake venom components in addressing cardiovascular diseases. It focuses on the mechanisms through which these components influence blood pressure regulation and clotting pathways, underscoring their importance in the continuous search for innovative medical treatments.

**Keywords:** Snake, Venom toxins, Therapeutic Agents, Cardiovascular Diseases

# **1.0 Introduction**

Snakes, members of the Phylum Chordata and Class Reptilia, are among the most evolutionarily adaptable and biologically diverse vertebrates (Database, 2023). Within the suborder *Serpentes* (Alejandro, 2007), snakes have developed an array of survival strategies, with venom emerging as one of their most remarkable adaptations (Gold *et al.,* 2002). Of over 4,000 snake species globally, around 600 (15-17%) are venomous, and approximately 200 of these are medically significant, presenting both public health risks (Nicola *et al.,* 2021). These venomous snakes belong to four primary families; *Viperidae, Atractaspididae, Elapidae,* and *Colubridae* with Viperidae further subdivided into the highly toxic *Viperinae* and *Crotalinae* subfamilies (de Franca and Tambourgi, 2023; Gutiérrez *et al.,* 2017).

Snake envenomation represents a significant global health challenge, with 4.5–5.4 million bites occurring annually, leading to tens of thousands of fatalities and countless cases of chronic disabilities caused by tissue damage and systemic complications (WHO, 2023). Beyond their role in envenomation, snake venoms are increasingly recognized for their untapped therapeutic potential, owing to their biologically active toxin mixtures with diverse pharmacological properties (Kodama *et al.,* 2015; Frangieh *et al.,* 2021; Lu *et al.,* 2023)

Composed predominantly of proteins and peptides, snake venom is a sophisticated arsenal targeting diverse physiological systems in prey, including the nervous, cardiovascular, and musculoskeletal systems (Frangieh *et al.,* 2021; Bedraoui *et al.,* 2024; Bittenbinder *et al.,* 2024). Enzymatic toxins like phospholipases, metalloproteinases, and serine proteases work alongside non-enzymatic molecules, including neurotoxins and cardiotoxins, to immobilize prey efficiently and initiate predigestion (Ledsgaard *et al.,* 2023; Vuong *et al.,* 2021; Monsalve *et al.,* 2020; Ferraz *et al.,* 2019; Costa *et al.,* 2014; Jacinthe *et al.,* 2021). The specificity and potency of these venom components make them highly effective, not only in an envenomation but also as therapeutic candidates (Darwish *et al.,* 2021).

Recent advances in biomedical research highlight snake venom's potential in addressing human diseases, particularly cardiovascular conditions such as hypertension, thrombosis, and heart failure (Kodama *et al.,* 2015; Chen *et al.,* 2018; Lazarovici, Marcinkiewicz, and Lelkes, 2019; Bayer, *et al.,* 2020; Frangieh *et al.,* 2021; Estrada *et al.,* 2022; Wang and Zou, 2023; Lu, *et al.,* 2023)

The strategy behind developing venom-derived drugs is based on the ability of snake venom compounds to modulate ion channels, such as Na+, K+, and Ca2+ ion channels, block receptors and membrane transporters and inhibit enzymes activity (Frangieh *et al.,* 2021; Bedraoui *et al.,* 2024; Averin and Utkin, 2021).

An example of this is captopril, the first drug derived from viper venom, which gained approval from the Food and Drug Administration for treating hypertension and congestive heart failure (Frangieh *et al.,* 2021). Captopril works by inhibiting the ACE enzyme, which is responsible for converting angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor, so its reduction leads to relaxation of blood vessels and reduced blood pressure (Kodama *et al.,* 2015; Frangieh *et al.,* 2021)

This review focuses on the application of snake venom in cardiovascular medicine, exploring the mechanisms by which venom components influence blood pressure regulation and clotting pathways. By elucidating the molecular and pharmacological actions of these compounds, this review aims to underscore their therapeutic potential and outline the challenges in developing venom-derived drugs for safe human use.

## **2.0 Methodology**

## **2.1 Search strategy**

Relevant papers were searched using electronic databases such as PubMed/MEDLINE, Embase, Cochrane Library, Scopus, and Google Scholar. The following search terms were employed: "antivenom" OR "venom-derived peptide" OR "snake venom" AND "cardiovascular disease" OR "hypertension" OR "atherosclerosis" AND "drug development" OR "mechanism of action" OR "ACE inhibition." This search strategy was designed to include all relevant articles on the pharmacological effects of snake venom on the cardiovascular system.

## **2.2. Inclusion and exclusion criteria**

**2.2.1 Inclusion criteria**

The inclusion criteria for relevant studies focus on research investigating snake venom toxins and their effects on cardiovascular diseases. This encompasses preclinical studies, including in vitro and in vivo experiments, and clinical research examining the cardiovascular impacts of venom components. Additionally, systematic reviews, meta-analyses, and randomized controlled trials evaluating snake venom's therapeutic potential for treating cardiovascular conditions were considered. Only published articles in English that were peer-reviewed, as well as conference proceedings and dissertations, were included in this review**.**

**2.2.2 Exclusion criteria**

The research's exclusion criteria involved several vital factors. Non-research-based literature, such as opinions, commentaries, and editorial articles, was not considered. Furthermore, studies focused exclusively on conditions unrelated to cardiovascular diseases, such as neurotoxicity or dermatological effects, were excluded. The criteria further stipulated that non-peer-reviewed sources or grey literature lacking sufficient scientific rigour could not be included. Finally, articles presenting incomplete data or unclear methodologies were excluded from the research review.

## **3.0 Biochemical Properties of Snake Venom Toxins**

Snake venom toxins are highly stable due to multiple disulfide bonds, making them resistant to degradation by enzymes in prey (Oliveira *et al.,* 2022). Many toxins are highly specific for certain physiological targets, such as nicotinic acetylcholine receptors or phospholipids in cell membranes (Sani *et al.,* 2019). This specificity allows venom toxins to have rapid and precise effects on biological processes. Venom contains a mixture of toxins that often work synergistically, enhancing each other's effects (Ferraz *et al.,* 2019). For instance, enzymes like hyaluronidase, metalloproteinases and PLA2s in venom can disrupt tissue barriers, allowing other toxins easier access to deeper tissues or the bloodstream (Ledsgaard *et al.,* 2023; Sani *et al.,* 2019).

## **3.1 Snake venom compositions**

Snake venoms comprise a mixture of biologically active proteins and polypeptides (Sani *et al.,* 2019) (comprising approximately 90–95% of a venom load), along with other non-protein components including carbohydrates, lipids, amines, and inorganic salts of which the majority (>90%) are peptides and proteins, with the dominant bioactivities including neurotoxicity, haemotoxicity and cytotoxicity depending on the snake species (Oliveira *et al.,* 2022; Ferraz *et al.,* 2019).

