

# Anti-inflammatory peptides and proteins from venomous snakes: a short review

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## Abstract

Inflammation can be acute or chronic. Chronic inflammation is a condition associated with several diseases like cardiovascular and neurodegenerative disorders, and even cancer. The venoms and poisons of several animal species, like bees and snakes, have been used in the Traditional Medicine of many regions for centuries. Although bee venom has been extensively explored and some of its components even experimentally proven to be functional as therapeutics, other animal venoms have been poorly studied in such matter.

Despite venomous snakebites are potentially dangerous and fatal to humans, several anti-inflammatory molecules have been found and characterized using experimental models, both *in vivo* and *in vitro*. In this review we enlist the polypeptides of venomous snakes that have been isolated and characterized for their anti-inflammatory activity to date. These molecules include the protein Crotoxin isolated from the South American rattlesnake *Crotalus durissus terrificus* and the few peptides isolated from some Asian elapid snakes. The physiological mechanism of action for each molecule is briefly described. This review highlights the importance of snakes as a source of biological active substances with therapeutic potential.

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## Introduction

Inflammation is a response to conditions such as injury or infections and can be acute or chronic.<sup>1</sup> Chronic inflammation is associated with diseases such as obesity, cardiovascular and neurodegenerative conditions, and cancer.<sup>2</sup> Other maladies like injuries and infections caused by bacteria produce acute inflammation involving white cells such as macrophages, monocytes and neutrophils and is beneficial since it is the first defense against the infection and has an important role in the healing process.<sup>3</sup> For the patients, chronic inflammation is a major problem since it is associated with pain, and this condition may imply months or even years of suffering, depending on the triggering disease such as type 2 diabetes, cardiovascular diseases, or cancer, considered some of the main causes of death in the world.<sup>4,5</sup>

For many years, venoms and poisons of animals have been explored in order to find molecules with therapeutic activity against pain, inflammation, and painful injuries. Bee venom, for instance, is used all over the world to treat pain and inflammatory issues.<sup>6</sup> One of its components, melittin, is used as an anti-inflammatory therapeutic in acne vulgaris, atherosclerosis, neurodegenerative diseases, and arthritis.<sup>7</sup> In southern Mexico, grinded tarantula spiders are used by shamans or healers to alleviate certain illnesses like pain, asthma, and other respiratory sickness.<sup>8</sup> The number of peptides derived from venomous animals with potential use against inflammatory conditions increases with time as venom research advances.<sup>9</sup>

Snakes are not the exception. These reptiles are known to all cultures of all epochs and have inspired fear and wonder through time.<sup>10</sup> Venomous snakes possess a variety of molecules capable of inducing severe damage in prey and potential predators including humans. Human envenomation by snakebite is a matter of concern by health institutions since mortality is still high despite the existence of antivenoms and modern palliative treatments. Interestingly, despite the nasty effects of snake bites, traditional medicine from

several countries such as China and India use some snake venoms to treat several ailments, including pain and inflammation. Recently, an interesting study showed the anti-inflammatory activity of the venom from several species of snakes along with some arachnids on joint inflammatory processes.<sup>11</sup> In this review, we enlist the anti-inflammatory properties of some venoms, and of the few isolated proteins and peptides found to date from distinct venomous snake species.

### Eligibility criteria, search strategies, and study selection

Published articles about snake anti-inflammatory activity were included. Conference abstracts and editorials were excluded as part of the eligibility criteria. A systematic search was carried out on PubMed and Google Scholar using the described strategies. The research was not date limited. To identify published articles, the following search terms were used: “anti-inflammatory peptides”, “snake anti-inflammatory peptides”, “venomous snake”, and “crotoxin”.

The data were independently extracted by three authors and compared. Any discrepancies were discussed. Full texts were retrieved and independently assessed by the same three authors. The selected articles were imported and merged into Mendeley reference management software.

