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Medicinal potentials of snake venom components: A review

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Abstract

Over the last several decades, research on snake venom toxins has provided not only new tools to decipher molecular details of various physiological processes, but also inspiration to design and develop a number of therapeutic agents. Snake venom, though greatly feared, is a natural biological resource, containing several active compounds that have been employed in the development of new drugs to treat diseases. Snake venom is highly modified saliva containing more than 20 different compounds with toxic and lethal properties, mostly proteins and polypeptides which facilitate the immobilization and digestion of prey, and defends against threats. Some of the proteins in snake venom have very specific effects on various biological functions including blood coagulation, blood pressure regulation, and transmission of the nervous or muscular impulse, and have been developed for use as pharmacological or diagnostic tools. Phospholipases A_2 hydrolyze phospholipids and thus could act on bacterial cell surfaces, providing novel antimicrobial (antibiotic) activities. Snake venom metalloproteinases, L-amino acid oxidases, and phospholipase A_2 are paving new ways in oncology treatment. *Agkistrodon acutus* toxin (ACTX-6) demonstrated cytotoxic activity to various cancer cells *in vitro.* Bradykinin potentiating peptide (BPP9) (inhibitor of angiotensin-converting enzyme), isolated from the *Bothrops jararaca* snake venom, is in use for the production of Captopril, a potent antihypertensive drug and thus aids in prevention of cardiovascular disorders including stroke and heart attack. A novel analgesic toxin (hannalgesin) from the venom of king cobra (*Ophiophagus hannah*) has been shown to have far stronger analgesic effect than morphine. An interesting neurotoxic peptide with analgesic properties was isolated from king cobra (*Ophiophagus hannah*) venom and is called hannalgesin

Keywords: Snake; Venom; Medicinal; Potentials

1. Introduction

Snake venoms are the secretion of venomous snakes, which are synthesized and stored in specific areas of their body *i.e.* venom glands [1, 2]. The secretion is a natural biological resource, containing a complex mixture of enzymes, peptides and proteins of low molecular weight with specific chemical and biological activities [3, 4, 5]. Many of these compounds are harmless but some are neurotoxic, cardiotoxic and cytotoxic at certain degree [6, 7]. They are thus responsible for death of humans and animals [8, 9]. They cause significant mortality and morbidity worldwide, and strike fear in most of us [10]. Annually, more than two million people are bitten by snakes, with a mortality rate of more than four percent [11, 10]. These proteins not only inflict death to humans and animals, but also contain several components that could be of therapeutic potential value [12, 4]. It can be used for the treatment of some diseases [11,13]. Cytotoxic effects of snake venom have potential to degrade/destroy tumor cells [14, 15]. Chinese physicians use snake venom products routinely to treat stroke and view them as effective and relatively safe [8, 16]. Another good

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example is the inhibition of the angiotensin-converting enzyme (ACE) by the bradykinin potentiating peptide (BPP9) isolated from the *Bothrops jararaca* snake venom, which was used for the development of Captopril, a potent antihypertensive [17]. Other examples are snake venom peptides that inspired the development of tirofiban and epifibatide which are used to treat coagulopathies [18]. Additionally, thrombolytic agents have been used in several cases of vascular disorder, for example, the batroxobin, a serineprotease isolated from *Bothrops atrox* and *B. moojeni* snake venoms, was used to treat vascular thrombosis [19]. Concerning the treatment of other critical diseases, there is a great interest in drug design, in which venom toxins could provide structural templates for the study of new molecules or cellular mechanisms [20]. Just as life-saving drugs might become poisons with indiscriminate use, a poisonous substance such as snake venom could be used as a drug with proper administration. An overview of various snake venom components that have prospects in health and diseases and have been employed in successful treatment of certain diseases are discussed in this review. Some of the included molecules are under clinical trial and may find application for various drug developments in the near future.

1.1. Venom peptides in cardiovascular disorders

Snake venoms have evolved over millions of years, and some toxins have evolved to specifically target various sites in the cardiovascular system of prey animals, producing prey hypotension. So far, a number of specific hypotensive peptides have been identified from different snake venoms. These snake hypotensive peptides are divided into five classes: bradykinin potentiating peptides, natriuretic peptides, sarafotoxins, Phospholipases A_2 and L-type Ca^{2+} channel blockers (Figure 1). They differ widely in their structure, mechanism and points of action. Each class has many different isoforms with similar structures but different hypotensive activities. In the last decade, research efforts on snake hypotensive peptides have produced great advance in their understanding and applications in designing antihypertensive agents [21].