## 3.1.1 Enzymes in Snake Venom

The unique biochemical stability and specificity of snake venom toxins are not only essential for their survival strategies but also lay the foundation for a variety of mechanisms that buttress their toxic effects. Among these, enzymatic components stand out for their role in degrading tissue barriers and altering blood flow, processes that are critical both for prey immobilization and potential therapeutic applications.

### 3.1.1.1 Phospholipase A2 (PLA2)

PLA2 (phosphatide 2-acylhydrolase, EC 3.1.14) They are usually small proteins that contain disulfide bonds, which stabilize their structure and make them resistant to degradation (Oliveira *et al.,* 2022) and its often one of the key components of snake venom, particularly in the venoms of elapids, viperids, and crotalids (Berg *et al.,* 2001). Snake venom phospholipase A2 enzymes (PLA2s) act by hydrolyzing the sn-2 ester bond in phospholipids, resulting in the release of free fatty acids, commonly arachidonic acid, along with lysophospholipids (Ferraz *et al.,* 2019) which in turn promotes inflammation and pain (Sofyantoro *et al.,* 2022). PLA2s can also contribute to muscle damage and myonecrosis (muscle cell death) (Sani *et al.,* 2019). Depending on the type, snake venom PLA2s can either promote or inhibit blood clotting. Some act as anticoagulants by disrupting platelet function, while others may induce coagulation cascades, leading to local clotting and hemorrhage (Oliveira *et al.,* 2022). Naja (cobra) and Bothrops (pit viper) venoms contain potent PLA2 enzymes, making them highly toxic and capable of rapid tissue degradation.

### 3.1.1.2 Snake Venom Metalloproteinases (SVMPs)

SVMPs are enzymes with a variable molecular mass ranging from 20 to 100 kDa (Tasoulis *et al.,* 2022). They are large proteins with multiple domains that bind to substrates with high specificity. These enzymes rely on divalent metal ions, like zinc, which are essential for maintaining their three-dimensional structure required for catalytic activity (Oliveira *et al.,* 2022). These zinc-dependent enzymes degrade extracellular matrix proteins, such as collagen, elastin, and fibrin. SVMPs disrupt blood vessel integrity, leading to hemorrhage, inflammation, and local tissue destruction (Ferraz *et al.,* 2019). They play a major role in venom-induced bleeding and contribute to necrosis at the site of the bite (Ledsgaard *et al.,* 2023; Munawar *et al.,* 2018). SVMPs are predominantly found in viper venoms, such as from the Russell’s viper (Daboia russelii) and Bothrops species, these enzymes causes extensive bleeding and tissue damage (Oliveira *et al.,* 2022).

### 3.1.1.3 Snake Venom Serine Proteinases (SVSP)

SVSP belong to the serine protease family, characterized by a conserved catalytic triad (Ser195-His57-Asp102) that is critical for enzymatic activity (Asega *et al.,* 2020). SVSP are enzymes that cleave peptide bonds in proteins (Vilca-Quispe *et al.,* 2023). They are smaller than metalloproteinases and contain catalytic triads that are essential for their activity SVSPs are similar to SVMPs in that they are primarily hemotoxic and act as procoagulants, disrupting blood coagulation, altering fibrinogen levels, affecting blood pressure, and inhibiting platelet aggregation (Yue *et al.,* 2021; Vaiyapur *et al.,* 2011).

## 3.1.2 Neurotoxins

Neurotoxins in snake venom target nerve cells, disrupting the transmission of electrical signals, often leading to paralysis (Marte *et al.,* 2022).

### 3.1.3.1Three-Finger Toxins (3FTx)

3FTx are a diverse group of neurotoxic proteins primarily found in the venoms of elapids, hydrophiids, and colubrids, α-Bungarotoxin from krait venom and cobratoxin from cobra venom are well-known examples. They are named for their distinctive three-fingered structure (Koludarov *et al.,* 2023). They are small, structurally stable peptides with a characteristic three-finger-like structure (Kessler *et al.,* 2017). They are resistant to degradation due to multiple disulfide bonds (Dyba *et al.,* 2021; Utkin, 2019). These toxins act as either agonists or antagonists on cholinergic receptors, particularly the nicotinic acetylcholine receptors at the neuromuscular junction. This binding leads to paralysis by blocking nerve impulse transmission to muscles (Kessler *et al.,* 2017; Yang, *et al.,* 2016; Roman-Ramos *et al.,* 2024).

### 3.1.2.2 Phospholipase A2 Neurotoxins:

Some PLA2 enzymes in snake venoms are modified to target neurons specifically (Tasoulis *et al.,* 2022). These neurotoxic PLA2s are structurally similar to other PLA2s but bind to receptors on nerve cells, disrupting neurotransmission (Sofyantoro *et al.,* 2022).

### 3.1.2.3 Cardiotoxins

Cardiotoxins, primarily found in elapid venoms, are polypeptides with a structure stabilized by disulfide bridges. These toxins are small and highly cationic, allowing them to interact with cell membranes effectively (Kodama *et al.,* 2015; Frangieh *et al.,* 2021). Cardiotoxins disrupt cardiac muscle cells by binding to the cell membrane, leading to cell depolarization, leakage of ions, and cell death (Antzelevitch, 2005). This results in arrhythmias, cardiac arrest, or heart failure in severe cases (Lei *et al.,* 2024). Cobra venoms, especially those of the Naja species, contain cardiotoxins that can cause rapid and severe cardiovascular symptoms (Laraba‑Djebar and Chérif, 2021; Averin and Utkin, 2021; Manjunatha and Yeow, 2020).

### 3.1.2.4 Hemotoxins

Snake venom hemotoxins are a complex mixture of proteins and peptides that primarily target the hemostatic system, leading to significant physiological effects (Talukdar *et al.,* 2022). The toxins are varied and consist of SVMPs, SVSPs, and toxic variants of Factor X and Factor V. (Kini and Koh, 2016) and prothrombin activators like oscutarin C and ecarin (Slagboom *et al.,* 2017), These toxins can disrupt blood coagulation, cause hemorrhage, and affect blood pressure, making them both dangerous to envenomated individuals and valuable for therapeutic applications (Gary *et al.,* 2021).