## Crotoxin

Viperid snakes, also known as vipers, are amongst the most feared animals in the world. Although their venoms are not considered within the most potent, their bite can inoculate large amounts, leading to serious threat and potential death. For instance, *Bitis gabonica* is considered the most dangerous viper in Africa, whereas *Bothrops asper* is its equivalent in south Mexico and all along to south America. This species is responsible for ca. 60% of ophidic accidents in Mexico with high mortality rates.<sup>12,13</sup> Moreover, the largest viper in the world, *Lachesis acrochorda*, that inhabits Panama, Colombia, and Ecuador, might inject up to 400 mg of venom, causing severe envenomation cases.<sup>14</sup> In Europe, (except for some Greek islands where *Macrovipera* spp. and *Montivipera* spp. snakes have been observed), only vipers of the *Vipera* genus inhabit, *V. ammodytes*, *V. aspis*, *V. berus*, and *V. ursinii*. These latter species are of medical importance since severe bites may induce hypotension, cardiac arrhythmias, coagulation disorders, among others. However, the medical attention and antivenom availability in the developed countries is far better available than in the third world countries, so mortality rate is low.<sup>15,16</sup>

The American Continent harbors a special and exclusive kind of vipers, the rattlesnakes. The name comes from a series of intertwined keratin rings at the end of the tail that form a rattle. The snake shakes this rattle when disturbed in order to warn about its presence, deterring potential predators. In several countries of America, it is believed that consuming rattlesnake, particularly the skin and the rattle, can cure cancer and other illnesses.<sup>17</sup> This has not been demonstrated, however, some isolated molecules from the venom of several species have shown remarkable activity against cancer cells.<sup>18</sup> The venom of rattlesnakes is highly hemotoxic and myotoxic due to the presence of Phospholipases A<sub>2</sub> (PLA<sub>2</sub>), serine proteases, and metalloproteases. It also contains L-Amino Oxidases (LAOs), Cysteine-Rich Proteins (CRISPs), natriuretic peptides, Kunitz-type peptides, and many others.<sup>19</sup> Together, all these components cause a severe inflammatory response, tissue damage and cardiovascular

effects leading to serious harm or even death if not properly treated. Interestingly, there is an exception, the venom of *Crotalus durissus terrificus* (Figure 1). In fact, this venom inhibits the inflammatory responses.<sup>20</sup>

In a study, *C. durissus terrificus* venom anti-inflammatory activity was compared with known anti-inflammatory pharmaceuticals (dexamethasone, indomethacin, L-nitroarginine methyl ester, and nimesulide) using the carrageenan-induced edema assay. The venom showed protection against inflammation up to 7 days before the injection of carrageenan in mice and reduced the edema when administered 1 and 48 h after carrageenan application. The venom also significantly reduced the migration of polymorphonuclear cells into the peritoneal cavity of mice, before and after the injection with carrageenan.<sup>21</sup> Subsequent studies showed that *C. d. terrificus* venom inhibits Calmette-Guérin bacillus-induced chronic paw edema in mice possibly by generating lipoxins as anti-inflammatory mediators.<sup>22</sup>

After many studies, this anti-inflammatory activity has been explained due to the existence of a molecule called Crotoxin (CTx), a potent neurotoxin, that also elicits myotoxic, nephrotoxic and cardiotoxic effects. It comprises ca. 60% of the total protein content of *C. d. terrificus* venom and it is the main lethal factor. This protein is a heterodimer composed of two subunits, a nontoxic polypeptide called Crotopotin (CA) and a basic phospholipase A<sub>2</sub> (Crotoxin B (CB); Figure 2). Although crotopotin is not toxic, it increases the activity of the phospholipase by enabling the complex CA-CB to reach the specific target at the neuromuscular junction.<sup>23</sup> Many isoforms of CTx exist in the venom of *C. durissus terrificus*, each of them with different pharmacological properties but their description is outside the scope of this review and can be revised.<sup>24</sup> Other *Crotalus* species also contain crotoxin isoforms or crotoxin-like molecules<sup>25,26</sup> in their venoms (Figure 3). Several studies have shown that crotoxin-rich phenotype venoms are responsible for the lethal activity of rattlesnake bites.<sup>27</sup>

Despite CTx is the main toxin involved in *C. d. terrificus* envenomation process, this molecule is of particular interest due to its therapeutic implications. In an attempt to elucidate the compound responsible for the long-lasting anti-inflammatory activity of *C. durissus terrificus* venom, a study carried out by Nunes and collaborators<sup>20</sup> determined that CTx alone inhibited the inflamma-



