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Review Article

THERAPEUTIC POTENTIAL OF SNAKE VENOM

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ABSTRACT

Annually 2.5 million people are bitten by snakes, more than 100,000 fatally. In India a large no of people suffer and die every year due to snake venom poisoning. Venom has been used in the treatment of a variety of pathophysiological conditions in Ayurveda, homeopathy and folk medicine. Snake venom is a natural biological resource, containing a complex mixture of enzymes, peptides and protein of low molecular weight with specific chemical and biological activities. Majorly it evolved a vast array of peptide toxins for prey capture and defense. These peptides act like an invaluable source of ligands by acting upon a wide variety of pharmacological targets. Snake venom contains several neurotoxic, cardiotoxic, cytotoxic, nerve growth factor, lectins, haemorrhagins, disintigrins, and many other different enzymes. These proteins not only responsible for death to humans and animals, but can also be used for the treatment of thrombosis, cancer, HIV, arthritis, against microbes, anti-viral and many other diseases. With the advent of biotechnology, the efficacy of such treatments has been substantiated by purifying components of venom and delineating their therapeutic properties. This review will focus on certain snake venom components and their applications in health and disease.

Keywords: Snake venom, peptides, disintegrins, thrombosis, hypertension, cancer.

INTRODUCTION

Paracelsus, the 15th century philosopher, had said – "In all things there is poison; there is nothing without poison. It only depends upon the doses, whether a poison is a poison or not". We now understand that in many cases it is the dose that differentiates a poison from a remedy, which means that any chemical can be toxic if the dose is high, and this is also the basis of modern toxicology. Paracelsus also said that a poison can counteract another and this is the foundation of chemotherapy, antibiotics and immune prevention. It is now well accepted that a poisonous substance could be used as a drug by proper administration, while a life-saving drug might become a poison with indiscriminate use. Many active secretions produced by animals have been employed in the development of new drugs to treat diseases such as hypertension and cancer. Snake bite injuries and deaths are socio-medical problems of considerable magnitude. In India a large number of people suffer and die every year due to snake venom poisoning. Snake venom, though greatly feared, is a natural biological resource, containing several components that could be of potential therapeutic value. Snake venom toxins contributed significantly to the treatment of many medical conditions. There are many published studies describing and elucidating the therapeutic potentials of snake venom. Snake venoms are the secretion of venomous snakes, which are synthesized and stored in specific areas of their body i.e. venom glands. Most of the venoms are complex mixture of a number of proteins, peptides, enzymes, toxins and non protein inclusions[1]. Many of them are harmless, but some can produce toxicity at certain degree. Snake venoms cause significant mortality and morbidity worldwide, and strike fear in most of us.

Composition of snake venoms

Snake venoms are complex mixtures; mainly it has proteins, which have enzymatic activities. Protein and peptides make 90 to 95 percent of the dry weight of venom. In addition to that snake venoms contain inorganic cations such as sodium, calcium, potassium, magnesium and small amounts of zinc, nickel, cobalt, iron, manganese. Zinc is necessary for anti-cholinesterase activity; calcium is required for activation of enzyme like phospholipase. Some snake venoms also contain carbohydrate, lipid, biogenic amines, and free amino acids[2]. Snake venoms contain at least 25 enzymes, but no single venom contains all of them. Enzymes are protein in nature, but few are depends on certain non protein prosthetic groups or cofactors.

Proteolytic Enzymes

These enzymes catalyze the breakdown of tissue proteins and peptides. They are also known as peptide hydrolases, protease, endopeptidases and proteinases. They have molecular weights between 20 000 and 95 000 Da. They may sometimes inactivated by eidetic acid and some reducing agents. Some metal ions help in catalysis and intrinsically in the activity of certain venom proteases and phospholipases[3].

Arginine ester hydrolase

This is one of the non-cholinesterase enzymes found in snake venoms. It causes hydrolysis of the ester or peptide linkage, to which an arginine residue contributes the carboxyl group. This activity was found in crotalid, viperid and some sea snake venoms but lacking in elapid venoms. Bradykinin-clotting activities of some venom related to esterase activities[4].

Thrombin

Thrombin releases fibrinopeptides A and B which are responsible for clotting of plasma.

Thrombin-like enzymes

They are glycoprotein in nature, and have molecular weights between the ranges of 29 000 to 35 000 Da. They act as defibrinating anticoagulants *in vivo*, whereas *in vitro* they clot plasma, citrated or heparinised plasma and also purified fibrinogen. Due to its action as defibrinating agent, more attention has been directed toward the characterization and study of the thrombin-like enzymes than toward those of the

other venom pro-coagulant or anti-coagulant enzymes. Thrombin like enzymes such as crotalase, agkistrodon, ancrod and batroxobin can be purified from different snake venoms. They have been used clinically in animals for therapeutic and investigative studies. Treatment with ancrod before the formation of the experimentally induced thrombus in dog, prevented thrombosis and ensured vessel patency. However, ancrod has no thrombolytic effect after thrombus formation. Crotalase has been employed to evaluate the role of fibrin deposition in burns in the animals. The role of fibrin deposition has been evaluated in tumor metastasis, in which fibrinogen removed by treatment with ancrod and also by batroxobin[5].

Collagenase

Collagenase is a proteinase enzyme, which specifically digests collagen. Some snakes contain collagenase which digests mesenteric collagen fibers but not the other protein[6].

Hyaluronidase

This enzyme referred as the "spreading factor". It is thought to be related to the extent of edema produced by the venom. It acts upon connective tissues and decreases their viscosity, catalyzes the cleavage of internal glycoside bonds in certain acid mucopolysaccharides. Breakdown in the hyaluronic barrier allows other fractions of venom to penetrate the tissues.

Phospholipase

Many PLA2 were found in venom. It has 120 amino acids and 14 cysteine residues forming 7 disulfide bonds. Venoms are the richest sources of PLA2. It catalyzes the calcium dependent hydrolysis of the 2-acyl ester bond thereby producing free fatty acids and lysophospho lipid. PLA2 can also cause hydrolysis of membrane phospholipids, and liberation of some bioactive products[7].

Phosphodiestsrase

It releases 5-mononucleotide from the polynucleotide chain and act as an exonucleotidase, thereby affecting DNA and RNA functions. It is found in all poisonous snakes[8].

Acetylcholinesterase

This is found in cobra and sea snake but absent in viperid and crotalid venoms. It catalyzes the hydrolysis of acetylcholine to choline and acetic acid.

RNase

This is present as the endopolynucleotidase RNase which has specificity toward pyrimidine containing pyrimidyladenyl bonds in DNA.

DNase

It gives oligonucleotides, which terminate 3′ monoesterified phosphate bond in DNA. 5′-Nucleotidase: Nucleotidase is a most active phosphatase in snake venoms, which hydrolyzes phosphate monoesters linked with a 5′ position of RNA and DNA. L-Amino acid oxidase (L-AAO): L-AAO gives yellow color to venom. It catalyzes the oxidation of L-α-amino acid and α-hydroxy acid.