### 3.1.2.5 Myotoxins

Myotoxins from snake venom are small, basic peptides that target muscle cell membranes, often by forming pores or disrupting membrane integrity (Bittenbinder *et al.,* 2024). They primarily affect the nervous system by interacting with ion channels and receptors involved in pain signaling pathways (Oliveira *et al.,* 2022). These toxins induce rapid muscle cell necrosis, leading to local swelling, pain, and the release of muscle proteins, such as myoglobin, into the bloodstream. If untreated, this can result in kidney damage and systemic toxicity (Gasanov *et al.,* 2014). Specific myotoxins, such as Lys49 myotoxins, activate purinergic receptors through ATP release, which triggers pain responses like thermal hyperalgesia and mechanical allodynia (Zhang *et al.,* 2017). Additionally, venom-derived peptides can selectively modulate the TRPV1 ion channel, a key player in nociceptive pathways, thus influencing pain perception (Hwang *et al.,* 2022). Some myotoxins also inhibit sodium channels, such as NaV 1.7, crucial for pain signaling, presenting a promising pathway for developing potent analgesics (Shahriyar and Chaim, 2022).

### 3.1.2.6 Bradykinin-Potentiating Peptides (BPPs)

BPPs, or bradykinin-potentiating peptides, are small peptides that are proline-rich oligopeptides and consist of 5 to 14 amino acids. They can be found in the venom of certain snakes (Kodama *et al.,* 2015; Frangieh *et al.,* 2021). These peptides inhibit the angiotensin-converting enzyme (ACE), which converts angiotensin I into angiotensin II, a potent vasoconstrictor and hypertensive agent. By inhibiting ACE, BPPs reduce the formation of angiotensin II, leading to lower blood pressure (Sciani and Pimenta, 2017; Gouda and Mégarbane, 2021)

### 3.1.2.7 Cytotoxins

Snake venom cytotoxins are amphipathic proteins that makeup approximately 40% to 70% of cobra venom, particularly from the *Naja* species (Feofanov *et al.,* 2005). The toxicity associated with cytotoxins involves several mechanisms, including the modulation of membrane-bound enzyme activity, depolarization of excitable membranes in heart cells and neurons, inhibition of platelet aggregation, induction of hemolysis and cytotoxic effects, and the potential to cause cardiac arrest (Dubovskii *et al.,* 2013). Cytotoxins cause localized damage to tissues, helping to immobilize and digest prey. These toxins result in swelling, necrosis, and cell death in the area surrounding the bite. It is widely accepted that the harmful effects of cytotoxins are primarily due to their ability to bind to cell membranes, altering the organization and function of lipid bilayers. (Gouda and Mégarbane, 2021).

## 2.2 Therapeutic Potential of Snake Venom Toxins

## 2.3.1 cardiovascular disease

These snake venom components include, in particular, bradykinin-potentiating peptides (BPPs), natriuretic peptides (NPs) (Koh and Kini, 2019; Bedraoui, *et al.,* 2024), sarafotoxins (SRTXs), and three-finger toxins (TFTs), including cobra cardiotoxins (CTs) (Laraba‑Djebar and Chérif, 2021), phospholipases A2 (PLA2s), and vascular endothelial growth factors (VEGFs) (Averin and Utkin, 2021; Frangieh *et al.,* 2021)

### 2.3.1.1 Bradykinin-potentiating peptides

Bradykinin-potentiating peptides (BPPs) and proline-rich oligopeptides found in snake venoms, primarily exert their antihypertensive effects by inhibiting angiotensin-converting enzyme (ACE) (Frangieh *et al.,* 2021; Soares *et al.,* 2005; Munawar, *et al.,* 2016; Pinheiro-Júnior, *et al.,* 2018). This inhibition reduces the formation of vasoconstrictor angiotensin II and prevents the degradation of bradykinin, a vasodilator (Cintra *et al.,* 1990). Elevated bradykinin levels enhance vasodilation by stimulating nitric oxide (NO) and prostaglandin release from endothelial cells, further relaxing blood vessels (Kodama, et al., 2015). This dual action; blocking angiotensin II formation and preserving bradykinin supports BPPs' blood pressure-lowering effects and inspired the development of captopril, the first venom-based ACE inhibitor (Ferreira, 1965).

Morais et al. (2011) identified Bj-PRO-5a, a compound isolated from *Bothrops jararaca* venom, which stimulates nitric oxide (NO) production and induces vasodilation in mice. The vasodilatory effect is mediated through bradykinin B2 and mAchR-M1 receptors, as confirmed by its inhibition with receptor-specific antagonists and NO synthase blockers. These findings suggest Bj-PRO-5a's potential therapeutic applications for cardiovascular and cognitive disorders.

Similarly, Claudiana et al. (2010) demonstrated that intracerebroventricular injection of the proline-rich peptide Bj-PRO-10c, also derived from *Bothrops jararaca* venom, significantly reduced mean arterial pressure (MAP) and heart rate (HR) in hypertensive rats. This antihypertensive effect is mediated by central nervous system (CNS) mechanisms involving Gi/o-protein pathways, calcium signaling, and neurotransmitter release (glutamate and GABA), independent of bradykinin and ACE inhibition.

In addition to inhibiting ACE, some BPPs kinetically modulate the activity of argininosuccinate synthase both in vitro and in vivo. This modulation stimulates nitric oxide (NO) production in endothelial cells, reduces blood pressure, and enhances the synthesis of protective molecules such as polyamines and agmatine. These molecules contribute to cardiovascular benefits, including a positive inotropic effect and potential modulation of Ca²⁺-ATPase activity in the sarcoplasmic reticulum, a key factor in heart failure (Averin & Utkin, 2021).

### 2.3.1.2 Natriuretic peptides

Natriuretic peptides (NPs) are synthesized as preprohormones, with ANP and BNP being biologically active forms that play crucial roles in cardiovascular regulation. NPs contain about 20 to 53 amino acid residues and are based on a conserved 17-aa sequence confined by a disulfide bond.

There are three isoforms of mammalian NPs: namely atrial NP (ANP), brain NP (BNP) and C-type NP (CNP) (Averin and Utkin, 2021). NPs exert their effects through three identified receptors; natriuretic peptide receptor-A, -B, and -C (NPR-A, NPR-B, NPR-C), which activate intracellular signaling pathways leading to increased cGMP levels and cardioprotective effects (Mangiafico *et al.,* 2013). Genetic studies indicate that variations in NP levels are associated with cardiac hypertrophy and fibrosis, highlighting their potential as therapeutic targets in heart failure (HF) (Kerkelä *et al.,* 2015). ANP and BNP can contribute to vasorelaxation and natriuresis in animal models and humans with congestive heart failure (CHF), whereas CNP is likely to have a paracrine regulatory role on the vascular tone. Atrial NPs are the key hormones in the regulation of pressure–volume homeostasis.

These peptides interact with membrane-bound NP receptors (NPRs) in the heart, vasculature, and kidneys, reducing blood pressure and circulation volume. A common property of NPs is the ability to induce an increase in NO production and activate protein kinase G, which mediates their vasorelaxant effect (Averin and Utkin, 2021).