**Figure 1.** *Crotalus durissus terrificus* (photo: William Quatman; permission via Flickr message. <https://www.flickr.com/photos/williamquatman/>).

tion before and after the injection of carrageenan to mice, while all the other components were discarded. The results showed that the formyl peptide receptors play a pivotal role in the anti-inflammatory effect. Moreover, CTx exerts a sustained down-modulatory effect on circulating and peritoneal neutrophils by impairing the spleen tyrosine kinase GTPase (Syk-GTPase) pathway in the bone marrow, downregulating *Syk* activity and its downstream proteins.<sup>29</sup>

In addition to its anti-inflammatory potential, since several

decades ago, researchers have also been investigating CTx for its participation on the innate and adaptative immune systems.<sup>30</sup> A study determined that CTx is able to modulate intestinal acute inflammation induced by Trinitrobenzene Sulfonic Acid (TNBS) in mice, making it a potential candidate for colitis treatment.<sup>31</sup> Crotoxin decreases the tumor growth in Walker 256 tumor-bearing rats by stimulating the release of nitric oxide (NO), H<sub>2</sub>O<sub>2</sub>, cytokines Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ), Interleukin (IL) 1 $\beta$  and IL-6, and glucose and glutamine metabolism.<sup>32</sup> A recent work in which CTx modulated the phenotypic reprogramming of macrophages showed that this protein could be used as a potential therapeutic to improve compromised immunity in several systems that include both tumor and healthy conditions.<sup>33</sup>

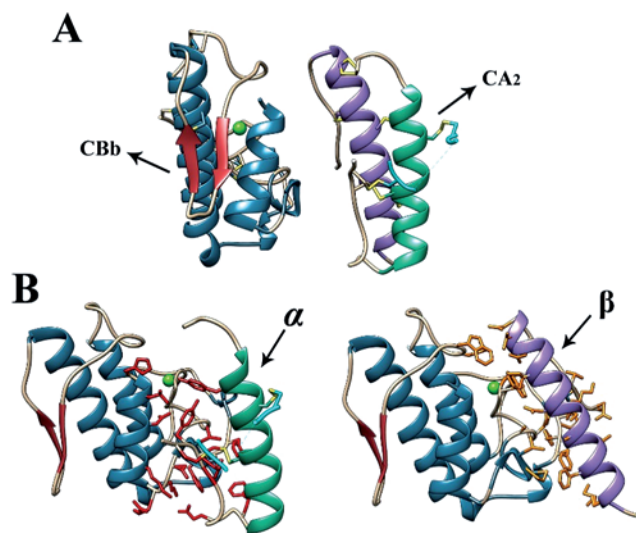


Figure 2. 3D structure of crotoxin.

## Other anti-inflammatory snake-derived peptides

### Anti-inflammatory peptides from elapid snakes

Elapid snakes are characterized by a neurotoxic venom and include some of the most lethal species such as cobras, coral snakes, kraits, mambas, and sea snakes. The venom contains neurotoxic peptides like three finger toxins and neurotoxic phospholipases that lack enzymatic activity. It also contains proteases, but the lethal factors are usually toxins that target the neuromuscular junction. To date, peptides with anti-inflammatory activity have been found in the elapid snakes of genera *Naja* (cobras), *Bungarus* (kraits), and *Hydrophis* (sea snakes), considered some of the most venomous and dangerous snakes in the world.<sup>34</sup>

Cobras are probably the best-known and even popular elapids. They are characterized by a spanning hood that expands upon alarm, aggression, or any potential danger.<sup>35,36</sup> The venoms