L-Acetate dehydrogenase

It catalyzes the equilibrium between lactic acid and pyruvic acid and found in all animal tissues.

Polypeptides

These are a low molecular weight protein that lacks enzymatic activity. More than 80 polypeptides were isolated from snake venoms with different pharmacological activities[9]. The venom components can also be grouped into a number of different categories depending on their haemostatic action: (i) enzymes that clot fibrinogen; (ii) enzymes that degrade fibrin (ogen); (iii) plasminogen activators; (iv) prothrombin activators; (v) factor V activators; (vi) factor X activators; (vii) anticoagulant activities including inhibitors of prothrombinase complex formation, inhibitors of thrombin, phospholipases, and protein C activators; (viii) enzymes with hemorrhagic activity; (ix) enzymes that degrade plasma serine proteinase inhibitors; (x) platelet aggregation inducers including direct acting enzymes, direct acting non-enzymatic components, and agents that require a cofactor; (xi) platelet aggregation inhibitors including: alpha-fibrinogenases, 5'-nucleotidases, phospholipases, and disintegrins.[10]

Therapeutic actions of snake venom

Use of snake venom in different pathophysiological conditions has been mentioned in Ayurveda, homeopathy and folk medicine. It is well known that snake venom is complex mixture of enzymes, peptides and proteins of low molecular mass with specific chemical and biological activities. Snake venom contains several neurotoxic, cardiotoxic, cytotoxic, nerve growth factor, lectins, disintegrins, haemorrhagins and many other different enzymes. These proteins not only inflict death to animals and humans, but can also be used for many diseases. Many toxins from snake venom are investigated and formulated into drugs for the treatment of conditions such as cardiovascular disorders, thrombosis, paralysis, various types of cancers, and also in nociception and arthritis.

Venom peptides having antifibrinogenolytic and fibrinolytic properties

The venoms from 3 snakes have been shown to induce defibrinogenation: ancrod from the venom of *Calloselasma rhodostoma* (formerly known as *Agkistrodon rhodostoma*), batroxobin from the venom of *Bothrops atrox moojeni*, and crotalase from the venom of *Crotalus adamanteus*. The purified fractions of ancrod, batroxobin, and crotalase possess coagulant, proteolytic and esterolytic properties, although their primary mechanism of action is a proteolytic effect on circulating fibrinogen. Ancrod cleaves only the A-fibrinopeptides, but not the B-fibrinopeptides, from fibrinogen; this contrasts with thrombin, batroxobin and crotalase, which cleave both fibrinopeptides A and B. Within minutes of administration of ancrod or batroxobin, there is a significant reduction in plasma fibrinogen levels, and these remain exceedingly low with repeated administration (once or twice daily). The rapid fall in plasma fibrinogen levels is accompanied by a slightly delayed but marked rise in the level of fibrinogen-fibrin degradation products. Plasminogen levels are decreased and blood viscosity is reduced, but formed elements in the circulating blood remain unaltered. Ancrod and batroxobin have been investigated in patients with stroke, deep-vein thrombosis, myocardial infarction, peripheral arterial thrombosis, priapism, and sickle-cell crisis; crotalase has not been administered to humans. However, results have been difficult to interpret, and additional well designed trials are needed to better define the optimum role of ancrod and batroxobin in the management of these conditions. Overall, treatment is well tolerated and serious

adverse events are infrequent. In the coagulation laboratory, ancrod, batroxobin and crotalase may be used as reagents to perform coagulation studies on specimens of blood that contain heparin. These venom fractions can be substituted for thrombin in performing the thrombin time and in removing fibrinogen from plasma for accurate determination of fibrinogen-fibrin degradation products[11]. Disintegrins are cysteine-rich low molecular weight polypeptides, which contain an RGD sequence recognized by integrins. Trigramin, from the venom of *Trimeresurus gramineus*, was the first venom disintegrin characterized as a competitive inhibitor of fibrinogen binding to the aIIbß3 integrin of platelets activated by ADP[12]. Following this, a number of other disintegrins isolated from different snake venoms have been reported and reviewed[13]. It is interesting that, unlike other RGD-containing ligands (i.e. fibrinogen), venom disintegrins bind to aIIbß3 integrin without requiring prior activation of this integrin. This is because disintegrins have a unique RGD-containing loop which can express the ligand-induced binding site (LIBS) on the ß3 subunit[14]. Recently, a relatively large disintegrin (28 kDa) containing an ECD sequence instead of RGD, isolated from the venom of *B. jararaca* has been reported. This disintegrin has exactly the same primary structure as the disintegrin-like domain of jararhagin and was therefore named jararhagin C[15]. Unlike jararhagin, which in our studies showed no interference with platelet response to ADP, jararhagin C inhibited both the ADP- and collagen-induced responses of platelets. Nevertheless, the finding that jararhagin C inhibits collagen-induced platelet aggregation confirms our conclusion that the disintegrin-like domain of the enzyme jararhagin recognizes the platelet collagen receptor, $a_2ß_1$ integrin. Disintegrins have the ability to inhibit the binding of RGD-containing ligands to platelet aIIbß3 integrin and, because of this; they impair platelet aggregation responses dependent on this receptor. Thus, platelets treated with disintegrins do not aggregate in response to collagen stimulation. However, these platelets show normal phosphorylation of the tyrosine kinase pp72syk[16,17]. Collagen first binds to the a2ß1 integrin, signaling for pp72syk phosphorylation and an inside-out activation of aIIbß3 integrin. In the disintegrin-treated platelets, the aIIbß3 integrin is already occupied by the venom ligand so that the aggregation response is lost. However, pp72syk phosphorylation is preserved, confirming that free a2ß1 can bind collagen and signals in these platelets. In this respect, we found results using both jararhagin and contortrostatin particularly revealing. Contortrostatin[18] is a dimeric RGD-containing disintegrin from *Agkistrodon contortrix contortrix* venom. Suboptimal ADP stimulation of jararhagin-treated platelets resulted in a full aggregation response to collagen and this could be inhibited by either RGDS peptide or contortrostatin[16]. Our explanation for this is that ADP caused activation of the aIIbß3 integrin in these platelets, which then bound collagen. Inhibition of this binding by contortrostatin emphasizes the importance of aIIbß3 in addition to a2ß1 integrin in the platelet/collagen interaction. Recently, disintegrins have been also shown to interfere with other integrin-mediated cell functions; for example, inhibition of tumor cell-extracellular matrix adhesion[19-21] and metastasis[18,22], of adhesion of human umbilical vein endothelial cells to matrix proteins[22], and also of egg fertilization through inhibition of sperm-oolemmal adhesion[23].