NPs play a crucial role in the venom's effectiveness by lowering blood pressure in the prey. This rapid decrease in blood pressure can lead to a swift loss of consciousness, immobilizing the prey and often resulting in its death. The ability of these peptides to induce such effects is a key aspect of their function in the context of snake predation (Erij, 2023). Over the last three decades, research has highlighted the potential of venom-derived natriuretic peptides in developing therapeutic options for heart failure. The first NP was discovered in the venom of the green mamba, and since then, these peptides have been recognized for their long half-lives and unique pharmacological profiles, which may differ from those of mammalian natriuretic peptides (Horng, 2013). This characteristic makes them promising candidates for drug development, as they may offer advantages in terms of efficacy and duration of action in therapeutic settings (Wei *et al.,* 2022).

### 2.3.1.3 Three finger Toxins

Three-finger toxins (TFTxs) are a diverse group of neurotoxic proteins primarily found in the venoms of elapids (such as cobras, kraits, and mambas), hydrophiids (sea snakes), and colubrids. They are named for their distinctive three-fingered structure (Dyba *et al.,* 2021). Structurally, TFTxs consist of 57 to 82 amino acid residues that fold into three β-stranded loops extending from a compact, hydrophobic core, stabilized by four conserved disulfide bridges (Kini & Koh, 2016). These loops resemble outstretched fingers, giving the toxins their characteristic name (Koludarov, *et al.,* 2023; Roman-Ramos, *et al.,* 2024).

Despite sharing the same tertiary structure of three loops forming a flat, triple-stranded anti-parallel β-sheet, the biological roles of TFTxs vary widely (Utkin, 2019; Kessler *et al.,* 2017). These toxins primarily modulate the activity of ion channels, receptors, and enzymes in their target organisms. For instance, key targets of TFTxs include nicotinic acetylcholine receptors (nAChRs), muscarinic acetylcholine receptors (mAChRs), and L-type calcium channels (Kessler *et al.,* 2017; Yang *et al.,* 2016). Binding to these targets can lead to physiological disruptions, such as paralysis, impaired neurotransmission, inhibition of platelet aggregation, or other effects that contribute to venom toxicity (Yang *et al.,* 2016)).

In snake venom, TFTxs play a critical role in subduing prey by immobilizing it. The neurotoxic effects of TFTxs, which often result in flaccid paralysis and respiratory failure in snakebite victims, are among the most recognized outcomes of these toxins (Dyba *et al.,* 2021). This paralysis occurs when specific TFTxs bind postsynaptically to acetylcholine receptors (AChRs) at neuromuscular junctions or inhibit acetylcholine breakdown.

However, the pharmacological effects of TFTxs are highly varied; beyond neurotoxicity, certain TFTxs induce effects such as cardiac arrest, cytolysis, analgesia, seizures, insulin secretion, and changes in memory, blood pressure, heart rate, or sperm motility. Some TFTxs inhibit platelet aggregation, blood coagulation, or cell adhesion, which aligns with their role in venom, allowing snakes to quickly and efficiently immobilize or digest their prey. For instance, cardiotoxic TFTxs can induce myocardial damage and arrhythmias, while cytotoxic TFTxs lyse cells and tissues, facilitating digestion (Koh *et al.,* 2018).

Interestingly, three-finger toxins from snake venoms also show significant therapeutic potential, particularly in cardiovascular medicine, due to their molecular interactions with cardiovascular cells. These toxins can modulate membrane properties and influence cellular signaling pathways, offering a range of medical applications. For example, KT-6.9, a three-finger toxin isolated and purified from *Naja kaouthia* venom, acts as an antiplatelet agent (Utkin, 2019). Similarly, calciseptine and FS2, also three-finger toxins purified from black mamba venom, function as L-type calcium channel blockers, inducing vasorelaxation in smooth muscle tissue and demonstrating hypotensive effects (de Weille *et al.,* 1991). Additionally, muscarinic toxin α (MTα), another three-finger toxin from snake venom, has been identified as a potent antagonist for the α2B adrenoreceptor, making it a potential treatment option for managing blood pressure disorders (Koivula *et al.,* 2010

### 2.3.1.4 Beta-Cardotoxin

β-cardiotoxin, isolated from the king cobra (*Ophiophagus hannah*) venom, as a compound capable of blocking β1 and β2 adrenergic receptors, leading to decreased heart rates both *in vivo* and *in vitro* without noticeable cytotoxicity due to structural features limiting membrane interaction. However, it exhibits cytotoxic effects on smooth muscle cells but not on skeletal cells or cardiac myocytes. Additionally, β-cardiotoxin shows direct negative inotropic and lusitropic effects without altering intracellular calcium concentration during systole, suggesting mechanisms independent of adrenergic receptor (AR) activation. This highlights its potential utility in pharmacological research targeting adrenergic receptor subtypes, which play critical roles in managing cardiovascular system (CVS) pathologies such as hypertension, chronic heart failure, and arrhythmias (Rajagopalan *et al.,* 2007).

## 2.3 Drugs Derived from Snake Venom

Snake venom has been used since ancient times for both biological and medicinal purposes. In Ayurveda, it was utilized for treating gastrointestinal diseases and arthritis from the 7th century onward, and ancient Greeks also noted its pharmacological effects. Its medicinal use continued into the 19th century, with cobra venom being used for conditions like heart disease and cancer since 1853. Small doses of cobra venom have shown potent analgesic effects, outperforming morphine without addiction. The development of 'captopril,' derived from Bothrops jararaca venom, marked a significant advancement in venom-based drugs, while recent research has improved the understanding of snake venom components.