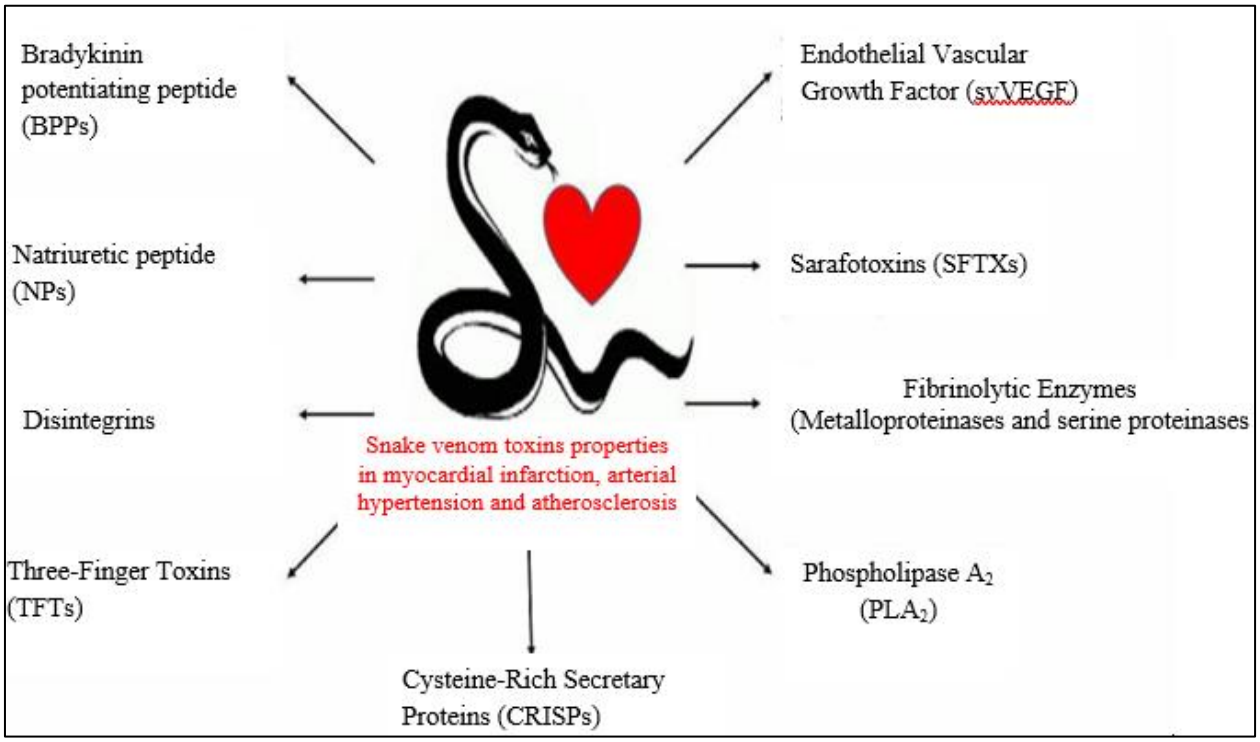

Figure 1 Snake venom peptides associated with cardiovascular diseases [22]

Bradykinin-potentiating peptide (BPP), causes hypotension on snakebite victims by acting as Angiotensin-Converting Enzyme inhibitor. Its principal function within the renin-angiotensin-aldosterone system (RAAS) (Figure 2) of snakebite victim is to prevent angiotensin II formation [23] The RAAS is activated primarily by decreased renal perfusion (mostly due to loss of blood volume or hypotension) and activation of renal β-adrenergic receptors. Once activated, the enzyme renin is secreted directly into circulation, initiating a metabolic cascade which ultimately results in the activation of angiotensin receptors and production of angiotensin II. Angiotensin II serves as a potent vasoconstrictor that also stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone acts upon the renal tubules thereby causing an increased retention of sodium and water at the expense of urinary potassium excretion. This RAAS activation process's net result is an increase in blood pressure and fluid retention.