Venom peptides in cardiovascular disorders

Hypertension, simply stated is when the blood pressure measurement exceeds 140/90 mmHg. Many physiological conditions can lead to high blood pressure and the long term effect of hypertension include heart failure, aneurysms, kidney failure, heart attacks, strokes and ruptures in the small blood vessels of the eyes contributing to blindness. In general, the venoms of rattlesnakes and other new world crotalids produce alterations in resistance of blood vessels, changes in blood cells and coagulation mechanism, direct or indirect changes in cardiac and pulmonary dynamics. There may be alterations in nervous system and respiratory system[24-27]. The potency of venom and its effect on human depend on the type and amount of venom injected and the site where it is deposited. Other parameters such as sex, general health, size and age are also influencing factors. Clinical experiments and history show that the death may occur within less than 1 h to several days while the most deaths occurred between 18 to 32 h. Snake venoms significantly lower the blood pressure in human victims and experimental animals. Hypotension and shock are associated with snake venom poisoning[28]. Experimentally, it has been found that an intravenous bolus injection of a Crotalus venom causes an immediate fall in blood pressure and varying degree of shock, associated with initial haem concentration followed by a decrease in haematocrit values[29]. Captopril was isolated from *Bothrops jararaca* venom is an example of a therapeutic derived from the snake venoms[30]. Increased blood volume in the lung and pulmonary artery pressure with a concomitant decrease in pulmonary artery flow and a relatively stable heart stroke volume are noticed. When Crotalus venom is given IV slowly for over a period of 30 minutes, there is hypo volume secondary to an increase in capillary permeability to proteins and RBCs. The experimental results showed initial haemoconcernatration, lactacidamiea and lipoprotienamia, respiration becomes labored and if period prolongs animal becomes oliguric, rales develop and the animal dies[31-36]. Significant contribution comes from the work of Shermann *et al*[37] He observed that Malayan pit Viper venom has blood thinning properties and could be effective in treating stroke patients. From a study of 500 stoke patients, 42 % who were given the snake venom drug (Ancord) within 3 h of stroke. Mayberg and fulan[38] reported that onset regained significant functioning compared to 34 % who got a placebo. The role of ancord in patients with heparin induced thrombocytopenia thrombosis has been clearly established[39]. Use of Ancord has been reported successive in cardiac catheterization and coronary artery bypass grafting[40]. The antithrombotic and thrombolytic activities of agkisacutacin (Agk), a component isolated from *Agkistrodon acutus* venom, were determined *in vitro* and *in vivo*. Agk can significantly inhibit thrombus formation and accelerates thrombolysis of pulmonary emboli in rates[41]. Recently, Gomes *et al*[42] identifies a non protein micromolecular toxin (mol. wt 260) from the Indian King Cobra venom. This toxin possesses antiarrythmic properties at microgram level.

Venom peptides in cancer therapy

Cancer is characterized by uncontrolled cell division, cell transformation, and escape of apoptosis, invasion, angiogenesis and metastasis. Induction of apoptosis is the most important mechanism of many anticancer agents. Snake venom disintegrins are the low molecular weight molecules with different structure, potency and specificity initially isolated from viperid snake venoms, usually contain integrin,

an agent for development of therapeutics for the treatment of cancer. Integrins are important in cell adhesion, cell migration, tissue organization, cell growth, homeostasis and inflammatory responses, so they are in the study for the development of drugs for the treatment of cancer[43]. The induction of the apoptosis manifests the control on the tumor size and number of tumor cells hence establishing the application of apoptosis inducers as vital components in the treatment of cancer. Torii *et al*. purified an apoptosis-inducing factor[44], apoxin I from rattlesnake venom and amino-terminal sequences of the purified apoxin-I similar to L-amino acid oxidases (LAO). After creation of the primary structure of apoxin-I by using cloned c-DNA, the authors demonstrated that apoxin-I likely to bind FAD to catalyze oxidative deamination of L-amino acids and apoptosis inducing activity. Naumann *et al*. isolated and purified L-amino acid oxidases (LAAOs) from *Bothrops leucurus* (Bl-LAAO) and reported biochemical features of Bl-LAAO associated with its effect on platelet function and cytotoxicity[45]. Cytotoxicity of Bl-LAAO was observed in the stomach cancer MKN-45, adeno carcinoma HUTU, colorectal RKO and human fibroblast LL-24 cell lines. The authors concluded that *B. leucurus* venom is cytotoxin acting primarily via the generation of high amounts of H_2O_2 which kills the cells. Kim *et al*. purified venom of king cobra, *Ophiophagus hannah* and determined the cytotoxic components in purified venom[46]. The components were mainly consistent of L-amino acid oxidase. The authors observed cytotoxic effects of L-amino acid oxidase on stomach cancer, murine melanoma, fibrosarcoma, colorectal cancer and Chinese hamster ovary cell lines. It was observed that cytotoxic protein causes inhibition of cell proliferation by 74 % according to [3H] thymidine uptake assay. Mechanism of enzyme action may be related to the inhibition of thymidine incorporation and an interaction with DNA. Gebrim *et al*[47] evaluated both *in vitro* and *in vivo* antitumor activity of p-bromophenacyl bromide (BPB) modified bothropstoxin-I from *Bothrops jararacussu* venom (BthTX-I). Different tumor cell lines were found to susceptible from lytic action of BPB-BthTX-I and also from synthetic peptide. Guo *et al*. studied pharmacokinetics of cytotoxin from Chinese cobra (*Naja naja atra*) venom in rabbits[48]. Plasma levels of the cytotoxin were analyzed by a biotinavidin enzyme-linked immunosorbent assay. Gomes *et al*. purified a lethal cardiotoxic-cytotoxic protein from the Indian monocellate cobra (*Naja kaouthia*) venom by ion-exchange chromatography and HPLC[49]. Cytotoxicity studies on human leukemic U937 and K562 cells showed a significant inhibition of cell proliferation in a dose and time dependent manner. In another work, the authors purified venom from Indian *Naja naja* through ion exchange chromatography and found that fraction 32 produced cytotoxic-cardiotoxic properties[50]. NN-32 showed cytotoxicity on EAC cells, increased survival time of inoculated EAC mice, reduced solid tumor volume and weight. NN-32 induced anticancer activity in EAC mice mediated through its apoptogenic-antioxidant property. Markland *et al*. isolated and characterized a lectin (BJcuL) from the venom of the snake *Bothrops jararacussu*[51]. The authors examined *in vitro* effect of the BJcuL on adhesion of human ovarian and breast cancer carcinoma cells and viability of these cell lines, as well as of human glioblastoma, human bladder carcinoma, human leukemia and bovine brain endothelial cells. BJcuL was found as a potent inhibitor of growth of some tumor cell lines and an endothelial cell line. Zhang *et al*[52] isolated ACTX-6 from *Agkistrodon acutus* snake venom and demonstrated cytotoxic activity to various cancer cells *in vitro*. The authors investigated the exact mechanism (induce cell apoptosis) of ACTX-6. The authors reported that ACTX-6-induced cell death through production of ROS (hydrogen peroxide). Sun *et al*. extracted specific protein Okinawa Habu apoxin protein-1 (OHAP-1) from *Okinawa habu* venom which is well known for its toxic effects[53]. In this study, it was investigated that OHAP-1 could induce apoptosis in some glioma cells and elucidated the possible mechanism involved. Induction of apoptosis was determined by using DNA gel electrophoresis, DNA flow cytometry and TUNEL assay. It was reported that apoptotic effect of OHAP-1 on malignant glioma cells could be through the generation of intracellular ROS and p53 protein expression. Karthikeyan *et al*[54] evaluated antitumor activity of the sea snake venom (*Lapemis curtus*) against Ehrlich's ascites carcinoma (EAC) in Swiss albino mice and HeLa and Hep2 tumor cell cultures. Decrease in tumor volume and viable tumor cell count was observed these characteristics were considered as an important indicator of reduction of tumor burden. Fue *et al.* studied snake venom-derived arginine-glycine-aspartic acid (RGD)-containing disintegrins (e.g. rhodostomin)[55], which inhibited the adhesion of breast and prostate carcinoma cells to bone extracellular matrices, without affecting the viability of tumor cells. It was reported that co-administration of disintegrin with tumor cells inhibited tumor growth in bone through the decrease of cell adhesion, migration and osteolysis in bone. Gomes *et al*[56] purified and crystallized heat stable protein toxin (drCT-I) from Eastern Indian *Daboia russelli russelli* venom. drCT-I was evaluated for anticancer activity against EAC cells *in vivo* and human leukemic cells (U937, K562) *in vitro*. drCT-I significantly decreased EAC cell count. The authors confirmed induction of apoptosis. It was found that drCT-I brought about apoptosis by G1 phase arrest of the cell cycle. Lin *et al*[57] isolated cardiotoxin III (CTX III), from *Naja naja atra* venom, and reported its anticancer activity. It was evidenced by accumulation of sub-G1 population, externalization of phosphatidylserine, release of cytochrome C, and activation of both capases-9 and caspase-3 that CTX III-induced cell apoptosis. Study showed that CTX III suppressed phosphorylation of JAK2, STAT3, Akt, and activation of PI3K. It was suggested that CTX III suppressed JAK2- and PI3K-activation in parallel with the inhibition of STAT3 and Akt phosphorylation. Nunes *et al*[58]. evaluated the anti-tumor potential as well as its cytotoxicity and hemolysis activity of BlL, a galactoside-binding lectin isolated from *Bothrops leucurus* venom. The authors verified induced apoptosis in K562 cells, by phosphatidylserine externalization analysis and mitochondrial membrane potential determination. Nolte *et al*[59]. purified BJcuL, a lectin from *Bothrops jararacussu* venom by affinity chromatography and observed its cytotoxic effects to gastric carcinoma cells MKN45 and AGS. BjcuL was examined on the cell morphology, cytoskeleton using fluorescence microscopy. The authors confirmed cytotoxicity of BJcuL on tumor cells mainly by altering cell adhesion and through induction of apoptosis.