**Table 1: Snake Venom Toxins with Therapeutic Potential Against Cardiovascular disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Toxins | Drug | Source | Main biological target | Mechanism of Action | References |
| Bradykinin-potentiating peptides (BPPs) | Captopril | Brazilian pit viper | Angiotensin converting  enzyme (ACE) | Captopril works by inhibiting the ACE enzyme, which is responsible for converting angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor, so its reduction leads to:  1.Relaxation of blood vessels.  2.Reduced blood pressure.  3.Decreased sodium and water retention. | Kodama *et al.,* 2015; Frangieh *et al.,* 2021; Lu *et al.,* 2023) |
| Echistatin | Tirofiban | Echis carinatus | Fibrinogen | Tirofiban blocks the glycoprotein IIb/IIIa receptor on platelets.  Preventing the binding of fibrinogen and other adhesive molecules to these receptors, it reduces clot formation. | (Wang and Zou, 2023; Lazarovici *et al.,* 2019) |
| Barbourin | Eptifibatide | Sistrurus miliarius barbourin | Fibrinogen | Eptifibatide binds reversibly to the glycoprotein IIb/IIIa receptor on platelets, which is the final common pathway for platelet aggregation.  By blocking fibrinogen and von Willebrand factor binding to these receptors, it inhibits platelet aggregation and thrombus formation. | (Adeoye *et al.,* 2024; Lazarovici *et al.,* 2019) |
| Snake venom thrombin-like enzyme (Batroxobin) | Reptilase/Plateltex | Bothrops atrox | Fibrinogen | Reptilase cleaves fibrinopeptide A from fibrinogen, converting it into fibrin. | (Lan *et al.,* 2024). |
| Metalloproteinase (Moojenin) | Defibrase | Bothrops moojeni | Fibrinogen | Defibrase acts by breaking down fibrin, a key protein involved in blood clot formation, and indirectly affecting the coagulation cascade | ((Estrada *et al.,* 2022; Chen *et al.,* 2018) |
| Snake venom thrombin-like enzyme | Vivostat | Bothrops moojeni | Fibrinogen | It involves the use of autologous blood to produce a fibrin-based sealant or platelet-rich fibrin (PRF), which aids in hemostasis, tissue sealing, and wound healing | (Bayer *et al.,* 2020) |

# 3.Conclusion

Snake venom toxins exhibit a wide range of biochemical properties, enabling them to target specific systems in the human body with remarkable precision and potency. This unique attribute has made them promising candidates for the development of novel drugs, particularly for cardiovascular diseases. However, their potent effects necessitate stringent controls to mitigate toxicity. Future venom research should prioritize the exploration of unstudied snake species to uncover novel bioactive compounds for drug development and diagnostic applications. Advances in ultrasensitive analytical techniques are essential to investigate components present in minute quantities, which may hold significant therapeutic potential.

Cutting-edge technologies, including recombinant DNA technology, proteomics, transcriptomics, and genomics, combined with structural determination methods such as X-ray crystallography and NMR spectroscopy, are revolutionizing snake venom research. These approaches facilitate a detailed biomolecular characterization of newly discovered compounds, potentially leading to the identification of innovative therapeutic agents.

As the understanding of molecular targets in various diseases expands, snake venoms can serve as a rich resource for discovering and designing new scaffolds for lead compounds. Nevertheless, critical challenges such as ensuring safety, managing toxicity, optimizing pharmacokinetics, and developing smart delivery systems for venom-derived drugs must be thoroughly addressed to unlock their full therapeutic potential.

# References

Adeoye O. Broderick J. Derdeyn CP, G. J. (2024). Adjunctive Intravenous Argatroban or Eptifibatide for Ischemic Stroke. *The Journal of Emergency Medicine, 391*(9), 810-820.

Alejandro, S. (2007). *"Diapsids III: Snakes" Father Sanchez's Web Site of West Indian Natural History*. Retrieved from http://www.kingsnake.com/Westindian/metazoa12.html.

Antzelevitch, C. (2005). Cellular, Molecular, and Pharmacologic Mechanisms Underlying Drug-Induced Cardiac Arrhythmogenesis. In J. Morganroth, and I. Gussak, *Cardiac Safety of Noncardiac Drugs.* (pp. 255-260). UK: Humana Press. doi:https://doi.org/10.1007/978-1-59259-884-7\_3

Asega, A. F., Menezes, M. C., Trevisan-Silva, D., Cajado-Carvalho, D., Bertholim, L., and Oliveira, A. K. (2020). Cleavage of proteoglycans, plasma proteins and the platelet derived growth factor receptor in the hemorrhagic process induced by snake venom metalloproteinases. *Scientific Report, 10*(1), 12912. doi:10.1038/s41598-020-69396-y

Averin, A., and Utkin, Y. N. (2021). Cardiovascular Effects of Snake Toxins: Cardiotoxicity and Cardioprotection. *ACTA NATURAE, 13*(3 (50)), 1-11.

Bayer, A., Höntsch, G., Kaschwich, M., Dell, A., Siggelkow, M., Berndt, R., . . . Cremer, J. (2020). Vivostat Platelet-Rich Fibrin® for Complicated or Chronic Wounds-A Pilot Study. *Biomedicines, 8*(8), 276. doi:10.3390/biomedicines8080276.

Bedraoui, A., Suntravat, M., El-Majjad, S., Enezari, S., Oukkachi, N., Sanchez, E., . . . Daouda, T. (2024). Therapeutic potential of snake venom: Toxin distribution and opportunities in deep learning for novel drug discovery. *Medicine in Drug Discovery , 100175*, 1-11. doi:https://doi.org/10.1016/j.medidd.2023.100175

Berg, O. G., Gelb, M. H., Tsai, M. D., and Jain, M. K. (2001). Interfacial enzymology: the secreted phospholipase A2 -paradigm. *Chem. Rev., 101*, 2613–54.

Bittenbinder, M., van Thiel, J., and Cardoso, F. (2024). Tissue damaging toxins in snake venoms: mechanisms of action, pathophysiology and treatment strategies. *Communication Biology*(358), 1-15. doi: https://doi.org/10.1038/s42003-024-06019-6

Camargo, L. C., Gering., I., Mastalipour, M. A., Kraemer‐Schulien, V., Bujnicki, T., Willbold, D., . . . Raphael, E. (2024). A Snake Venom Peptide and Its Derivatives Prevent Aβ42 Aggregation and Eliminate Toxic Aβ42 Aggregates In Vitro. *ACS Chemical Neuroscience, 15*, 2600−2611. doi:https://doi.org/10.1021/acschemneuro.4c00089?urlappend=%3Fref%3DPDFandjav=VoRandrel=cite-as

Chen, J., Sun, D., Liu, M., Zhang, S., and Ren, C. (2018). efibrinogen Therapy for Acute Ischemic Stroke: 1332 Consecutive. *Cases of Sceintific Report, 8*(1), 9489. doi:10.1038/s41598-018-27856-6

Cintra, A., Vieira, C., and Giglio, J. (1990). Primary Structure and Biological Activity of Bradykinin Potentiating Peptides from Bothrops Insularis Snake Venom. *Journal of Protein Chemistry, 9*(2), 221–227.

Claudiana, L., Claudiana, L., Mirian, A. F., Juliano, R. G., Eduardo, F. O., Ivo, L., . . . Henning, U. (2010). The central nervous system as target for antihypertensive actions of a proline-rich peptide from Bothrops jararaca venom. *Cytometry Part A, 77*(3), 220-230. doi:doi: 10.1002/CYTO.A.20860

Costa, R., Burin, S., Menaldo, D., de Castro, F., and Sampaio, S. (2014). Snake venom L-amino acid oxidases: an overview on their antitumor effects. *Journal of Venomous Animals and Toxins including Tropical Diseases, 20*(23), 1-7. doi:http://www.jvat.org/content/20/1/23

Darwish, D., Masoud, H., Abdel-Monsef, M., Helmy, M., and Zidan, H. I. (2021). Phospholipase A2 enzyme from the venom of Egyptian honey bee Apis mellifera lamarckii with anti-platelet aggregation and anti-coagulation activities. *Journal of Genetic Engineering and Biotechnology, 19*(10), 1-10.

