# The potential benefits of snake venom

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**Abstract.** Snake venom is one of the most lethal saliva toxins in the world. It consists of more than 20 distinct compounds, mainly of which are proteins， peptides or polypeptides. Proteins are responsible for 90%-95% of snake venom's dry weight and are capable of some biological uses. The venom facilitates digestion and immobilization of prey and can help the snake to resist threats as well. Snake bites can easily kill a human or any other animal species. There are multiple sorts of snake venom with different toxicity abilities, causing various physiological effects. While snake venom is considered as a highly risky toxin, it still can be used to benefit human beings. For example, in the biomedical area, specific snake venom can treat serval diseases and even has a cosmetic effect. This article will solve the question that how snake venom can be lethal and beneficial at the same time, and how it be used to contribute to biological resources.

**Keywords:** snake venom, toxicity, treating potential.

## 1. Introduction

Snake venom is a highly toxic saliva stored in a large gland called alveoli before it's injected. Normally salivary glands are located on each side of the head, usually below and behind the eyes. Snakes injected their venom by biting prey, releasing the venom when penetrates the prey's skin. Snakes have different shapes and lengths of fangs due to evolution, and studies showed that those differences are because of various biomedical properties of their prey [1]. Annually, there are about 2.5 million people attacked by snake, and more than one hundred thousand would die because of that [2]. Because of the small body shape of snakes, a lot of people wouldn't aware until they are bitten. The symptom of a snake bite is the puncture mark at the wound firstly, accompanied by the severe pain around bite site. Sometimes there would be redness, swelling and bleeding around the bite. If it goes seriously, there will be nausea, vomiting, or diarrhea situations, then rapid heart rate, and slow pulse, which is life threat. There would be more fatal cases if people don't seek medical help immediately. World Health Organization (WHO) has already listed snake bite as a neglected tropical disease (NTD). Averagely, the $LD_{50}$ of snakes in mice is 0.03mg/kg, and there are 130-250 milligrams of venom yield in mice. Although the pathological effect is diverse, it can be classified into three categories: neurotoxicity, hemotoxicity, and cytotoxicity. [3]

According to Casewell's study, the pathological consequences of neurotoxicity will result in respiratory failure and neuromuscular paralysis by blocking neuromuscular transmission. Three-finger toxins (3FTxs), a small toxin protein, play important roles in neurotoxicity toxins, which inhibits the binding of acetylcholine [4]. Hemotoxic venom is always produced by snakes of the family Viperidae, including rattlesnakes, mostly in Latin American countries, as shown in Roldán-Padrón's article. [5] The pathological effect of hemotoxicity acts on blood vessels and components of the coagulation cascade, causing bleeding problems like hypotension or systemic hemorrhage [3]. There are four main hemotoxic enzymes: snake venom serine proteases (SVSP), snake venom hyaluronidases (SVH), snake venom metalloproteases (SVMP), and phospholipases A2 (PLA2). However, the information and studies on SVH aren't popular [5]. The pathological consequence of cytotoxicity is at the region around the bite site, showing situations like swelling, blistering, and local tissue necrosis [3].

There are two major enzymes of snake venom which are phospholipase A2 (PLA2) and L-amino acid oxidase (LAAO), which demonstrate cytotoxic effects on cancer cells [6]. It is also said that PLA2 can catalyze the hydrolysis of phospholipids, producing free fatty acids and lysophospholipids.

The venom PLA2 possesses presynaptic or postsynaptic neurotoxicity and systemic or local myotoxicity. For LAAOs, some enzymes show potent platelet inhibitory actions, while others induce platelet aggregation [6]. Although there are three different types of snake venom, snake venom mainly consistes of proteins and enzymes, but different enzyme families and proteins are from distinct snake venom and they have their own specific treatments.

It seems like snake venom is dangerous and scary to people, but more and more studies are showing that it's beneficial to humans and the biomedical area. In Hiu's paper, it's said that LAAO and PLA2 are more effective in cancer cells than in normal cells. Therefore, they can be potential elements as treatment of cancer. Besides, snake venom can also be used as pain-killing agents. What enzymes are safe to use, how to distinguish them and how to purify them are crucial to know for the future use of snake venom.