Hypertension is a result of complex interplay of genetic and environmental factors [24]. It involves an intricate pathophysiology, with angiotensin converting enzyme playing a key role in the regulation of blood pressure [25]. The knowledge of the role of ACE in increasing the blood pressure is the basis for the use of the snake venom ACE inhibitor, bradykinin potentiating peptide, in the management of high blood pressure. Administration of an ACE inhibitor blocks the conversion of angiotensin I to angiotensin II and thereby increase venous capacity, promote water and sodium excretion at the expense of potassium retention, and decrease cardiac output. The stimulant effect of angiotensin II on aldosterone synthesis is enhanced under hyponatremia (low sodium level) and hyperkalemia (high potassium level). These patients rely upon the RAAS to maintain hemodynamic stability and are rendered hyper-responsive to ACE inhibitor-induced lowering of their blood pressure [23]. The first bradykinin potentiating peptide, isolated from the *Bothrops jararaca*, venom became the precursor of today's most commonly used antihypertensive drugs like Captopril or Lisinopril. The drug is developed from a bradykinin-potentiating peptide that inhibits the production of Angiotensin-II protein; essentially the drug stops the production of Angiotensin-II which controls the dilation and constriction of blood vessels and arteries. The regulation of Angiotensin-II allows for capillaries to return to their normal pressure levels.

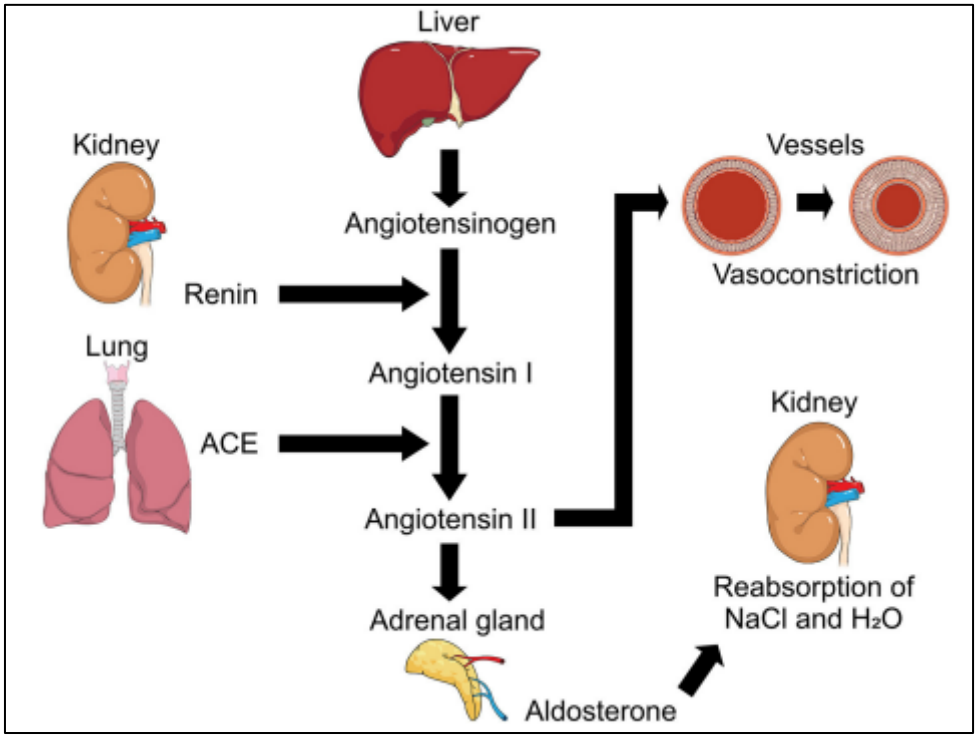

Figure 2 Renin-Angiotensi-Aldosterone System (RAAS) [26]

1.2. Anticancer activities of snake venom

Cancer is characterized by uncontrolled cell division, cell transformation, and escape of apoptosis, invasion, angiogenesis and metastasis [27, 28]. Induction of apoptosis is the most important mechanism of many anticancer agents [29].