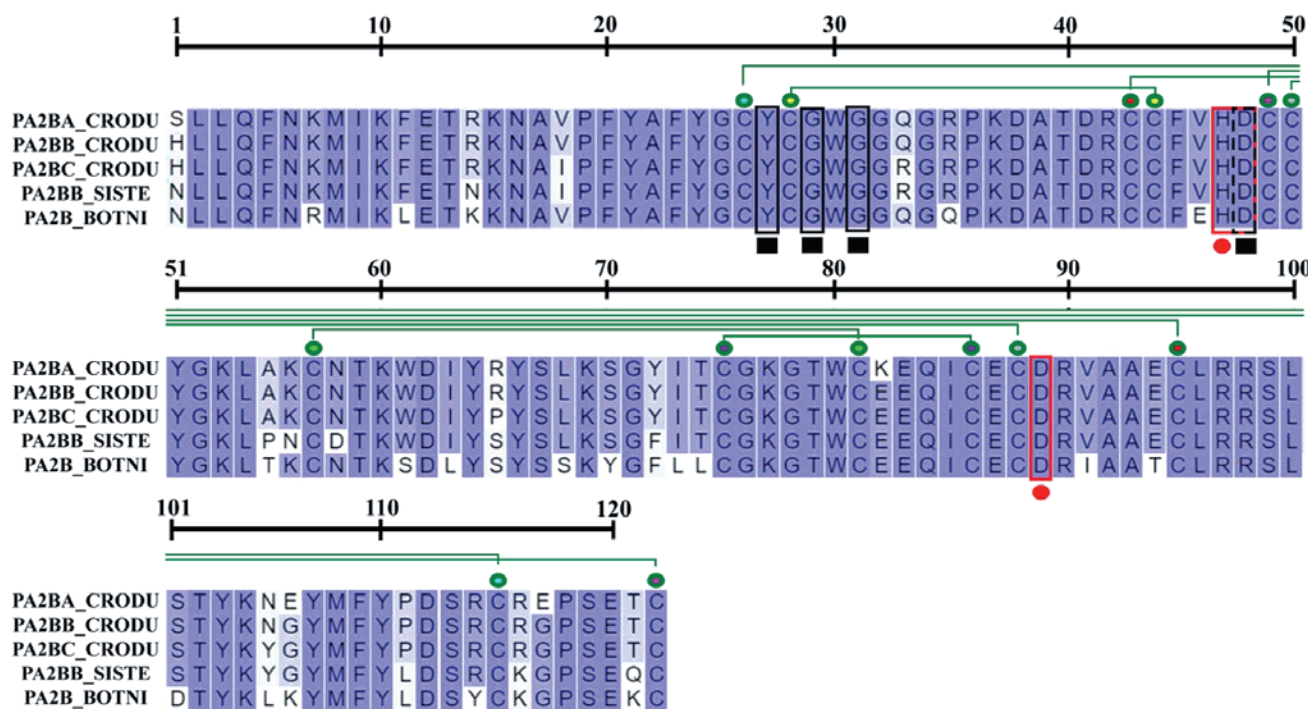


Figure 3. Amino acid alignment of crotoxin and crotoxin-like peptides. The numbers correspond to each amino acid residue.

from cobras have been used in the traditional medicine of countries like India and China.<sup>37</sup> The venoms from *Naja kaouthia* (Figure 4, A) and the Chinese cobra *N. naja atra* (Figure 4, B) have been tested for their anti-inflammatory and antinociceptive effects with positive results. For instance, a study showed that the treatment of arthritis-induced rats with the venom of the Indian monocellate cobra *N. kaouthia*, significantly protects against arthritis by modulating inflammatory markers. The study also showed that the venom restores paw and ankle volume, weight, and several blood compounds to normal measures. Later, this same venom showed antiarthritic activity in rats with arthritis-induced by Freund's Complete Adjuvant (FCA) model.<sup>38</sup>