Venom Peptides against Viral Infections

In recent years, a considerable progress has been made in understanding viral biology and numerous clinical trials have been conducted with various candidate antiviral drugs, 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[60]. Another study that demonstrated the potential therapeutic value of venoms was developed using *Naja nigricollis* venom in human erythrocytes infected with the Sendai virus. 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 nigrocollis* 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[61]. L-amino acid oxidases (LAAO), flavoenzymes obtained from the venom of *Bothrops jararaca*, were found to show antiviral activity against the dengue virus. In a recent study, in cells infected with the dengue type 3 virus (DENV-3) and treated with LAAO isolated from the venom of *Bothrops jararaca*, there was a reduction in viral load compared to cells infected with the same virus and not treated with enzymes from the venom[62]. Metalloproteinase inhibitors present in snake venom may prevent the production of new viruses by inhibiting protease enzymes[63,64]. Protease inhibitors commonly block the protease enzyme and prevent the cell from producing new viral particles. Immunokine, an oxidized derivative of the α-toxin extracted from *Naja siamensis* snake venom has shown to inhibit the infection of lymphocytes by HIV and feline immunodeficiency virus (FIV) through the chemokine receptors CCR5 and CXCR4[65]. A group of investigators in Asia reported a remarkable similarity between the 164-174 sequence of the short segment of gp120 of HIV-1 and 30-40 amino acid residues of the long-chain neurotoxins in the venom of snakes such as *Naja siamensis* and *Bungarus multicinctus*[66,67]. Therefore, both are able to compete for the same receptor or HIV binding site. LAAO, obtained from the venom of the Asian snake *Trimeresurus stejnegeri*, was purified and cloned. At concentrations that had little effect on cell viability, LAAO was able to inhibit the infection and replication of HIV-1 in a dose-dependent manner. This was the first report of potential antiviral activity shown by LAAO extracted from snake venom[68]. LAAO, present in the venom of *Crotalus atrox*, *Pseudechis australis* and *Trimeresurus stejnegeri* inhibit the infection and replication of HIV through the p24 antigen in a dose-dependent manner[68,69]. The presence of the p24 antigen is directly related to viral load[70]. As well as binding to the cell membrane protein, hydrogen peroxide (H_2O_2), an oxygen free radical, is able to inhibit infection and the replication of HIV, further improving its antiviral effect. In contrast, catalases use H_2O_2 as a substrate, degrading it and thus reducing its antiviral effect[68]. LAAO is also an important component of the venom of the snake *Calloselasma rhodostoma*, found in southeastern Asia, which induces cell apoptosis and exerts antibacterial and anti-HIV effects[71]. Some studies conducted with the venoms of various snakes such as *Crotalus adamanteus*, *Oxyuranus microlepidotus*, *Bungarus candidus*, *Hydrophis cyanocinctus*, *Naja naja*, *Notechis aterater*, *Naja sumatrana* and *Naja kaouthia* have demonstrated an anti-HIV effect[72-74]. Another example of the anti-HIV effect of bio molecules extracted from venoms is phospholipase A2 (PLA2). This phospholipase has been associated with a variety of biological effects such as avoiding the intracellular release of the virus capsid protein through an unknown mechanism, suggesting that this substance block the entry of the virus into the cells prior to and regardless of the use of a co-receptor. The antiviral activity appears to involve a specific interaction between PLA2 and the host cells. Venom PLA2 protects the primary leukocytes in human blood from the replication of HIV-1 variants[63,64]. PLA2, found in the venom of many snakes, has been shown to block entry of the virus into the cells prior to the virus uncoating process by preventing the intracellular release of proteins from the viral capsid[75]. A study developed with 12 synthetic peptides derived from PLA2, contained in venom, showed an anti-HIV effect. The p3bv peptide prevents HIV-1 from binding to the T cells, since it binds to the CXCR4 receptor[76]. Therefore, the viral particles are unable to bind to cells and after a certain period of time they become unviable since they are unable to multiply. Against HIV: In a study conducted by Villarrubia *et al.*[77], crotoxin – a phospholipase isolated from the venom of *Crotalus durissus terrificus* (PLA2-Cdt) – showed *in vitro* activity against HIV. The anti-HIV effect of PLA2-Cdt (inhibition of gp24) is probably the result of its capacity to destabilize some binding receptors (cell-surface heparins). Chemokine and their derivatives forma class of HIV inhibitors that show promise as potential therapeutic agents[75]. These substances are able to compete with the glycoprotein (gp120) from the viral envelope to bind with the receptor[78-80]. Furthermore, various low-molecular-weight compounds that bind to CXCR4 and inhibit HIV-1 replication have been identified[77]. The ability of peptides and small molecules to block the entry of HIV through binding with CXCR4 has already been described[81-83].