Snake venom disintegrins, a low molecular weight molecules with different structure, potency and specificity initially isolated from viperid snake venoms, is an agent for development of therapeutics for the treatment of cancer. They are primarily known for their ability to inhibit integrins, which are cell adhesion receptors involved in various bioprocesses such as cell migration, proliferation, and survival [30]. Disintegrins cause hemorrhage by inhibiting platelet aggregation and induce apoptosis and necrosis in tissues they come in contact with [31]. Integrins are important in cell adhesion, cell migration, tissue organization, cell growth, hemostasis and inflammatory responses. Integrins are transmembrane receptors that have been shown to play a significant role in cancer progression and metastasis [32]. Integrins are divided into two subunits, α and β [33]. Many disintegrins (DIS) have been shown to bind to numerous integrins, such as α2β1, which are expressed by a wide variety of cells, namely those involved in tumor development [30]. An RGD-DIS isolated from the *Porthidium lansbergii*, also known as Lans berg's hognosed pitviper, inhibited the adhesion and migration of MCF7 and MDA-DB 231 breast cancer cells by binding to integrins α2 and/or β1 [34]. Moreover, the RGD-DIS DisBa-01 isolated from the *β. alternatus* binds to αvβ3 integrin, which could prevent cell migration and adhesion in

breast tumor cell 4T1BM2 [35, 36]. So, they are in the study for the development of drugs for the treatment of cancer [17].

ACTX-6 (98kDa proteins containing two subunits) was isolated from *Agkistrodon acutus* snake venom and demonstrated cytotoxic activity to various cancer cells *in vitro* [37]. The authors investigated the exact mechanism of ACTX-6 and reported that ACTX-6 induced cell death through production of reactive oxygen species (hydrogen peroxide). The induction of the apoptosis manifests the control on the tumour size and number of tumour cells hence establishing the application of apoptosis inducers as vital components in the treatment of cancer.

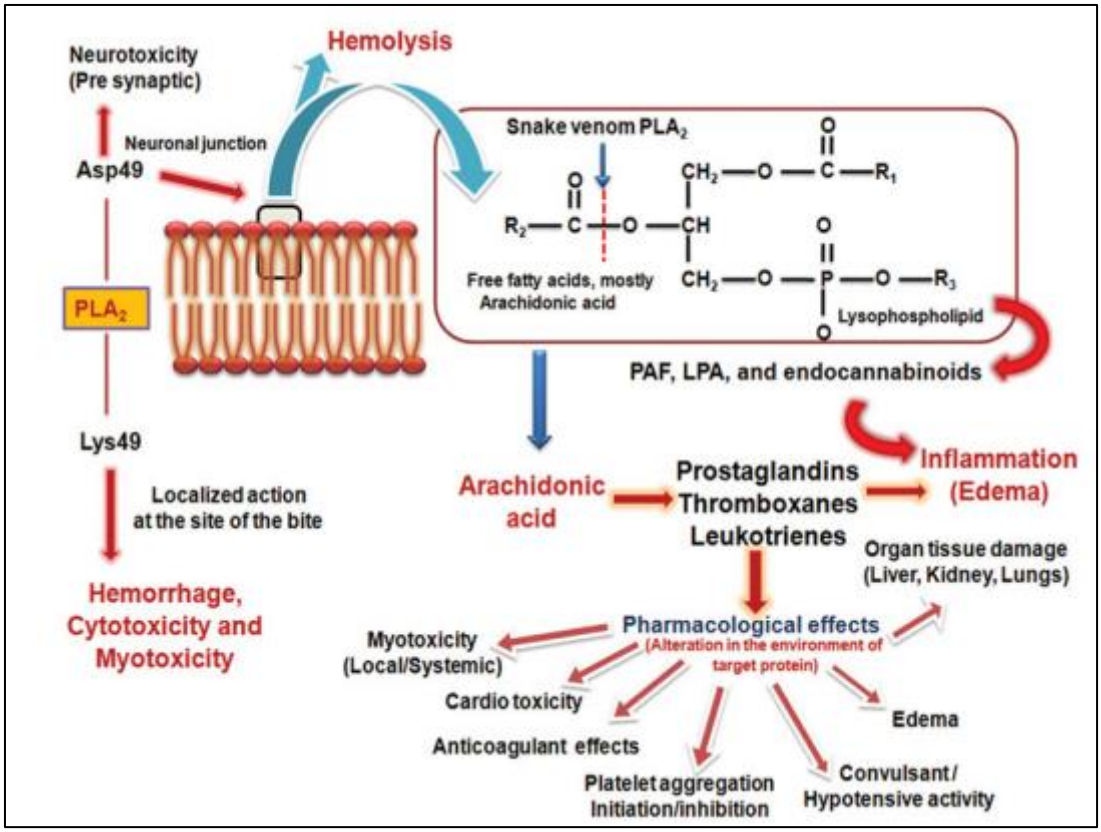

Figure 3 Mechanism of action of snake venom phospholipase A_2 [48]