Database. (2023). *The Reptile.* Retrieved from http://www.reptile-database.org/db-info/SpeciesStat.html

de Franca, S., and Tambourgi, D. (2023). Hyaluronan breakdown by snake venom hyaluronidases: From toxins delivery to immunopathology. *Frontier Immunolnogy*, 1125899. doi:https://doi.org/10.3389/fimmu.2023.1125899

de Weille, J., Schweitz, H., Maes, P., Tartar, A., and Lazdunski, M. (1991). Calciseptine, a peptide isolated from black mamba venom, is a specific blocker of the L-type calcium channel. *National Academy of Sciences of the United States of America , 15*(88(6)), 2437-40.

Dubovskii, P., Konshina, A., and Efremov, R. (2013). Cobra cardiotoxins: membrane interactions and pharmacological potential. *Current Medicinal Chemistry., 21*, 270–287.

Dyba, B., Rudolphi-Szydło, E., Barbasz, A., Czyzowska, A., Hus, ˙., Petrilla, V., . . . Bocian, A. (2021). Effects of 3FTx Protein Fraction from Naja ashei Venom on the Model and Native Membranes: Recognition and Implications for the Mechanisms of Toxicity. *Molecules, 26*( 2164), 1-22. doi:https://doi.org/10.3390/molecules26082164

Erij, M. (. (2023). Snake Venom Components as Therapeutic Drugs in Ischemic Heart Disease. . *Biomolecules, 7*. doi:doi10.3390/biom13101539

Estrada, J., Rodrigues, K., Maciel, A., Bannwart, C., Dias, W., Hamoy, M., . . . Prado, A. (2022). BmooMPα-I, a Metalloproteinase Isolated from Bothrops moojeni Venom, Reduces Blood Pressure, Reverses Left Ventricular Remodeling and Improves Cardiac Electrical Conduction in Rats with Renovascular Hypertension. *Toxins (Basel)., 14*(11), 766. doi:10.3390/toxins14110766

Feofanov, A., Sharonov, G., Astapova, M., Rodionov, D., and Utkin, Y. (2005). Cancer cell injury by cytotoxins from cobra venom is mediated through lysosomal damage. *Biochemistry Journal, 390*, 11-18.

Ferraz, C., Arrahman, A., Xie, C., Casewell, N., Lewis, R., and Kool, J. F. (2019). Multifunctional Toxins in Snake Venoms and Therapeutic Implications: From Pain to Hemorrhage and Necrosis. *Frontier Ecololgy Evolution, 7*(218), 1-19. doi:https://doi.org/10.3389/fevo.2019.00218

Ferreira, S. (1965). Bradykinin-Potentiating Factor (BPF) Present in the Venom of Bothrops Jararaca. *British Journal of Pharmacology and Chemotherapy, 24*, 163–169.

Frangieh, J., Rima, M., Fajloun, Z., Henrion, D., J.-M., S., Legros, C., and Mattei, C. (2021). Snake Venom Components: Tools and Cures to Target Cardiovascular Diseases. *Molecules, 26*(2223), 1-14. doi:https://doi.org/10.3390/molecules26082223

Frangieh, J., Rima, M., Fajloun, Z., Henrion, D., Sabatier, J.-M., Legros, C., and Mattei, C. (2021). Snake Venom Components: Tools and Cures to Target Cardiovascular Diseases. *Molecules, 26*(2223), 1-14. doi:https://doi.org/10.3390/molecules26082223

Freuville, L., Matthys, C., Quinton, L., and Gillet, J.-P. (2024). Venom-derived peptides for breaking through the glass ceiling of drug development. *Frontier Chemistry., 12*(1465459). doi:doi: 10.3389/fchem.2024.1465459

Gary, W., Moore., G., and Moore, W. (2021). Snake Venoms in Diagnostic Hemostasis and Thrombosis. . *Seminars in Thrombosis and Hemostasis*, 15-20. doi:doi: 10.1055/S-0041-1732465

Gasanov, S., Dagda, R., and Rael, E. (2014). Snake Venom Cytotoxins, Phospholipase A2s, and Zn2+-dependent Metalloproteinases: Mechanisms of Action and Pharmacological Relevance. *Journal of Clinical Toxicology, 4*(1). doi:doi: 10.4172/2161-0495.1000181.

Gold, B., Dart, R., and Barish, R. (2002). Bites of venomous snakes. *New England Journal of Medicine, 347*(5), 347–56. doi:10.1056/NEJMra01347

Gouda, A., and Mégarbane, B. (2021). Snake venom-derived bradykinin-potentiating peptides: A promising therapy for COVID-19? *Drug Development Research*(82), 38–48. doi:https://doi.org/10.1002/ddr.21732

Gutiérrez, J., Calvete, J., Habib, A., Harrison, R., Williams, D., and Warrell, D. (2017). Snakebite envenoming. *Nature Reviews Disease Primers, 3*(17063), 1-10. doi:10.1038/nrdp.2017.63

Hernández-Kelly, L., and Ortega, A. (2020). A unique snake venom neuritogenesis mechanism: A cornerstone in the treatment of neurodegenerative diseases? *Journal of Neurochemistry, 1*(3), 1-3. doi:DOI: 10.1111/jnc.15196

Horng, H. C. (2013). Chronic natriuretic peptide protein therapeutics. *BMC Clinical Pharmacology, 3*. doi:doi: 10.1186/2050-6511-14-S1-O1

Hwang, S.-M., Jo, Y.-Y., Cohen, C., Kim, Y.-H., Berta, T., and Park, C.-K. (2022). Venom Peptide Toxins Targeting the Outer Pore Region of Transient Receptor Potential Vanilloid 1 in Pain: Implications for Analgesic Drug Development. *International Journal of Molecular Sciences, 23*(10), 5772. doi:https://doi.org/10.3390/ijms23105772

Jacinthe, F., Mohamad, R., Ziad, F., Daniel, H., Jean-Marc, S., Christian, L., and César, M. (2021). Snake Venom Components: Tools and Cures to Target Cardiovascular Diseases. *Molecules,, 6*, 12-18. doi:doi: 10.3390/MOLECULES26082223

Kerkelä, R., Ulvila, J., and Magga, J. (2015). Natriuretic Peptides in the Regulation of Cardiovascular Physiology and Metabolic Events. *Journal of the American Heart Association, 4*(e002423), 1-14. doi:DOI: 10.1161/JAHA.115.002423

Kessler, P., Marchot, P., Silva, M., and Servent, D. (2017). The Three-Finger Toxin Fold: A Multifunctional Structural Scaffold Able to Modulate Cholinergic Functions. *Journal of Neurochemistry., 142*, 7–18.