Venom peptides for new promises

Many types of venom have antibacterial properties. For example, Stiles *et al.*[84] found 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. Antibacterial and antiparasitic effects of the venom of the *Marajo´ lancehead* (*Bothrops marajoensis*) were shown to be caused by PLA2 and L-amino acid oxidase toxins[85]. Eric Linguelia *et al*[86] identified the proteins from the black mamba (*Dendroaspsis polylepsis*) that cause increase in pain threshold in comparison to opiates by acting on different site that is acid-sensing ion channels(ASICs), suggesting that they offer several potential targets for future drug development.

CONCLUSION

It may be concluded that the snake venom may serve as a starting material for drug design to combat several pathophysiological problems. But due to very few clinical studies are available so there extensive need is required to run research programs to clinically work out the several different areas like cardiovascular, anti cancer, neurological, with a view to develop new drugs to combat human suffering and death globally.

REFERENCES

1. Leon G, Sanchez L, Hernandez A, Villalta M, Herrera M, Segura A, *et al*. Immune response towards snake venoms. Inflamm Allergy Drug Targets 2011; 10: 381–398. http://dx.doi.org/10.2174/1871528 11797200605 PMid:21824081
2. Santos MMDV, Santana CD, Giglio JR, Da Silva RJ, Sampaio SV, Soares AM, *et al*. Antitumoural effect of an L-amino acid oxidase isolated from *Bothrops jararaca* snake venom. Basic Clin Phramacol Toxicol 2008; 102: 533–542. http://dx.doi.org/10.1111/j.1742-7843.2008.00229.x PMid:18346051
3. Kitchens CS, Eskin TA. Fatality in a case of envenomation by *Crotalus adamanteus* initially successfully treated with polyvalent ovine antivenom followed by recurrence of defibrinogenation syndrome. J Med Toxicol 2008; 4: 180–183. http://dx.doi.org/10.1007/BF03161198 PMCid:PMC3550043
4. Biardi JE, Chien DC, Coss RG. California ground squirrel (Spermophilus beecheyi) defenses against rattlesnake venom digestive and hemostatic toxins. J Chem Ecol 2006; 32: 137–154. http:// dx.doi.org/10.1007/s10886-006-9357-8 PMid:16525875
5. Antunes TC, Yamashita KM, Barbaro KC, Saiki M, Marcelo L Santoro. Comparative analysis of newborn and adult *Bothrops jararaca* snake venoms. Toxicon 2010; 56: 1443–1458. http://dx.doi.org/10.1016 /j.toxicon.2010.08.011 PMid:20816886
6. Sales PBV, Santoro ML. Nucleotidase and DNase activities in Brazilian snake venoms. Compr Biochem Physiol 2008;147C: 85–95.
7. Chu CW, Tsai TS, Tsai IH, Lin YS, Tu MC. Prey envenomation does not improve digestive performance in Taiwanese pit vipers (Trimeresurus gracilis and T. stejnegeri stejnegeri) Compr Biochem Physiol 2009; 152A: 579–585.
8. Wuster W, Peppin L, Pook CE, Walker DE. A nesting of vipers: phylogeny, historical biogeography and patterns of diversification of the Viperidae (Squamata: Serpentes) Mol Phylogenet Evol 2008; 49: 445–459. http://dx.doi.org/10.1016/j.ympev.2008.08.019 PMid:18804544
9. Tsai CH, Yang SH, Chien CM, Lu MC, Lo CS, Lin YH, *et al*. Mechanisms of cardiotoxin III-induced apoptosis in human colorectal cancer colo205 cells. Clin Exp Pharmacol Physiol 2006; 33: 177–182. http://dx.doi.org/10.1111/j.1440-1681.2006.04334.x PMid:16487259
10. Markland FS. Snake venoms and the hemostatic system.Toxicon 1998; 369120: 1749-800. http://dx.doi.org/10.1016/S0041-0101(98)00126-3
11. Bell WR Jr. Defibrinogenating enzymes, Drugs 1997; 54 Suppl 3: 18-30. http://dx.doi.org/10.2165/00003495-199700543-00005 PMid:936 0849
12. Huang TF, Holt JC, Lukasiewcz H and Niewiarowski S Trigramin. A low molecular weight peptide inhibiting fibrinogen interaction with platelet receptors expressed on glycoprotein IIb/IIIa complex. Journal of Biological Chemistry 1987; 262: 16157-16163. PMid:3680247
13. Niewiarowski S, MacLane MA, Klocsewiak M and Stewart GJ. Disintegrins and other naturally occurring antagonists of platelet fibrinogen receptor. Seminars in Hematology 1994; 31: 289-300. PMid:7831574
14. Juliano D, Wang Y, Marcinkiewcz C, Rosenthal LA, Stewart GJ and Niewiarowski S. Disintegrin interaction with avß3 integrin on human umbilical vein endothelial cells: expression of ligand-induced binding site on ß3 subunit. Experimental Cell Research 1996; 225: 132-142. http://dx.doi.org/10.1006/excr.1996.0164 PMid:8635506
15. Usami Y, Fujimura Y, Miura S, Shima H, Yoshida E, Yoshioka A, Hirano K, Suzuki M and Titani K. A 28 kDa-protein with disintegrin-like structure (jararhagin-C) purified from *Bothrops jararaca* venom inhibits collagen- and ADP-induced platelet aggregation. Biochemical and Biophysical Research Communications 1994; 201: 331-339. http://dx.doi.org/10.1006/bbrc.1994.1706 PMid:8198592
16. Kamiguti AS, Markland FS, Zhou Q, Laing GD, Theakston RDG and Zuzel M. Proteolytic cleavage of the B, subunit of platelets $\alpha_2\beta_1$ integrins by the matalloproteinases jarahagin compromises collagen stimulated phosphorylation of $pp72^{syk}$. Journal of biological chemistry 1997; 272: 32599-32605. http://dx.doi.org/10.1074/jbc.272.51.32599 PMid:9405475
17. Clark EA, Trikha M, Markland FS and Brugge JS. Structurally distinct disintegrins contortrostatin and multisquamatin differentially regulate platelet tyrosine phosphorylation. Journal of Biological Chemistry 1994; 269: 21940-21943. PMid:7520909