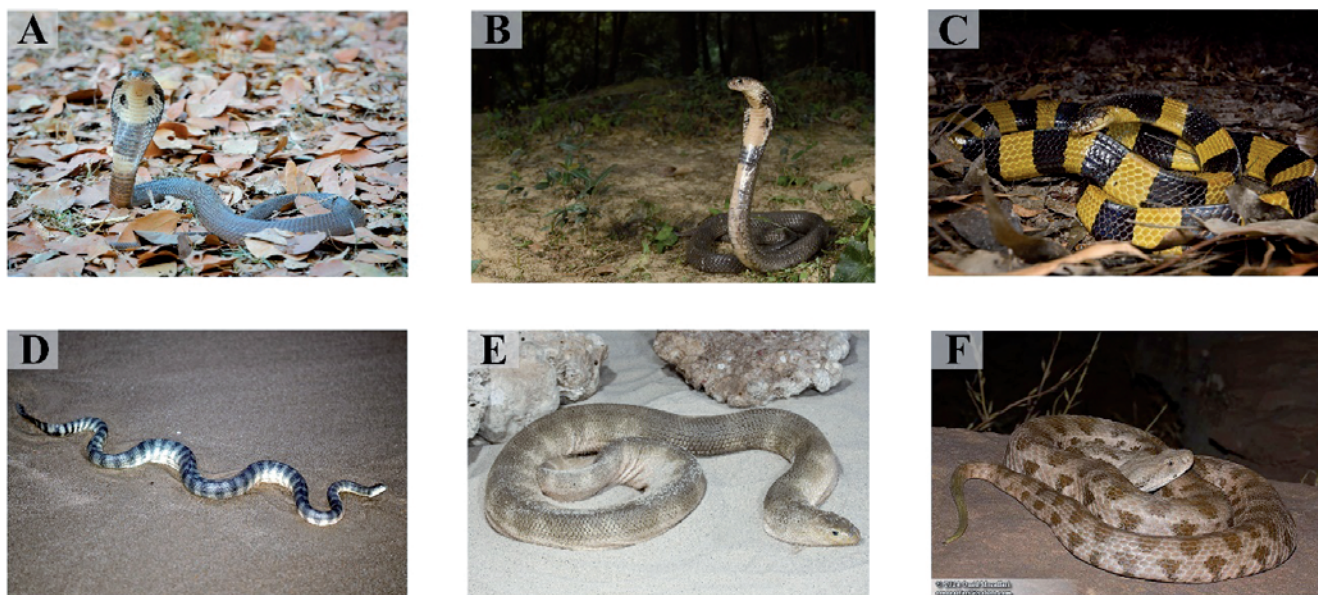
Likewise, a study on the Chinese cobra *N. naja atra* venom showed that the denatured venom elicits strong anti-inflammatory and antinociceptive effects on rheumatoid arthritis models by oral administration on Kunming mice and Sprague-Dawley rats.<sup>39</sup> Cobrotoxin is the 7 kDa weight  $\alpha$ -neurotoxin isolated from this cobra. This peptide binds to the  $\alpha 7$ -nAChR nicotinic receptor with high affinity. A study showed that cobrotoxin is blocked by atropine and naloxone, exerting its antinociceptive activity via the cholinergic system and not the opioid system.<sup>40</sup> Later, it was established that it exhibited dose-dependent analgesic effect against inflammatory pain using the formalin test.<sup>41</sup> This peptide induces anti-inflammatory effect on rheumatoid arthritis inhibiting the production of proinflammatory cytokines.<sup>37,42</sup>

*Bungarus* spp. snakes, also known as kraits, are highly toxic elapids widely distributed in Asia. Their venoms induce a descending flaccid paralysis that may end in death by respiratory failure.<sup>43</sup> Cathelicidin-BF from *Bungarus fasciatus* (Figure 4, C) is a peptide with antimicrobial activity against several pathogens such as ciprofloxacin-resistant *Escherichia coli* and *Staphylococcus aureus*, among others. This peptide also showed

inflammation suppression in piglet intestine by reducing the phosphorylation of I kappa B-alpha protein (IKB- $\alpha$ ) and nuclear factor kappa-B (NF- $\kappa$ B) *in vivo* and *in vitro*.<sup>44</sup> Another study demonstrated that cathelicidin-BF inhibits dextran sulfate sodium-induced colitis in mice.<sup>45</sup> Moreover, the intraperitoneal injection attenuates inflammation, improves intestinal morphology by increasing villous height in jejunum and ileum and villous ratio to crypt depth, and enhances intestinal epithelial barrier function in piglets.<sup>46</sup> These results suggest that this peptide could be considered as a potential therapeutic agent targeting bowel diseases. A recent study showed that cathelicidin-BF inhibits NF- $\kappa$ B activity in mouse chondrocytes playing an anti-inflammatory role in osteoarthritis.<sup>47</sup>

Sea snakes inhabit the tropical and subtropical areas of the Pacific and Indian oceans although they can be also found in some lakes of Southeast Asia. Their venom is more potent than that from cobras and kraits. Sea snake bites are rare due to their timid behavior and many of them are considered as gentle and inoffensive. However, there are aggressive species such as *Hydrophis schistosus* (Figure 4, D).<sup>48</sup>

