

MINI-REVIEW

Snake Venom: A Potent Anticancer Agent

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Abstract

Since cancer is one of the leading causes of death worldwide, and there is an urgent need to find better treatment. In recent years remarkable progress has been made towards the understanding of proposed hallmarks of cancer development and treatment. Treatment modalities comprise radiation therapy, surgery, chemotherapy, immunotherapy and hormonal therapy. Currently, the use of chemotherapeutics remains the predominant option for clinical control. However, one of the major problems with successful cancer therapy using chemotherapeutics is that patients often do not respond or eventually develop resistance after initial treatment. This has led to the increased use of anticancer drugs developed from natural resources. The biodiversity of venoms and toxins makes them a unique source from which novel therapeutics may be developed. In this review, the anticancer potential of snake venom is discussed. Some of the included molecules are under clinical trial and may find application for anticancer drug development in the near future.

Keywords: Radiation therapy - chemotherapy - immunotherapy - hormonal therapy - venoms- toxins

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Introduction

Cancer is the major public burden in all developed and developing countries. A total of 1,638,910 new cancer cases and 577,190 deaths from cancer are projected to occur in year 2012 (Siegel et al., 2012). Currently, 1 in 4 deaths in U.S. is due to cancer. It's a multi-genic and multi-cellular disease that can arise from all cell types and organs with a multi-factorial etiology (Baskar et al., 2012). In all types of cancer, genetic alterations give rise to changes in expression, activation or localization of regulatory proteins in the cells, affecting the signaling pathways that alter their response to regulatory stimuli and allow the unrestricted cell growth.

Since cancer is the leading cause of death worldwide, there is an urgent need of finding a better way to treat it. Various therapies have been used for treating cancer such as chemotherapy, radiotherapy, immunotherapy and gene therapy (Baskar et al., 2012).

Out of the therapies being used for treatment, chemotherapy remains the predominant option. One of the main obstacle in chemotherapy is that patients eventually gets resistant after some time (Lai et al., 2012). Radiotherapy/radiation therapy being an important part of cancer treatment, contributes to almost 40% of curative/successful treatment for cancer. Its main aim is to decline the multiplication potential of cancer cells (Baskar et al., 2012). But challenge in using radiotherapy for cancer treatment is to increase/maximize effect of radiation doses on cancer cells, while minimizing its effect on surrounding

normal cells. Since there are several cases documenting either acute, or late radiation toxicity, therefore, it limits the usage of radiation therapy (Barnett et al., 2009).

Immunotherapy for cancer treatment has become a more promising approach in the past decades (Kruger et al., 2007). It is used in the early stage of the tumor development (Geissler and Weth, 2002). Immune targets don't play a significant role in the life or death of the cancer cells since they serve only to direct immune effectors to the tumor cells (Orentas et al., 2012). It mainly focuses on empowering the immune system to overcome the tumor rather than producing widespread cyto-toxicity to kill tumor cells. Many anti-cancer immuno-therapies use tumor-associated antigens as vaccines in order to stimulate immune response against cancer cells (Hammerstrom et al., 2011). Since, the tumor invokes multiple immune-suppressive mechanism to defend itself, hence, we need to overcome it so as to make immunotherapy a suitable option for treating cancer (Berzofsky et al., 2012).

Surgery, chemotherapy and radiotherapy provide inadequate effect or affect normal cells along with the diseased one. It leads to search for cancer cure from natural products. Anticancer drug developments from natural biological resources are ventured throughout the world. The biodiversity of venoms or toxins made it a unique tool from which new therapeutic agents may be developed. Snake venom has been shown to possess a wide spectrum of biological activities. Snakes use their venom to alter biological function and that's what a medicine does too. Therefore, venoms have always been the topic of interest

Types of Snake Venom

Venom is nothing but a secretion of venomous animals, which are synthesized in a specific part of their body, called venom gland. It's a modified saliva containing a mixture of different bioactive proteins and polypeptides used by an animal for defense or to immobilize its prey (Gomes et al., 2010). Not only the venom of every snake is different but a subtle difference exists between different species, between juveniles and adults, even among the snake of same species but of different geographical regions. Approximately 90-95% of venom's dry weight is composed of protein. These proteins may be toxic or non-toxic. Venoms are sub-divided into cytotoxins, cardiotoxins, neurotoxins, and hemotoxins (Ferrer, 2001).

Neurotoxins have an adverse effect on central nervous system resulting in heart failure and/or breathing problems. They have the ability to inhibit ion movement across the cell membrane or communication between neurons across the synapse (Bradbury and Deane, 1993). This toxin attacks the cholinergic neurons mimicking the shape of acetylcholine and therefore fits into its receptor site, blocking the binding of acetylcholine.

Toxins that cause destruction of RBCs are collectively known as Hemotoxins. It targets the circulatory system and muscle tissue of the host causing scarring, gangrene.

Cardiotoxins are those compounds which are toxic specifically to heart. It binds to particular sites on muscle cells of the heart preventing muscle contraction (Yang et al., 2005).