18. Trikha M, De Clerck Y and Markland FS. Contortrostatin, a snake venom disintegrin, inhibits ß1 integrin-mediated human metastatic melanoma cell adhesion and blocks experimental matastasis. Cancer Research 1994; 54: 4993-4998. PMid:7520832
19. Knudsen KA, Tuszynski GP, Huang TF and Niewiarowski S. Trigramin, an RGD-containing peptide from snake venom, inhibits cell-substratum adhesion of human melanoma cells. Experimental Cell Research 1988; 179: 42-49. http://dx.doi.org/10.1016/0014-4827(88)90346-1
20. Sheu JR, Lin CH and Huang TF. Triflavin, an anti platelet peptide, inhibits tumor cell-extracellular matrix through an arginine-glycine-aspartic acid-dependent mechanism. Journal of Laboratory and Clinical Medicine 1994; 123: 256-263. PMid:8301202
21. Beviglia L, Stewart GJ and Niewiarowski S. Effect of four disintegrins on the adhesive and metastatic properties of B16F10 melanoma cells in a murine model. Oncology Research 1995; 7: 7-20. PMid:7549046
22. Morris VL, Schmidt EE, Koop S, MacDonald IC, Grattan M, Khokha MA, MacLane MA, Niewiarowski S, Chambers AF and Groom AC. Effects of the disintegrin eritostatin on individual steps of hematogenous metastasis. Experimental Cell Research 1995; 219: 571-578. http://dx.doi.org/10.1006/excr.1995.1266 PMid:7641809
23. Bronson RA, Gailit J, Bronson S and Oula L. Echistatin, a disintegrin, inhibits sperm-oolemmal adhesion but not oocyte penetration. Fertility and Sterility 1995; 64: 414-420. PMid:7615123
24. Gallacci M, Cavalcante WLG. Understanding the *in vitro* neuromuscular activity of snake venom Lys49 phospholipase A2 homologues. Toxicon 2010; 55: 1–11. http://dx.doi.org/10.1016/j.toxicon.2009.10.025 PMid:19874839
25. Marcussi S, Sant Ana CD, Oliveira CZ, Rueda AQ, Menaldo DL, Beleboni RO, *et al*. Snake venom phospholipase A2 inhibitors: medicinal chemistry and therapeutic potential. Cur Topics Med Chem 2007; 7: 743–756. http://dx.doi.org/10.2174/156802607780487614
26. Gutierrez JM, Alexandra R, Escalante T, Díaz C. Hemorrhage induced by snake venom metalloproteinases: biochemical and biophysical mechanisms involved in microvessel damage. Toxicon 2005; 45: 997–1011. http://dx.doi.org/10.1016/j.toxicon.2005.02.029 PMid:15922771
27. Marshall DM. Enzyme activities and biological functions of snake venoms. Appl Herpetol 2005; 2: 109–123. http://dx.doi.org/ 10.1163/1570754043492135
28. Aguilar I, Guerrero B, Salazar AM, Giron ME, Perez JC, Sanchez EE, *et al*. Individual venom variability in the South American rattlesnake Crotalus durissus cumanensis. Toxicon 2007; 50: 214–224. http://dx.doi.org/10.1016/j.toxicon.2007.03.012 PMid:17482229
29. Gutierrez JM, Ownby CL. Skeletal muscle degeneration induced by venom phospholipases A2: insights into the mechanisms of local and systemic myotoxicity. Toxicon 2003; 42: 915–931. http://dx.doi.org/10.1016/j.toxicon.2003.11.005 PMid:15019491
30. Yamazaki Y, Takani K, Atoda H, Morita T. Snake venom vascular endothelial growth factors (VEGFs) exhibit potent activity through their specific recognition of KDR (VEGF receptor 2) J Biol Chem 2003; 278: 51985–51988. http://dx.doi.org/10.1074/jbc.C300454200 PMid:146 00159
31. Chippaux JP, Williams V, White J. Snake venom variability: methods of study, results and interpretation. Toxicon 1991; 29: 1279–1303. http://dx.doi.org/10.1016/0041-0101(91)90116-9
32. Warrell DA. Snake venoms in science and clinical medicine. Russell's viper: biology, venom and treatment of bites. Trans R Soc Trop Med Hyg 1989; 83: 732–740. http://dx.doi.org/10.1016/0035-9203(89) 90311-8
33. Shashidharamurthy R, Jagadeesha DK, Girish KS, Kemparaju K. Variation in biochemical and pharmacological properties of Indian cobra (*Naja naja*) venom due to geographical distribution. Mol Cell Biochem 2002; 229: 93–101. http://dx.doi.org/10.1023/A:1017972511272 PMid:11936852
34. You WK, Choi WS, Koh YS, Shin HC, Jang Y, Chung KH. Functional characterization of recombinant batroxobin, a snake venom thrombin-like enzyme, expressed from Pichia pastoris. FEBS Letters 2004; 571: 67–73. http://dx.doi.org/10.1016/j.febslet.2004.06.060 PMid:15280019
35. Mackessy SP. Biochemistry and pharmacology of colubrid snake venoms. J Toxicol Toxin Rev 2002; 21: 43–83.
36. Jin H, Varner J. Integrins: roles in cancer development and as treatment targets. Br J Cancer 2004; 90: 561–565. http://dx.doi.org/10.1038/ sj.bjc.6601576 PMid:14760364 PMCid:PMC2410157
37. Shremann DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, Hsu CY and Levy DE. Intravenous ancord STAT study, a randomized controlled trail, stroke treatment with ancord trail, JAMA 2000; 283: 2395. http://dx.doi.org/10.1001/jama.283.18.2395
38. Mayberg MR and Furlan A. Ancord is snake venom an antidote for snake, JAMA 2000; 283: 2440. http://dx.doi.org/10.1001 /jama.283.18.2440 PMid:10815092
39. Carter CJ. New development in acute anticoagulant therapy what improves over traditional heparin are on the horizon, Postgrad Med 1996; 99: 129. PMid:8668626
40. Lathan LO and Staggers SL. Ancord: the use of snake venom in the treatment of patients with heparin- induced thrombocytopenia and thrombosis undergoing coronary artery bypass grafting: nursing management, Heart Lung 1996; 25: 451. http://dx.doi.org/10.1016/S 0147-9563(96)80046-X
41. Li S, Ji H, Cheng X, Li Bx and Ng TB. Anti thrombolytic and Thrombolytic activities of A gkisacutacin, a snake venom proteinase in experimental animal. Gen Pharmacol 2000; 35: 179. http://dx.doi. org/10.1016/S0306-3623(01)00097-0