## 2. Hemotoxicity

### 2.1. Phospholipase A2 (PLA2)

Although venomous has its bad reputation because of its toxicity, heart attacks and blood disorders can be treated by using the medicine extracted from hemotoxins [7]. Specifically, these medicines can help to decrease the possibilities of problems like kidney disease, heart failure, and disparities. Even some enzymes are the key element to heal cancer. For example, phospholipase type A2 from Tunisian viper, Cerastes cerastes, can be used in antitumor activities.

PLA2 consists of fatty acid and phospholipid at the sn-2 position, in which the bond is hydrolyzing between the second fatty acid also called "tail". The fatty acids are cleaved in the position of two phospholipids. From now, there are about 30 isoforms different in size, location, and function, which can be subdivided into six groups due to their structure. Those six families are: cytosolic PLA2 (cPLA2), calcium-independent PLA2 (iPLA2), secretory PLA2 (sPLA2), lysosomal PLA2 (LyPLA2), platelet activating factor acetylhydrolases (PAF- AH), and the recently discovered adipose specific PLA2 (AdPLA2) [8]. Table 1 summarizes the characteristics of PLA2 families.

**Table 1** Phospholipase A2 classification and pathologies associated with secretory phospholipase A2. [9]

| **PLA2 family** | **Group** | **Gene name** | **Source** | **MW (kDa)** | **Catalytic Residues** | **[$Ca^{2+}$]** | **Pathologies** |
|---|---|---|---|---|---|---|---|
| CPLA2 | IVA to F | PLA2G4A to F | Human/ murine | 60-85 | Ser/Asp | uM | N/A |
| iPLA2 | VIA to F | PLA2GVIA to F | Human/ murine | 28-146 | Ser/Asp | None | N/A |
| PAF-AH | VIIA&VIIB | PLA2G7A, PLA2G7B | Human/ murine/pro-cine/bovine | 40-45 | Ser/His/Asp | None | N/A |
| | VIIIA&VIIIB | PLA2G8A, PLA2G8B | Human | ~26 | Ser/His/Asp | | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ly-PLA2 | XV | PLA2G15 | Human | ~45 | Ser/His/Asp | None | N/A |
| AdPLA2 | XVI | PLAG16 | Human Adipocyte | ~18 | His/Cys | None | N/A |
| sPLA2 | IA | PLA2G1A | Cobras and Kraits | ~14 | His/Asp | mM | N/A |
| | IB | PLA2G1B | Human/ porcine/ pancreas | ~14 | | | N/A |
| | IIA | PLA2G2A | Human synovial/ Rattlesnakes | ~14 | | | Arthritis, atherosclero-sis, sepsis, cancer |
| | IIB | PLA2G2B | Gaboon viper | ~14 | | | N/A |
| | IIC | PLA2G2C | Rat/muri-ne testis/Hu-man/mur-ine | ~14 | | | N/A |
| | IID | PLA2G2D | Human/murine/ pancreas/spleen | ~14 | | | Chronic obstructive pulmonary disease, asthma |
| | IIE | PLA2G2E | Human/murine/ brain/ heart/ uterus | ~14 | | | Ulcerative colitis, chronic rhinosinusitis |
| | IIF | PLA2G2F | Human/murine/ testis/ embryo | ~14 | | | Atopic dermatitis, colorectal cancer |
| | III | PLA2G3 | Lizard/be-e/human/murine | ~55 | | | Colorectal cancer, atherosclerosis |
| | V | PLA2G5 | Human/murine | ~14 | | | Arthritis, atherosclerosis,sepsis, cancer, chronic hepatitis |
| | IX | PLA2G9 | Heart/ lung/mar-cophage Metazoa-n | ~14 | | | N/A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | X | PLA2G10 | Human spleen/ thymus/ leukocyte | ~17 | | | Arthritis, atherosclerosis, sepsis, cancer |
| | XIA | PLA2G11A | Green rice shoots | ~13 | | | N/A |
| | XIB | PLA2G11B | Green rice shoots | ~13 | | | N/A |
| | XIIA | PLA2G12A | Human murine | ~14 | | | Kuhnt-Junius degeneration, malignant glioma |
| | XIIB | PLA2G12B | Human murine | ~14 | | | Acute pancreatitis |
| | XIII | PLA2G13 | Parvovir-us | <10 | | | N/A |
| | XIV | PLA2G14 | Symbioti-c fungus/ bacteria | 13-19 | | | N/A |