Cobras, mambas, sea snakes, kraits and coral snakes contain neurotoxic venom whereas viperidae family members such as rattle snake, copper heads, and cotton heads have hemotoxic venoms. Some snakes contain combinations of both neurotoxins and hemotoxins.

Basic Composition of Snake Venom

As said earlier, venom is not composed of a single substance but it's a cocktail of hundreds, or even thousands of different peptides, proteins, enzymes, and chemicals. There are approximately 20 different type of toxic enzymes known to us till now found to be present in snake venom in varying combinations and concentrations. Most common snake venom enzymes include acetylcholinesterases, L-amino acid oxidases, serine proteases, metalloproteinases, and phospholipases-A(2). Higher catalytic efficiency, thermal stability, and resistance to proteolysis make these enzymes attractive models for every researcher (Kang et al., 2011).

Cholinesterase

It attacks the nervous system, relaxing the muscles to the point where the victim has very little or no control. It plays a lead role in the cholinergic system where it functions in the rapid termination of nerve impulse transmission. Its high reactivity towards organophosphorus compound suggests that exogenous cholinesterases can serve as an effective therapeutic agent in the treatment of

prophylaxis and organophosphorus poisoning (Cohen et al., 2001).

L-amino acid oxidase (LAAO)

It is a dimeric flavoprotein which contains a non-covalently bound FAD as a co-factor. It constitutes 1-9% of the total venom protein and is responsible for the light yellowish color of the venom and catalyzes the stereospecific de-amination of an L-amino acid substrate to an alpha-keto acid along with the production of ammonia and hydrogen peroxide. It has been found that LAAO from snake venom can induce apoptosis in mammalian endothelial cells possible due to the production of high concentration of hydrogen peroxide (Pawelek et al., 2000).

Hyaluronidase

It is actually an endoglycosidase as it degrades the beta-N-acetyl-glucosaminidic linkages in HA polymer (Lokeshwar and Selzer, 2008). It is virtually present in all snake venom and has been known as "spreading factor". It damages the extra cellular matrix at the site of bite leading to the severe morbidity. It helps in rapid spreading of other toxins by destroying the integrity of the extra cellular matrix of the tissue. In spite of its role as a spreading agent, it is required to explore its function as a therapeutic agent for inhibiting the systemic distribution of venom and also for minimizing local tissue destruction at the site of bite (Kemparaju and Girish, 2006).

Phospholipases A2

PLA(2) plays an important role in many biological events such as cell signaling and cell growth, generation of pro-inflammatory lipid mediators such as prostaglandin, and leukotrienes (Rodrigues et al., 2009). These are the enzymes that hydrolyze the sn-2 acyl ester bond of various phospholipids to produce free fatty acids and lysophospholipids. Mammalian PLA (2) plays important role in various biological processes such as phospholipid metabolism, and remodeling, homeostasis of cellular membrane, host defense, and mediator production as well as signal transduction (Gao et al., 2005). Whereas, snake venom are chemically complex mixture of various active proteins or peptides belonging to Ca²⁺ dependent secretory PLA (2), which serve not only as digestive enzyme but also plays important role as a defense weapon by immobilizing the prey (Wei et al., 2009). It has other pharmacological properties as anti-platelet, anticoagulant, hemolytic, neurotoxic, myotoxic. It has been classified into two broad groups, 1PLA (2), found mainly in the venom of cobras, kraits, and sea snakes, and 2PLA (2), found in venom of vipers and pit vipers (Armugam et al., 2009).

Metalloproteinase

This enzyme belong to the family of zinc endopeptidase that degrades protein of extra cellular matrix and components of hemostatic system (Panfoli et al., 2010). It has ability to disrupt microvessels, which is then responsible for provoking local and systemic hemorrhagic and also contribute to other pathways that lead to local tissue damage. It might also prove cytotoxic to endothelial cells (Escalante et al., 2011).

Other enzymes

Proteinases, adenosine triphosphate, phosphodiesterases, etc. proteinases are important in digestion and they break down victim's tissue at an accelerated rate. Adenosine triphosphate when enters victim's body, it results in deep shock, and phosphodiesterases are responsible for negative cardiac reaction in victim and also a rapid drop in blood pressure.

Anticancer Activity of Snake Venom

Claude Bernad, father of physiology, was the first one to realize the involvement of some components of snake venom in different therapeutic potential. Use of venom for the treatment of cancer in laboratory animal was first reported by Calmette, 1993. It was found that the snake venom toxin from *Vipera lebetina turnica* induces apoptotic cell death of ovarian cancer cells through the inhibition of NF- κ B and STAT3 signal accompanied by inhibition of p50 and p65 translocation into nucleus. This toxin increases the expression of pro-apoptotic protein Bax and Caspase-3 but down-regulates the anti-apoptotic protein Bcl-2 (Song et al., 2012). The anticarcinogenic activities of crude venom of Indian monocellate Cobra (*Naja kaouthia*) and Russell's viper (*Vipera russelli*) were studied on carcinoma, sarcoma and leukemia models. Under in vivo experiments, it was observed that life span of EAC (Ehrlich ascites carcinoma) mice got increased with the strengthening of impaired host anti-oxidant system. In case of in vitro study, venom showed potent cytotoxic and apoptogenic effect on human leukemic cells (U937/K562) by reducing cell proliferation rate and produced morphological alterations (Debnath et al., 2007).