Kini, R., and Koh, C. (2016). Snake venom three-finger toxins and their potential in drug development targeting cardiovascular diseases. *Biochemical Pharmacology*(114105), 1-30. doi:https://doi.org/10.1016/j.bcp.2020.114105

Kodama, R., Cajado-Carvalho, D., Kuniyoshi, A., Kitano, E., Tashima, A., Barna, B., . . . Portaro, F. (2015). New proline-rich oligopeptides from the venom of African adders: Insights into the hypotensive effect of the venoms. *Biochimica et Biophysica Acta, 1850* (2015), 1180–1187. doi:http://dx.doi.org/10.1016/j.bbagen.2015.02.005

Koh, C. Y., Modahl, C. M., Kulkarni, N., and Kini, R. M. (2018). oxins are an excellent source of therapeutic agents against cardiovascular diseases. *In Seminars in Thrombosis and Hemostasis, 44*(7), 691-706.

Koh, C., and Kini, R. (2019). Biochemists’ bliss: harnessing the power of snake toxins to treat cardiovascular diseases. *Venoms and Toxins*, 10-14.

Koivula, K., Rondinelli, S., and Näsman, J. (2010). The three-finger toxin MTalpha is a selective alpha(2B)-adrenoceptor antagonist. *Toxicon, 56*(3), 440-447. doi:doi: 10.1016/j.toxicon.2010.05.001

Koludarov, I., Senoner, T., Jackson, T., Dashevsky, D., Heinzinger, M., Aird, S., and Rost, B. (2023). Domain loss enabled evolution of novel functions in a gene superfamily. *bioRxiv*, 1-30. doi:https://doi.org/10.1101/2023.13.15.520616

Lan, D., Zhang, X., Huang, X., Li, J., Song, J., Zhou, D., and Meng, R. (2024). Anti-inflammatory Effect of Batroxobin Combined With Anticoagulation in Patients With Cerebral Venous Thrombosis. *Clinical and Applied Thrombosis/Hemostasis (CATH), 10760296241264516*, 1-22. doi:10.1177/10760296241264516.

Laraba‑Djebar, F., and Chérif, F. (2021). Bioactive Molecules Derived from Snake Venoms with Therapeutic Potential for the Treatment of Thrombo‑Cardiovascular Disorders Associated with COVID‑19. *The Protein Journal, 40*, 799–841. doi:https://doi.org/10.1007/s10930-021-10019-4

Lazarovici, P., Marcinkiewicz, C., and Lelkes, P. (2019). From Snake Venom's Disintegrins and C-Type Lectins to Anti-Platelet Drugs. *Toxins Basel, 11*(5), 303. doi:10.3390/toxins11050303.

Ledsgaard, L., Wade, J., Jenkins, T., Boddum, K., Oganesyan, J., . Harrison, J., . . . Karatt-Vellatt, A. (2023). Discovery and optimization of a broadlyneutralizing human monoclonal antibody neutralizing human monoclonal antibody against long-chain α-neurotoxins from snakes. *Nature Communications, 14*(682), 1-9. doi:https://doi.org/10.1038/s41467-023-36393-4

Lei, M., Salvage, S., Jackson, A., and Huang, C.-H. (2024). Cardiac arrhythmogenesis: roles of ion channels and their functional modification. *Frontier Physiology, 15*(1342761.), 1-23. doi:doi: 10.3389/fphys.2024.1342761

Lu, H., Jiang, X., He, L., Ji, X., Li, X., Liu, S., . . . Zhang, W. (2023). Endothelial Sp1/Sp3 are essential to the effect of captopril on blood pressure in male mice. *Nature Communication, 14*(1), 5891. doi:10.1038/s41467-023-41567-1

Mangiafico, S., Costello-Boerrigter, L., Andersen, I., Cataliotti, A., and Burnett, J. J. (2013). Neutral endopeptidase inhibition and the natriuretic peptide system an evolving strategy in cardiovascular therapeutics. *European Heart Journal, 34*, 886–893.

Manjunatha, R., and Yeow, K. C. (2020). Snake venom three-finger toxins and their potential in drug development targeting cardiovascular diseases. *Biochemical Pharmacology*, 1-30. doi:https://doi.org/10.1016/j.bcp.2020.114105

Marte, F., Sankar, P., and Cassagnol, M. (2022). Captopril. *Treasure Island (FL): In StatPearls;*, 85-96.

Monsalve, R., Gutierrez, R., Hoof, I., and Lombardero, M. (2020). Purification and molecular characterization of phospholipase, antigen 5 and hyaluronidases from the venom of the Asian hornet (Vespa velutina). *PLoS One, 15*, e0225672.

Morais, K., Hayashi, M., Bruni, F., Lopes-Ferreira, F., Camargo, A., Ulrich, H., and Lameu, C. (2011). Bj-PRO-5a, a natural angiotensin-converting enzyme inhibitor, promotes vasodilatation mediated by both bradykinin B2 and M1 muscarinic acetylcholine receptors. *Biochemical Pharmacology, 81*(2011), 736–742.

Munawar, A., Ali, S., Akrem, A., and Betzel, C. (2018). Review: Snake Venom Peptides: Tools of Biodiscovery. *Toxins, 10*(474), 1-29. doi: doi:10.3390/toxins10110474

Munawar, A., Zahid, A., Negm, A., Akrem, A., Spencer, P., and Betzel, C. (2016). Isolation and Characterization of Bradykinin Potentiating Peptides from Agkistrodon Bilineatus Venom. *Proteome Science., 14*(1), 1-10.

Nicola, M., Pontara, A., Kass, G., Kramer, N., Avella, I., and Pampena, R. (2021). Vipers of Major Clinical Relevance in Europe: Taxonomy, Venom Composition, Toxicology and Clinical Management of Human Bites. *Toxicology., 453* , 152724. doi:10.1016/j.tox.2021.152724

Oliveira, A. L., Viegas, M., da Silva, S., Soares, A., Fernandes, M., and Fernandes, F. (2022). The chemistry of snake venom and its medicinal potential. *NATuRe RevIew*, 1-19. doi:https://doi.org/10.1038/s41570-022-00393-7

Pinheiro-Júnior, E., Boldrini-França, J., de Campos Araújo, L., Santos-Filho, N., Bendhack, L., Cilli, E., and Arantes, E. (2018). LmrBPP9: A Synthetic Bradykinin-Potentiating Peptide from Lachesis Muta Rhombeata Venom That Inhibits the AngiotensinConverting Enzyme Activity in Vitro and Reduces the Blood Pressure of Hypertensive Rats. *Peptides, 102*, 1–7.