In this study, sPLA2 families are mostly analyzed. From now, sPAL2 has 17 isoforms (Group I-III, V, IX-XIV). Normally, sPLA2 families are generally lighter than other PLA2 groups (around~13-14 kDa), except for group III [10]. Among all of those isoforms listed above, 11 of them are found in mammalian cells, that will promote inflammation. Additionally, sPLA2 needs calcium to fulfill its function and they need mM concentrations to operate. Consequently, sPLA2 isoforms usually work at the extracellular side of the cell [11]. According to Quach's article, sPLA2 hydrolyzes a large quantity number of phospholipids substrates by using its isoforms which generally function extracellularly on phospholipids mostly. It is also demonstrated that studying about the characteristics of isoforms of sPLA2 is significant to supervise the pathogenesis process and possible pharmacological targets to treat associated diseases. According to Zouari-Kessentini's studies, the presence of pharmacological sites on sPLA2 will allow it to bind to specific membrane-soluble proteins that join in the sPLA2 mechanism progression.

Although, the isoforms of sPLA2 may be the potential solutions to some associated disease, their overexpression of them lead to problems. The overexpression of the isoforms during the inflammation period and its related diseases like arthritis or sepsis. The promotion of inflammation is always because the catalyzation of the first step of arachidonic acid pathway by breaking phospholipids, forming fatty acids. There is also overexpression in different kinds of cancer. Some of the isoforms will cause the development of tumors. For example, the overexpression of sPLA2 isoforms is related to the poor clinical prognosis in prostate cancer [12]. On the other hand, the overexpression of some of the selected isoforms of sPLA2 in gastric cancer shows good performance in clinical studies [13].

Some of the studies have suggested that sPLA2 isoforms have an oncogenic role, and it's related to mammal inflammation, which will not be discussed thoroughly in this paper. However, this is not the whole story. Conversely, sPLA2 in Group V has anti-inflammatory effects by cleaning the residuals of the immune complex through cysteinyl leukotriene receptor phagocytosis [14]. Besides, isoforms of Group X sPLA2 have a negative relationship with colorectal cancer metastasis [15]. CC-PLA2-1, CC-PLA2-2, and MVL-PLA2 are sPLA2 isoforms from Cerastes cerastes venom, which presents high enzymatic activity. According to Zouari-Kessentini's paper, cell adhesion and migration are two fundamental steps in multiple diseases, as well as cancer. It is also said that the

adhesion and migration of human HT1080 and IGR39 cells can be inhibited from those enzymes, stopping future fibrinogen and fibronectin.

Above all, sPLA2 has effects on angiogenesis. Angiogenesis is very important to the body's works, like healing and embryo process [16]. However, these processes are also significant in the pathogenesis of some diseases, for example arthritis and cancer. Angiogenesis then plays a vital role in sustaining oxygen and nutrients in malignant cells for tumors to expand larger than microscopic size [16]. The good news is that CC-PLA-1 and CC-PLA-2 inhibit angiogenesis as well as the growth factors which induce angiogenesis, like VEGF and bFGF [17]. It is said that the anti-angiogenesis effect of PLA2 is because of the blockage of $\boldsymbol{\alpha}$v$\boldsymbol{\beta}$3 and $\boldsymbol{\alpha}$5$\boldsymbol{\beta}$1 integrins, which is well documented in the angiogenesis process. However, the inhibition of angiogenesis will also block the operation of VEGF and its receptors [16].

Generally speaking, all of those inconsistencies show that sPLA2 does not just have a single effect on the pathological areas, and sPLA2 isoforms can only be beneficial to specific cancer or disease due to their own structure and function. There's no direct relationship delivers that sPLA2 isoforms are involved in tumor promotion. Besides, the right does and using methods of venom used in healing disease is rigorous, and there should be certain rigorous demands for using snake venom in the biomedical area.