42. Gomes A, Saha Archita, Biswas AK and Dasgupta SC. Occurrence of non protein micro molecular toxin from the Indian King Cobra Ophiophagus Hannah venom, (unpublished data)
43. Koh CY, Kini RM. From snake venom toxins to therapeutics - Cardiovascular examples. Toxicon 2012; 59: 497–506. http://dx.doi.org/10.1016/j.toxicon.2011.03.017 PMid:21447352
44. Torii S, Yamane K, Mashima T, Haga N, Yamamoto K, Fox JW, *et al*. Molecular cloning and functional analysis of apoxin I, a snake venom-derived apoptosis-inducing factor with L-amino acid oxidase activity. Biochemistry 2000; 39: 3197–3205. http://dx.doi.org/10.1021/bi992416z PMid:10727211
45. Naumann GB, Silva LF, Silva L, Faria G, Richardson M, Evangelista K. Cytotoxicity and inhibition of platelet aggregation caused by an L-amino acid oxidase from *Bothrops leucurus* venom. Biochim Biophys Acta 2011; 1810: 683–694. http://dx.doi.org/10.1016/j.bbagen.2011.04.003 PMid:21539897
46. Ahn MY, Lee BM, Kim YS. Characterization and cytotoxicity of L-amino acid oxidase from the venom of king cobra (Ophiophagus hannah) Int J Biochem Cell Biol 1997; 29: 911–919. http://dx.doi.org/10.1016/S1357-2725(97)00024-1
47. Gebrim LC, Marcussi S, Menaldo DL, De Menezes CSR, Nomizo A, Hamaguchi A. Antitumor effects of snake venom chemically modified Lys49 phospholipase A2-like BthTX-I and a synthetic peptide derived from its C-terminal region. Biologicals 2009; 37: 222–229. http://dx.doi.org/10.1016/j.biologicals.2009.01.010 PMid:19264509
48. Guo MP, Wang QC, Liu GF. Pharmacokinetics of cytotoxin from chinese cobra (*Naja naja atra*) venom. Toxicon 1993; 31: 339–343. http://dx.doi.org/10.1016/0041-0101(93)90151-8
49. Debnath A, Saha A, Gomes A, Biswas S, Chakrabarti P, Giri B, *et al*. A lethal cardiotoxic-cytotoxic protein from the Indian monocellate cobra (*Naja kaouthia*) venom. Toxicon 2010; 56: 569–579. http://dx.doi.org/10.1016/j.toxicon.2010.05.016 PMid:20595038
50. Das T, Bhattacharya S, Halder B, Biswas A, Gupta SD, Gomes A. Cytotoxic and antioxidant property of a purified fraction (NN-32) of Indian *Naja naja* venom on Ehrlich ascites carcinoma in BALB/c mice. Toxicon 2011; 57: 1065–1072. http://dx.doi.org/10.1016/j.toxicon.2011.04.012 PMid:21530568
51. De Carvalho DD, Schmitmeier S, Novello JC, Markland FS. Effect of BJcuL (a lectin from the venom of the snake *Bothrops jararacussu*) on adhesion and growth of tumor and endothelial cells. Toxicon 2001; 39: 1471–1476. http://dx.doi.org/10.1016/S0041-0101(01)00106-4
52. Zhang L, Cui L. A cytotoxin isolated from Agkistrodon acutus snake venom induces apoptosis via Fas pathway in A549 cells. Toxicol *In vitro* 2007; 21: 1095–1103. http://dx.doi.org/10.1016/j.tiv.2007.04.008 PMid:17544616
53. Sun LK, Yoshii Y, Hyodo A, Tsurushima H, Saito A, Harakuni T, *et al*. Apoptotic effect in the glioma cells induced by specific protein extracted from Okinawa habu (Trimeresurus flavoviridis) venom in relation to oxidative stress. Toxicol *In vitro* 2003; 17: 169–177. http://dx.doi.org/10.1016/S0887-2333(03)00010-9
54. Karthikeyan R, Karthigayan S, Sri Balasubashini M, Somasundaram ST, Balasubramanian T. Inhibition of Hep2 and HeLa cell proliferation *in vitro* and EAC tumor growth *in vivo* by Lapemis curtus (Shaw 1802) venom. Toxicon 2008; 51: 157–161. http://dx.doi.org/10.1016/j.toxicon.2007.08.012 PMid:17936322
55. Yang RS, Tang CH, Chuang WJ, Huang TH, Peng HC, Huang TF, *et al*. Inhibition of tumor formation by snake venom disintegrin. Toxicon 2005; 45: 661–669. http://dx.doi.org/10.1016/j.toxicon.2005.01.013 PMid:15777962
56. Gomes A, Choudhury SR, Saha A, Mishra R, Giri B, Biswas AK, *et al*. A heat stable protein toxin (drCT-I) from the Indian viper (*Daboia russelli russelli*) venom having anti proliferative, cytotoxic and apoptotic activities. Toxicon 2007; 49: 46–56. http://dx.doi.org/10.1016/j.toxicon.2006.09.009 PMid:17055549
57. Lin KL, Su JC, Chien CM, Chuang PW, Chang LS, Lin SR. Down-regulation of the JAK2/PI3K-mediated signaling activation is involved in Taiwan cobra cardiotoxin III-induced apoptosis of human breast MDA-MB-231 cancer cells. Toxicon 2010; 55: 1263–1273. http://dx.doi.org/10.1016/j.toxicon.2010.01.017 PMid:20144642
58. Nunes ES, Souza MA, Vaz AF, Silva TG, Aguiar JS, Batista AM. Cytotoxic effect and apoptosis induction by *Bothrops leucurus* venom lectin on tumor cell lines. Toxicon 2012; 59: 667–671. http://dx.doi.org/10.1016/j.toxicon.2012.03.002 PMid:22445823
59. Nolte S, De Castro DD, Barea AC, Gomes J, Magalhães A, Mello Zischler LF. A lectin purified from *Bothrops jararacussu* venom, induces apoptosis in human gastric carcinoma cells accompanied by inhibition of cell adhesion and actin cytoskeleton disassembly. Toxicon 2012; 59: 81–85. http://dx.doi.org/10.1016/j.toxicon.2011.10.012 PMid:22079298
60. Petricevich VL, Mendoça RZ. Inhibitory potential of *Crotalus durissus terrificus* venom on measles virus growth. Toxicon 2003; 42(2): 143-53. http://dx.doi.org/10.1016/S0041-0101(03)00124-7
61. Borkow G, Ovadia M. Selective lysis of virus-infected cells by cobra snake cytotoxins: a sendai virus, human erythrocytes and cytotoxin model. Biochem Biophys Res Commun 1999; 264(1): 63-8. http://dx.doi.org/10.1006/bbrc.1999.1483 PMid:10527842
62. Sant'Ana CD, Menaldo DL, Costa TR, Godoy H, Muller VD, Aquino VH, *et al*. Antiviral and antiparasite properties of an L-amino acid oxidase from the snake *Bothrops jararaca*: cloning and identification of a complete cDNA sequence. Bio chem Pharmacol 2008; 76(2): 279-88. http://dx.doi.org/10.1016/j.bcp.2008.05.003 PMid:18555977
63. Fenard D, Lambeau G, Valentin E, Lefebvre JC, Lazdunski M, Doglio A. Secreted phospholipases A(2), a new class of HIV inhibitors that block virus entry into host cells. J Clin Invest 1999; 104(5): 611-8. http://dx.doi.org/10.1172/JCI6915 PMid:10487775 PMCid:PMC408539
64. Da Silva JO, Fernandes RS, Ticli FK, Oliveira CZ, Mazzi MV, Franco JJ, *et al*. Triterpenoid saponins, new metalloprotease snake venom inhibitors isolated from *Pentaclethra macroloba*. Toxicon 2007; 50(2): 283-91. http://dx.doi.org/10.1016/j.toxicon.2007.03.024 PMid:17517426
65. Shivaji PG. Therapeutic alternatives from venoms and toxins. Indian J Pharmacol 2007; 39(6): 260-64. http://dx.doi.org/10.4103/0253-7613.39143
66. Neri P, Bracci L, Rustici M, Santucci A. Sequence homology between HIV gp120, rabies virus glycoprotein, and snake venom neurotoxins. Is the nicotinic acetylcholine receptor an HIV receptor? Arch Virol 1990; 114(3-4): 265-9. http://dx.doi.org/10.1007/BF01310756 PMid:2241576
67. Sönnerborg A, Johansson B. The neurotoxin-like sequence of human immunodeficiency virus gp120: a comparison of sequence data from patients with and without neurological symptoms. Virus Genes 1993; 7(1): 23-31. http://dx.doi.org/10.1007/BF01702346
68. Zhang YJ, Wang JH, Lee WH, Wang Q, Liu H, Zheng YT, *et al*. Molecular characterization of *Trimeresurus stejnegeri* venom L-amino acid oxidase with potential anti-HIV activity. Biochem Biophys Res Commun 2003; 309(3): 598-604. http://dx.doi.org/10.1016/j.bbrc.2003.08.044 PMid:12963032
69. Du XY, Clemetson KJ. Snake venom L-amino acid oxidases. Toxicon 2002; 40(6): 659-65. http://dx.doi.org/10.1016/S0041-0101(02)00102-2
70. Brown AE, Vahey MT, Zhou SY, Chung RC, Ruiz NM, Hofheinz D, *et al*. Quantitative relationship of circulating p24 antigen with human immunodeficiency virus (HIV) RNA and specific antibody in HIV-infected subjects receiving antiretroviral therapy. The RV43 Study Group. J Infect Dis 1995; 172(4): 1091-95. http://dx.doi.org/10.1093/infdis/172.4.1091 PMid:7561186
71. Moustafa IM, Foster S, Lyubimov AY, Vrielink A. Crystal structure of LAAO from *Calloselasma rhodostoma* with an L-phenylalanine substrate: insights into structure and mechanism. J Mol Biol 2006; 364(5): 991-1002. http://dx.doi.org/10.1016/j.jmb.2006.09.032 PMid:17046020 PMCid:PMC2018609
72. Radis Baptista G, Moreno FB, de Lima Nogueira L, Martins AM, De Oliveira D, Toyama MH, *et al*. Crotacetin, a novel snake venom C-type lectin homolog of convulxin, exhibits an unpredictable antimicrobial activity. Cell Bio chem Biophys 2006; 44(3): 412-23. http://dx.doi.org/10.1385/CBB:44:3:412
73. Perumal Samy R, Pachiappan A, Gopalakrishnakone P, Thwin MM, Hian YE, Chow VT, *et al*. *In vitro* antimicrobial activity of natural toxins and animal venoms tested against *Burkholderia pseudomallei*. BMC Infect Dis 2006; 6(1): 100. http://dx.doi.org/10.1186/1471-2334-6-100 PMid:16784542 PMCid:PMC1569838
74. Nair DG, Fry BG, Alewood P, Kumar PP, Kini RM. Antimicrobial activity of omwaprin, a new member of the waprin family of snake venom proteins. Bio chem J 2007; 402(1): 93-104. http://dx.doi.org/10.1042/BJ20060318 PMid:17044815 PMCid:PMC1783991
75. Berger EA, Murphy PM, Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annu Rev Immunol 1999; 17(1): 657-700. http://dx.doi.org/10.1146/annurev.immunol.17.1.657 PMid:10358771
76. Fenard D, Lambeau G, Maurin T, Lefebvre JC, Doglio A. A peptide derived from bee venom-secreted phospholipase A2 inhibits replication of T-cell tropic HIV-1 strains via interaction with the CXCR4 chemokine receptor. Mol Pharmacol 2001; 60(2): 341-7. PMid:11455021
77. Chan DC, Kim PS. HIV entry and its inhibition. Cell 1998; 93(5): 681-4. http://dx.doi.org/10.1016/S0092-8674(00)81430-0
78. Howard OM, Oppenheim JJ, Wang JM. Chemokines as molecular targets for therapeutic intervention. J Clin Immunol 1999; 19(5): 280-92. http://dx.doi.org/10.1023/A:1020587407535 PMid:10535604
79. Villarrubia VG, Costa LA, Díez RA. Fosfolipasas A2 segregadas (sPLA2): ¿amigas o enemigas?¿Actores de la resistencia antibacteriana