More than 19 species of sea snakes inhabit the seas in China being *Hydrophis curtus* (Figure 4, E) and *H. cyanocinctus* the most dangerous.<sup>49</sup> According to Wang and collaborators, the venom of *H. cyanocinctus* has been used in this country to treat rheumatism for centuries.<sup>49</sup> The first marine snake cathelicidin was isolated and characterized from this species.<sup>50</sup> Cathelicidins are antimicrobial peptides that have been identified in several vertebrate species. This molecule, called Hc-CATH, is a 30 amino acid residues peptide that possesses both antimicrobial and anti-inflammatory activity, this latter by inhibiting the Lipopolysaccharide (LPS) induced production of nitric oxide and pro-inflammatory cytokines (Table 1).



**Figure 4.** A) *Naja kaouthia* (photo: Gregory Greene; License: CC BY-NC 4.0. <https://www.inaturalist.org/observations/20695696>); B) *Naja atra* (photo: Dash Huang; License: CC BY-NC-SA 2.0. <https://www.flickr.com/photos/121917432@N02/>); C) *Bungarus fasciatus* (photo: Tontantravel; License: CC BY-SA 2.0 <https://www.flickr.com/photos/tontantravel/>); D) *Hydrophis schistosus* (photo: en\_shtein; License CC BY-NC 4.0. <https://www.inaturalist.org/observations/147087682>); E, *Hydrophis curtus* (photo: Anders Zimny; permission via Flickr message. [https://www.flickr.com/photos/zimny\\_anders/](https://www.flickr.com/photos/zimny_anders/)); F) *Macrovipera lebetina* (photo: Omid Mozaffari; License: CC BY 2.0. [https://www.flickr.com/photos/omid\\_mozaffari/](https://www.flickr.com/photos/omid_mozaffari/)).

A nine amino acid residues peptide H-TL1, later called Hydrostatin SN-1, from this same species, induces *in vitro* and *in vivo* anti-inflammatory activity.<sup>51</sup> The TNF- $\alpha$  is implicated in inflammation and in the pathogenesis of several diseases such as cancer and rheumatoid arthritis.<sup>51</sup> By means of several techniques such as Enzyme-Linked Immunosorbent Assay (ELISA), surface plasmon resonance, and the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide (MTT) assay, it was observed that the peptide inhibited the interaction between TNF- $\alpha$  and the tumor necrosis factor 1 (TNFR1) and diminished the cytotoxicity of TNF- $\alpha$  in L929 mouse fibroblasts.<sup>51</sup> Moreover, another study revealed that H-TL1 also protected mice against induced colitis.<sup>52</sup> Later experiments increased the evidence of the anti-inflammatory properties of Hydrostatin SN-1 *in vitro* and *in vivo*.<sup>53</sup> In these experiments, the peptide suppressed the TNRF-1-mediated mRNA expression of proinflammatory cytokines and diminished the inflammation related pathological damage to colon tissue in IL-10 knockout (KO) mice, providing evidence to consider Hydrostatin SN-1 as a potential TNRF1 antagonist compound.

### Anti-inflammatory peptides from viper snakes

True vipers pertain to Viperinae subfamily and comprise ca. 101 species and their venoms differ from elapid venoms in that

they bear higher amounts of Cysteine-Rich Secretory Proteins (CRISPs), C-type lectins (snaclecs), disintegrins, and natriuretic peptides, in addition to the characteristic high content of Phospholipases A<sub>2</sub> (PLA<sub>2</sub>), Metalloproteases (SVMPs), and Serine Proteases (SVSPs).<sup>54</sup>