## 3. Neurotoxins

### 3.1. A-neurotoxins

Besides hemotoxicity, neurotoxins are also one of the most potent toxic effects of snake venom. They also contribute to clinical studies. Neurotoxins-based medicine can be used to treat brain strokes, Alzheimer disease, Parkinson's, and other related problems[7]. Additionally, neurotoxins can also be applied in anesthetic studies. Among all the neurotoxin elements in snake venom, the α-neurotoxins bind to nicotinic acetylcholine receptors (nAChRs) is the most well studied [18]. A-neurotoxins are a group of neurotoxin peptides and members of the three-figure toxin protein family. The general structure of α-neurotoxins contains 60-75 amino acid residues 4-5 disulfide bonds, three loops also called fingers, and a C-terminal tail. There are usually two types of α-neurotoxins which are: short-chain neurotoxins and long-chain neurotoxins. (Shown in Figure 2). The major difference between these two is the short type has 60-62 amino acid residues, while there are 66 or more residues in the long chain one. The short chain neurotoxins have only four disulfide bonds, but the long chain neurotoxins have one more disulfide bond on the second "finger" loop, including a longer C-terminal tail. They have a similar three-dimensional structure, but the characteristics and kinetic of association with the receptor are distinct.

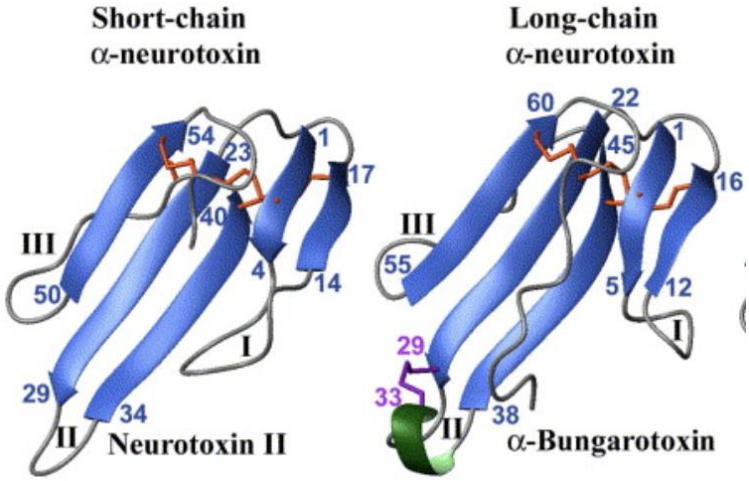


**Figure 1** Two classic structures of α-neurotoxins [19]

According to Koh's paper, nAChRs can help to reversibly blocking the transmission of nerves by competitively binding to the nAChRS located at the postsynaptic membranes of skeletal muscle and neurons. If things become serious, the prevention of neuromuscular transmission would lead to asphyxiation.

There are workable future applications of α-neurotoxins in many disease treatments. According to Koh, neurotoxins extracted from cobra venom have huge effects on the analgesia of animal models [18]. Cobrotoxin is a short-chain post-synaptic α-neurotoxin and α-cobra- toxin from the Naja genus, including cobra, which has been discovered that it shows analgesic activity. Additional evidence shows that cobrotoxin can even take place of anaesthetic drug like morphine because it can suppress the effect of morphine withdrawal [20]. In the experiment on mice, the toxin isolated from King cobra, *Ophiophagus hannah*, did not increase the conclusion threshold in the dose range of 8-64ng/g when the electroshock testing arrived at its maximum capacity [21]. It is also said that when the dose range comes to 16-32ng/g, there would be analgesic phenomena without any neurological and muscular deficits. There are already precedents that people use polypeptides or peptides toxins in medicine production [19]. For instance, the $Ca^{2+}$ channel blocker ω-conotoxin MVIIA, which is also called Ziconotide is a treatment for chronic pain in the market in Tsetlin and Hucho et al. Consequently, we can expect that it's highly possible that there would be more and more drugs based on neurotoxins like α-neurotoxins to have pain-killing function goes into the market. Not only snake venom can be used to produce clinical supplies, it can also be used in the cosmetic area. It can help to relax the facial muscles and even prevent wrinkles by paralyzing the muscle that can form wrinkles. Currently, there are beauty makeup products based on snake venom on the market or on websites like Amazon or eBay.