y antivirus de la inmunodeficiencia humana? Med Clin (Barc) 2004; 123(19): 749-57. http://dx.doi.org/10.1016/S0025-7753(04)74656-4 http://dx.doi.org/10.1157/13069312
80. Ferreira SH. A bradykinin-potentiating factor (bfp) present in the venom of *Bothrops jararaca*. Br J Pharmacol Chemother 1965; 24(1): 163-9. http://dx.doi.org/10.1111/j.1476-5381.1965.tb02091.x PMid:14302350 PMCid:PMC1704050
81. Doranz BJ, Grovit Ferbas K, Sharron MP, Mao SH, Goetz MB, Daar ES, *et al*. A small-molecule inhibitor directed against the chemokine receptor CXCR4 prevents its use as an HIV-1 coreceptor. J Exp Med 1997; 186(8): 1395-400. http://dx.doi.org/10.1084/jem.186.8.1395 PMid:9334380 PMCid:PMC2199097
82. Murakami T, Nakajima T, Koyanagi Y, Tachibana K, Fujii N, Tamamura H, *et al*. A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection. J Exp Med 1997; 186(8): 1389-93. http://dx.doi.org/10.1084/jem.186.8.1389 PMid:9334379 PMCid:PMC2199089
83. Schols D, Este JA, Henson G, De Clercq E. Bicyclams, a class of potent anti-HIV agents, are targeted at the HIV co receptor fusin/CXCR-4. Antiviral Res 1997; 35(3): 147-56. http://dx.doi.org/10.1016/S0166-3542(97)00025-9
84. Stiles BG, Sexton FW, Weinstein SA. Antibacterial effects of different snake venoms: purification and characterization of antibacterial proteins from *Pseudechis australis* (Australian king brown or mulgasnake) venom. Toxicon 1991; 29: 1129–41. http://dx.doi.org/10.1016/0041-0101(91)90210-I
85. Costa Torres AF, Dantas RT, Toyama MH, Diz FE, *et al*. Antibacterial and antiparasitic effects of *Bothrops marajoensis* venom and its fractions: phospholipase A2 and L-amino acid oxidase. Toxicon 2010; 55: 795–804. http://dx.doi.org/10.1016/j.toxicon.2009.11.013 PMid:19944711
86. Helen Shen. Deadly snake venom delivers pain relief, Nature News; 2012.

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