L-Amino acid oxidases (LAAOs) are homodimeric proteins with a molecular weight of about 60–70 kDa per monomer and a non-covalently bound flavin adenine dinucleotide (FAD) as a prosthetic group [38]. LAAO have two domains that work together to facilitate the enzyme's catalytic activity: a FAD binding domain and a substrate-binding domain. L-amino acid oxidases mechanism of action involves the stereospecific oxidation of L-amino acids, converting them into their corresponding α-keto acids, along with the concomitant production of hydrogen peroxide (H_2O_2) and ammonia [39]. The cytotoxic effects of LAAO are primarily attributed to the generation of H_2O_2, which can cause oxidative stress, leading to cellular damage and apoptosis. Furthermore, LAAO have been reported to exhibit selective cytotoxicity towards certain cancer cells, making them potential candidates for the development of novel anti-cancer therapies [40]. The LAAO isolated from the South American rattlesnake, *Crotalus durissus terrificus*, showed anti-tumor activity in several cancer cell lines [41]. Moreover, the LAAO extracted from *Ophiophagus hannah*, known as the king cobra, has been shown to have potent anti-proliferative properties against both human breast and lung cancer cells [42] An apoptosis-inducing factor, apoxin I was purified from rattlesnake venom and amino-terminal sequences of the purified apoxin-I was similar to L-amino acid oxidases (LAAO). After creation of the primary structure of apoxin-I by using cloned c-DNA, the authors demonstrated that apoxin-I likely bind FAD to catalyze oxidative deamination of L-amino acids, an apoptosis inducing activity [43].

Secreted Phospholipase A_2 (PLA_2) are a heterogeneous family of enzymes that play a significant role in the toxicity of snake venoms. These enzymes share a conserved structural scaffold, with a molecular weight of 13–19 kDa, 5–8 disulfide bridges, and an ability to form dimers in aqueous environments [44]. PLA_2 exert their toxic effects by specifically catalyzing the hydrolysis of the sn-2 ester bond in glycerophospholipids, resulting in the release of fatty

acids and lysophospholipids [45] (Figure 3). The mechanisms of action of PLA_2 depend on the specific group of enzymes and their target sites. Group I PLA_2 are primarily neurotoxic, acting on neuromuscular junctions and causing paralysis. In contrast, Group II PLA_2 exhibit a wide range of pharmacological effects, such as myotoxicity, anti-coagulant activity, and local tissue damage [46, 47].

Studies have shown that BnSP-6, a Lys-49 PLA_2 isolated from the venom of *B. pauloensis*, has anti-tumoral effects on human breast cancer cell line MDA-MB-231, killing cells through a mechanism that combines apoptotic and autophagic components [49]. Another study showed that Asp-49 PLA_2 from the venom of *B. jararacussu* has anti-tumor and anti-metastatic effects on the same cell line suggesting that this protein may be used for drug development for the treatment of breast cancer [50]. Additionally, CC-PLA_2-1 and CC-PLA_2-2, isolated from the venom of *Cerastes cerastes* (Horned desert viper), have been shown to effectively inhibit tumor cell adhesion and migration by interfering with α5β1 and αv integrins, resulting in angiogenesis blocking [51]

1.3. Antiviral activities of snake venom

In recent years, a considerable progress has been made in understanding viral biology [52] and numerous clinical trials have been conducted with various candidate antiviral drugs [53]. Many obstacles remain to be overcome, including antigen diversity, the high frequency of viral mutations, and the destruction of the immune system cells after infection and imperfect animal models, among others. The antiviral activity of snake venoms represents a new and promising therapeutic alternative against the resistance mechanisms developed by viruses. A new study employed non-cytotoxic venom fractions from *Crotalus durissus terrificus* (Cdt) and identified the effect of this snake venom against the measles virus. At concentrations below 100 µg/mL, the Cdt venom showed no cell cytotoxicity. Replication of the measles virus was inhibited in Vero cells when the venom was added either prior to or during cell infection by the virus. The concentrations that successfully inhibited replication of the measles virus were 0.1 µg/mL and 100 µg/mL, respectively [54].