The potential use of several viper venoms as potential therapeutics for cardiovascular issues has been proposed by Kakumanu and collaborators.<sup>55</sup> For instance, *Macrovipera lebetina* (Figure 4, F) is a viper that inhabits several North African countries and the Middle East and causes severe edema, hemorrhage, inflammation and necrosis during envenoming.<sup>56</sup> A 4 kDa peptide named lebetin 2 (L2) was isolated from its venom and has structural homology with the Atrial Natriuretic Peptide (ANP), the B-type natriuretic peptide, and the Dendroaspis natriuretic peptide L2; it promotes anti-inflammatory M2-macrophages, attenuating fibrosis and necrosis damage in the infarcted myocardium.<sup>57</sup> The mechanism by which this peptide exerts its response consists of stimulating the natriuretic peptide receptors through the activation of IL-10 signaling, thus, regulating the release of cytokines.<sup>58</sup> Many other snake-derived peptides have been and are still being studied for their potential therapeutic applications for treating cardiovascular and inflammatory issues and can be consulted elsewhere.<sup>59</sup>

**Table 1.** Elapids anti-inflammatory peptides. Asterisks (\*) denote the presence of signal peptide in the respective sequence. The signal peptide sequence is highlighted in cyan.

Name/Accession number	Organism	Sequence	Observation	Reference
Hydrostatin SN-1	<i>Hydrophis cyanocinctus</i>	DEQHLETELHHTLTSVLTAN GFQ	Inhibits TNF/TNFR1 DOWNSTREAM targets at both mRNA and protein levels	(52)(53)
Mambalgin/3SX1_DENPO*	<i>Dendroaspis polylepis</i>	MMKTL <sup>LL</sup> LL <sup>LV</sup> VTIVCLDLGYS LKCYQHGGKVVTC <sup>HR</sup> DMKFC YHNTGMPFRNLK <sup>L</sup> LILQGCSSS CSETENKCCSTDR <sup>C</sup> NK	Decreases carrageenan-induced inflammatory pain through inhibition of ASIC channels in knock-down and knock-out mice	(60)
Cobrotoxin/3S1CB_NAJAT*	<i>Naja atra</i>	MMKTL <sup>LL</sup> LL <sup>LV</sup> VTIVCLDLGYT LECHNQSSQTPTTTGCSGGE TNCYKKRWRDHRGYRTERGCG CPSVKNGIEINCC <sup>T</sup> TDRCNN	Inhibits NF- $\kappa$ B pathway in rat arthritis model	(37)
Cathelicidin-BF/CAMP_BUNFA	<i>Bungarus fasciatus</i>	KKFFR <sup>L</sup> LK <sup>S</sup> VK <sup>K</sup> RAKEFF <sup>K</sup> K <sup>P</sup> R VIGVSIPF	Inhibits the nuclear factor- $\kappa$ B signaling pathway suppressing intestinal inflammation	(44)
Hc-CATH/A0A0G3DRW6_HYDCY	<i>Hydrophis cyanocinctus</i>	KKFFR <sup>L</sup> LK <sup>S</sup> VRR <sup>A</sup> VKKFR <sup>K</sup> K <sup>P</sup> R LIGLSTLL	Inhibits LPS-induced production of NO and pro-inflammatory cytokines	(50)
Lebetin-2/LEB_MACLB	<i>Macrovipera lebetina</i>	GDNKPPK <sup>K</sup> GPPNGCF <sup>G</sup> HKIDRIG SHSGLGCNKVDDNKG	Inflammatory-cell modulation by examining M1/M2 macrophage recruitment in the infarcted heart. Anti-inflammatory response to lipopolysaccharide by regulating the release of inflammatory cytokines via stimulating of natriuretic peptide receptors and promoting M2 macrophage polarization through activation of IL-10 signaling	(57) (58)
			Improves cardiac function and reduces necrosis, fibrosis and inflammation in a reperfused MI model	(61)

TNF, Tumor necrosis factor; TNFR1, Tumor necrosis factor receptor 1; ASIC, Acid-sensing ion channel; NF- $\kappa$ B, nuclear factor kappa-B; LPS, Lipopolysaccharide; IL-10, Interleukin 10; NO, nitric oxide.

## Conclusions

The research on venomous snakes is important not only for the manufacture of antivenoms, but for the development of new therapeutic agents as well. Snake venoms are a rich source of molecules with noxious effects that can be converted into beneficial products for human health improvement. To date, just a handful of peptides and proteins with anti-inflammatory activity from snakes have been discovered but hundreds of species remain unexplored. The anti-inflammatory compounds in snake venoms should be explored in order to find new potential therapeutic agents to treat inflammation-related conditions such as arthritis and neurodegenerative illnesses, among others.

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