Scientists isolated muscarinic acetylcholine receptors (mAChRs), a neurotoxin, from green mamba venom. The muscarinic toxin (MT1-7) can also be used in physiological areas due to its potency and characteristics [18]. It is documented that there's a decrease in the variety of the neuronal AChRs as a result of Alzheimer's disease, which is a neurodegenerative disease[21]. From now there's no drug can stop the progress in Alzheimer's disease. According to World Alzheimer Report in 2015, the number of the elder population, who are over 60, is increasing, as well as the prevalence of chronic diseases, especially those popular among elder people. More seriously, the incidence of dementia increases as years passed. For people aged from sixty to sixty four, there is 0.003 percent to have Alzheimer's disease, and the number increases to 0.175 when the people are over 95. However, peptides isolated from snake venom provide optimistic prospects in treating Alzheimer's disease. As mentioned in Koh's article, subtype-specific mamba toxins can explain the involvement of muscarinic receptors in Alzheimer's disease. Peptides and polypeptides are important elements for Alzheimer's disease healing. Proteins derived from RVV-V peptides can disrupt the preformed Aβ-amyloid fibrils and spilt them into two, and protect human neuronal cells from the toxicity of Aβ-amyloid fibrils [22]. As a result, those proteins or peptides isolated from snake venom, like Russell's Viper's, provide opportunities and available references for treating Alzheimer's diseases.

## 4. Limitations

Although huge amount of evidence show that snake venom has biological friendly ingredients, that can be used in treating disease, whether medicine based on snake venom can be used widely and safely is still under suspicion. Pal's paper demonstrates that cobroxin and nyloxin are two venom-based medications for pain relief for arthritis and other disorders in the market. However, it is officially prohibited by US Food and Drug administration in 1970 because of its infectiveness [20]. There are very few available clinical studies using snake-venom based drugs, and extensive research on clinical work is urgently needed. There are also pharmacological properties found in anti-snake venom, as well as snake venom [7]. However, side effects are also shown in this article, for example, anaphylactic effects like hard breathing, reddening of the skin, or swelling phenomenon on the face or eyes. It's also possible to have pyrogen effects like fever and inflammation of joints.

Herbal components could be used to neutralize snake venom, managing the bites by stopping pain, controlling infections, adjusting the immune system, and improving the quality of life by ejecting energies [7]. Based on that fact, whether the negative effects and uncertainties of snake-venom based drugs can be avoided by plants' constitutions is worth thinking or not. It seems like there are some elements that have the potential to be used in the biomedicine area, but careful examination and multiple in vivo studies need to be taken before using the drugs on humans.

Lastly, moral standards and ethics problems need to have a look. Thousands of animals are essential for using when new drugs are conducted. All the in vivo experiments will use the animals approved by the Animal Wafare and Ethical Review Board of diverse universities, which in specific pathogen free conditions under licensed [4]. Probably, animals advocates would also cause future problems to performing more in vivo experiments.

## 5. Conclusion

Although snake venom is mostly considered as a toxic substance at first, there are multiple beneficial effects discovered by biomedical experts as time passes. There are various kinds of snake venom based on their functions and mechanism, and two of them are discussed in this passage: hemotoxicity and neurotoxicity. Some representative enzymes or proteins are selected to further illustrate their effects on biochemistry use. Snake venom based on hemotoxicity always causes problems in the blood system, but they are potential anti-cancer drugs and solutions to kidney problems, stroke, and heart attack. PLA2 is representative of hemotoxicity elements. It is mostly transformed from fatty acids and phospholipids. There is a large group of PLA2, including a huge amount of isoforms. sPLA2 family is the one that may be used in future biomedical applications. It can help to resist the development of cancer and inflammation as well. However, it does not mean that sPLA2 is a hundred percent safe. There are still problems. It will cause inflammation in some mammals and has negative effects on some specific kinds of cancers. These inconsistencies increase the uncertainties of using snake venom-based drugs for lethal diseases like cancer. Besides hemotoxicity, neurotoxicity is also one of the kinds of snake venom that produce benefits in the biomedical area. The nAChRs proteins are the key element in analgesia activities by preventing the transmission of neuromuscular. It's encouraging to find that this protein extracted from King cobra may replace morphine since there's no withdrawal reaction for the new anesthetics. As a matter of fact, there are successful in vivo experiments on mice, and whether venom-based anesthetics can be put on humans in surgeries is still a question worth investigating. As a neurotoxin, it also has a role in neuro related disease treatment like Alzheimer's disease. However, from now, there's no solid evidence showing that venom-based drugs can completely treat Alzheimer's disease. From all the above, leaving the traditional prejudice about snake venom, people have to admit that this seemingly risky chemical element is starting to make its way into the medical field. However, whether drugs or products based on snake venom can successfully be used in clinical areas is still unknown. Multiple studies and experiments need be done to ensure the safe use of snake venom. It's lucky to find that snake venom is highly possible to turn its notorious reputation into a good one.

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