Some researchers have reported the antiviral activity of snake venom components against measles virus, Sendai virus, yellow fever virus, dengue virus and human immunodeficiency virus (HIV) [54, 55, 56; 57]. Snake venom are thus sources of promising candidates for new antiviral drugs. The benefit of treating a patient with multidrug-resistant HIV with a snake venom preparation in addition to the antiretroviral therapy have been demonstrated in clinical practice [58]. The result was an elevated T $CD4^+$ cell count and a decreased viral load. It was thus suggested that this activity may be related to the presence of some snake venom molecules, homogenous to HIV-1 glycoprotein or proteases [58, 59]. The said homology occurs in highly conserved amino acid residues (positions between 30 to 40) of snake venom neurotoxins long loop and the sequence 164 to 174 of short segment HIV-1 gp120. The result is that both may compete for the same receptor or binding site and present anti-HIV activity [59]. Some antiretroviral patents had been generated from the homology in sequence between HIV gp120 and snake neurotoxins, such as cobratoxin and bungarotoxin [60, 61, 62]. Another study that demonstrated the potential therapeutic value of venoms was developed using *Naja nigricollis* venom in human erythrocytes infected with the Sendai virus [63]. This research found that cells infected by the Sendai virus were ten times more susceptible to lysis when exposed to two of the five venoms tested. Four cytotoxins isolated from *Naja nigricolis* snake venom also showed that cells infected by the virus were ten times more susceptible to the cytotoxic action of the venom when compared to normal cells. Therefore, the study showed the clinical importance of the selective destruction of cells infected with the Sendai virus by the venom [63].

L-amino acid oxidase (LAAO) also play important role as anti-HIV, antimicrobial and antiparasitic activities. TSV-LAO, isolated from *Trimeresurus stejnegeri* snake venom, seems to be the first snake venom L-amino acid oxidase reported to present antiviral activity [64]. TSV-LAO is a glycoprotein with a molecular weight of about 58 kiloDalton that also forms homodimers, similar to LAAOs from other snake venoms. Its precursor sequence (obtained from cDNA analysis) codes for a polypeptide of 516 amino acid residue which includes an 18-amino acid potential signal peptide that is identical to those of LAAOs from other snakes. It has been reported that TSV-LAO inhibited HIV-1 infection and replication in a dose-dependent manner by inhibiting syncytium formation and HIV-1 p24 antigen expression [64]. Another LAAO isolated from Bothrops jararaca venom and denominated BjarLAAO-1, reduced the viral load in cells infected with dengue virus type 3 strain exposed to the toxin with respect to the controls [65]. It is similar to other snake venom LAAOs with a cDNA-deduced sequence having 484 amino acid residues. Their mechanism of action involves production of hydrogen peroxide as a free radical, which appears to enhance their antiviral activity [64].

Phospholipase A_2 is another protein found in snake venom that has antiviral activity. They interact with the host cells and prevent the intracellular release of virus capsid protein which suggest they block viral entry into the cells before virion uncoating [66, 67, 68]. PLA_2-Cdt, a phospholipase A_2 isolated from *Crotalus durissus terrificus venom,* inhibited both dengue virus (DENV) and yellow fever virus (YFV) in Vero E6 cells [69]. It has been proposed that PLA_2-Cdt cleaves

glycerophospholipid virus envelope and destabilizes protein on the virion surface, which partially exposes the genomic RNA and culminates with viral inactivation, making it unable to access the cell receptor [69]

1.4. Antimicrobial properties of snake venom

More than 700 antimicrobial peptides have already been identified in all living species including bacteria, fungi, amphibians, fish, insects and mammals. These molecules are 5kDa peptides with a high level of basic and hydrophobic amino acids. They present a broad antimicrobial spectrum against bacteria, fungi or parasites, by acting through insertion into the cell membrane or binding to receptors. These molecules are promising for development of antibiotics, especially for treatment of multiresistant microorganisms ([70,71]**.**