Rajagopalan, N., Pung, Y., Zhu, Y., Wong, P., Kumar, P., and Kini, R. (2007). Beta-cardiotoxin: a new three-finger toxin from Ophiophagus hannah (king cobra) venom with beta-blocker activity. *Official publication of the Federation of American Societies for Experimental Biology Journal, 21*(13), 3685-95. doi:10.1096/fj.07-8658com

Roman-Ramos, H., Prieto-da-Silva, Á., Dellê, H., Floriano, R., Dias, L., Hyslop, S., . . . de Oliveira, J. (2024). The Cloning and Characterization of a Three-Finger Toxin Homolog (NXH8) from the Coralsnake Micrurus corallinus That Interacts with Skeletal Muscle Nicotinic Acetylcholine Receptors. *Toxins,, 16*(164), 1-25. doi:doi: 10.3390/toxins16040164

Sani, I., Umar, A., Hassan, S., Faruq, U., Abdulhamid, A., Bello, F., and Fakai, I. (2019). Major Enzymes from Snake Venoms: Mechanisms of Action and Pharmacological Applications. *Asian Journal of Biological Science, 12* (3), 396-403. doi:DOI: 10.3923/ajbs.2019.396.403

Sciani, J., and Pimenta, D. (2017). The modular nature of bradykininpotentiating peptides isolated from snake. *Journal of Venomous Animals and Toxins including Tropical Diseases, 23*(45), 1-8. doi:DOI 10.1186/s40409-017-0134-7

Shahriyar, K., and Chaim, O. (2022). Exploring Venom Toxins as Molecular Models for Chronic Pain Treatment. *Journal of Student Research, 11*(1), 1-10. doi:https://doi.org/10.47611/jsrhs.v11i1.2365

Slagboom, J., Kool, J., Harrison, R., and Casewell, N. (2017). Haemotoxic snake venoms: their functional activity, impact on snakebite victims and pharmaceutical promise. *British Journal of Haematology, 177*, 947–959. doi:doi: 10.1111/bjh.14591

Soares, M., Oliveira-Carvalho, A., Wermelinger, L., Zingali, R., Ho, P., Junqueira-de-Azevedo, I., and Diniz, M. (2005). Identification of Novel Bradykinin-Potentiating Peptides and C-Type Natriuretic Peptide from Lachesis Muta Venom. *Toxicon, 36*, 31–38.

Sofyantoro, F., Yudha, D., Lischer, K., Nuringtyas, T., Putri, W., Kusuma, W., . . . Swasono, T. (2022). Bibliometric Analysis of Literature in Snake Venom-Related Research Worldwide (1933–2022). *Animals, 12*(2058), 1-20. doi:https://doi.org/10.3390/ani12162058

Talukdar, A., Maddhesiya, P., Namsa, N., and Doley, R. (2022). Snake venom toxins targeting the central nervous system. *Toxin Reviews*, 1-25. doi:10.1080/15569543.2022.2084418

Tasoulis, T., Pukala, T., and Isbister, G. (2022). Abundance in Snake Venom Proteomes. *Front. Pharmacol., 12*(768015), 1-13. doi:https://doi.org/10.3389/fphar.2021.768015

Tsai, T., Wang, Y., and Tsai, I. (2022). Sequence determination and bioinformatic comparison of ten venom serine proteases of Trimeresurus gracilis, a Taiwanese endemic pitviper with controversial taxonomy. *Toxicon , 206*, 28-37.

Utkin, Y. N. (2019). Last decade update for three-finger toxins: Newly emerging structures and biological activities. *World Journal of Biological Chemistry, 10* (1), 17-27. doi:https://dx.doi.org/10.4331/wjbc.v10.i1.17

Vaiyapur, S., Wagstaff, S., . Harrison, R., Gibbins, J. M., and Hutchinson, E. (2011). Evolutionary Analysis of Novel Serine Proteases in the Venom Gland Transcriptome of Bitis gabonica rhinoceros. *PLoS ONE, 6*(6), e21532. doi:10.1371/journal.pone.0021532

Vilca-Quispe, A., Alvarez-Risco, A., Gomes Heleno, M., Ponce-Fuentes, E., Vera-Gonzales, C., Zegarra-Aragon, H., . . . Ponce-Soto, L. (2023). Biochemical and hemostatic description of a thrombin-like enzyme TLBro from Bothrops roedingeri snake venom. *Frontier Chemistr., 11*(1217329), 1-11. doi:doi: 10.3389/fchem.2023.1217329

Vuong, N., Jackson, T., and Wright, C. (2021). Role of Phospholipases A2 in Vascular Relaxation and Sympatholytic Effects of Five Australian Brown Snake, Pseudonaja spp., Venoms in Rat Isolated Tissues. *Frontier Pharmacology, 12*(754304.), 1-21.

Wang, J., and Zou, D. (2023). Tirofiban-induced thrombocytopenia. *Annual Medicine, 55*(1), 2233425. doi:10.1080/07853890.2023.2233425.

Wei, F., Ang, C., Yeow, K., R., and Manjunatha, K. (2022). From Snake Venoms to Therapeutics: A Focus on Natriuretic Peptides. *Pharmaceuticals, 5*, 10-23. doi:doi: 10.3390/ph15091153

WHO. (2023). *Snakebite Envenoming Key Facts.* Retrieved from https://www.who.int/news-room/factsheets/detail/snakebite-envenomin.

Yang, D., Deuis, J., Dashevsky, D., Dobson, J., Jackson, T., Brust, A., . . . Hendrikx, I. (2016). The Snake with the Scorpion’s Sting: Novel Three-Finger Toxin Sodium Channel Activators from the Venom of the Long-Glanded Blue Coral Snake (Calliophis bivirgatus). *Toxins, 8*(303), 1-40.

Yue, Y., Yu, H., Li, R., and Li, P. (2021). Tropical Exposure to Nemopilema nomurai Venom Triggers Oedematogenic Effects: Enzymatic Contribution and Identification of Venom Metalloproteinase. *Toxins (Basel), 13*, 44.

Zhang, C., Medzihradszky, K., Sánchez, E., Basbaum, A., and Julius, D. (2017). Lys49 myotoxin from the Brazilian lancehead pit viper elicits pain through regulated ATP release. *Proceedings of the National Academy of Sciences*, 1-9. doi:doi:10.1073/pnas.1615484114/-/DCSupplemental