In the case of snake venoms, despite heavy snake oral and fang contamination with a wide variety of potentially pathogenic bacteria, envenomation is a process associated with a low incidence of bacterial infection ([72]. Therefore, this feature could indicate the presence of antibacterial molecules in the snake venoms that would protect the snakes during feeding. Some of the first reports about antibacterial activity in snake venoms were in 1948, and in 1968, involving *Elapidae* and *Viperidae* venoms [73]. *Viperidae* were described as having antimicrobials against the *Sarcina* species, while in the *Elapidae* family, a lytic factor or cytotoxin composed of a basic, low molecular weight protein, was found in *Naja* sp. and *H. haemachatus*. They were able to disrupt *Staphylococcus aureus* and *E. coli* phospholipid membranes respectively [73].

Not only peptides but also enzymes are involved in the antimicrobial activity of snake venoms. *Crotalus adamanteus* L-aminooxidase affects Gram-positive bacteria, while those from *Agkistrodon halys pallas, Bothrops alternatus* and *Trimerusurus jerdoni* have an inhibitory activity against *E. coli*, and *S. aureus*, *Pseudomonas aeruginosa* and *Bacillus megaterium*, respectively [74].

Many types of venom have antibacterial properties. For example, two antibacterial bioactive L-amino acid oxidase components in King brown (*Pseudechis australis*) venom that were 70 and 17.5 times more effective *in vitro* than tetracycline, a drug of choice for *Aeromonas* infections, have been found. Antibacterial and antiparasitic effects of the venom of the *Marajo lancehead* (*Bothrops marajoensis*) were shown to be caused by PLA_2 and L-amino acid oxidase toxins [75].

1.5. Analgesic properties of snake venom

An interesting neurotoxic peptide with analgesic properties was isolated from king cobra (*Ophiophagus hannah*) venom and is called hannalgesin [76]. The preclinical and early clinical development of this agent for acute pain relief is being handled by a company in France. The peptide is administered sublingually and is a non-opioid, water-soluble 11-amino acid peptide derived from hannalgesin. Studies in preclinical models have demonstrated the drug to be safe and to have analgesic properties, and while the mechanism of action is not fully understood, preclinical studies have shown that it has a far stronger analgesic effect than morphine. It is believed to operate via a neural nitric oxide synthetase-dependent mechanism that results in the activation of the endogenous enkephalin system.

There are several other promising leads for new venom-derived painkillers. Researchers in France announced the discovery of two peptides from black mamba (*Dendroaspis polylepis*) venom that can block acid-sensing ion channels (ASICs). ASICs are expressed within both the peripheral nervous system and the central nervous system and play a key role in the pain pathway in humans. The two peptides are each composed of 57 amino acids and 8 cysteine residues and only differ by one amino acid residue. They are called mambalgins [77]. They are members of the three-finger toxin (TFT) family, a superfamily of nonenzymatic proteins found in all families of snakes, but are main venom components of snakes from the *Elapidae* family. TFT family members have a common structure of three beta-stranded loops extending like three outstretched fingers from a small, globular, central core that is cross-linked by four conserved disulfide bonds. In mice, the mambalgins showed potent analgesic effects, as powerful as morphine, with no toxicity observable. The peptides also induced less tolerance than morphine to repeated drug exposure and no respiratory distress. These peptides have the potential to help in the understanding of pain as well as to be developed as novel, powerful, naturally occurring peptides of potential therapeutic value as analgesics. They show potent activity against different ASIC channel subtypes, thereby providing potentially novel targets for therapeutic intervention. The mambalgins are being developed into a human pain therapeutic by the same French pharmaceutical company that is developing the hannalgesin-derived peptide.

2. Conclusion

Snake venoms are the complex mixtures of several biologically active proteins, peptides, enzymes, and organic and inorganic compounds. Researchers have tried to understand the mechanism of toxicity of some of these compounds. The available information serves as tool for development of therapeutically active drugs against some diseases. With additional effort, it is expected that more drugs can be derived from venom compounds.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare no conflicts of interest concerning the publication of this article

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