From past few decades, research has been undertaken on isolation and characterization of the snake venom cytotoxin. Cytotoxins exhibit various physiological effects as cytotoxicity, inhibition of platelet aggregation, cardiac arrest, hemolysis, etc. Cytotoxin or Cardiotoxin are polypeptide of 60-70 amino acid residues long found in snakes of elapid family having various pharmacological effects such as depolarization of muscles, and haemolysis (Ferrer, 2001). Cardiotoxin-3 (CTX-3), a basic polypeptide of 60 amino acid residue present in *Naja naja atra* venom has been reported to possess anti cancer property. It induces apoptotic cell death accompanied by upregulation of both Bax and endonuclease G, and down regulation of Bcl-x in K562 cells which was confirmed by DNA fragmentation (Yang et al., 2006). In a study carried out by different group of scientists on the same cell line, CTX-3 was reported to show apoptotic cell death through activation of Caspase-12 and JNK pathway which then triggered Ca^{2+} influx because of rapid increase in cytosolic Ca^{2+} concentration (Yang et al., 2008). Two different studies were carried on HL-60 cells using CTX-3. It has been reported that anti-proliferative property of CTX-3 mediated through apoptosis by a significant increase in sub G1 population and the activation of c-JUN-N-terminal kinase (Chien et al., 2008). According to another study, apoptosis was induced by activation of both endoplasmic reticulum pathway of apoptosis and mitochondrial death pathway, indicated by increased level of Ca^{2+} and

glucose-related protein 78 (GRP 78) (Chien et al., 2008). When MDA-MB-231 (Human breast cancer) cells were exposed by CTX-3, it induces apoptosis which was confirmed by accumulation of sub-G1 population and loss of mitochondrial membrane potential (Lin et al., 2010). CTX-3 down regulates NF- κ B in MCF-7 (human breast cancer) cells leading to the suppression of proliferation and induction of apoptosis which was confirmed by sub-G1 population, phosphatidylserine externalization, and poly (ADP-ribose) polymerase (Chiu et al., 2009). Later on, it was found that CTX-3 induces apoptosis in A549 cells by inactivating the EGFR, P13-K/Akt and JAK/STAT3 signaling pathways (Su et al., 2010).

drCT-1 is a heat stable, 7.2 kDa protein toxin isolated from Indian russell's viper (*Daboia russelli russelli*) venom and is supposed to possess anti-proliferative, cytotoxic, and apoptotic property. In vivo and in vitro experiments were done using drCT-1 on EAC mice and human leukemic cells (U937/K562) respectively. It showed decrease in EAC cell count, cell viability, and an increased survival time of diseased mice and showed a dose, and time dependent inhibition of U937 and K562 cells because of apoptosis through G1 phase arrest of the cell cycle (Gomes et al., 2007).

Disintegrins also possess the ability to inhibit tumor behavior both in vitro and in vivo. RGD containing disintegrins are non-enzymatic proteins that inhibit cell-cell interactions, cell-matrix interactions, and signal transduction. Salmosin, a disintegrin isolated from Korean snake venom, effectively suppressed growth of metastatic tumor as well as solid tumor in mice (Kang et al., 1999). This antimetastatic activity was resulted from blockage of integrin-mediated adherence of $\alpha v \beta 3$ integrin mediated proliferation of the melanoma cells (Bradbury and Deane, 1993). Contortrostatin (CN) is a homodimeric disintegrin found in southern copperhead snake venom. Its anti-cancer effect was studied on OVCAR-5 (human epithelial carcinoma cell line of ovary) cells. CN effectively blocks the adhesion of OVCAR-5 cells to several extracellular matrix proteins and inhibits tumor cell invasion through an artificial basement membrane (Markland et al., 2001).

Condrostatin, a homodimeric disintegrin, isolated from copper head snake venom, was found to be a potent inhibitor of in vitro beta 1 integrin-mediated cell adhesion and in vivo lung colonization (Bradbury and Deane, 1993).

Snake venom containing cystatin (sv-cyst), a member of cysteine protease family inhibitors, has been reported to play an important role in tumor invasion and metastasis. In a study carried out on MHCC97H (liver cancer) cells, sv-cyst has shown inhibition of tumor cell invasion and metastasis through the reduction of the proteinases activity and epithelial-mesenchymal transition (EMT) with a decreased activity of cathepsin B, MMP-2 and 9, and EMT change index, and increased activity of E-cadherin, and decrease in the activity of N-cadherin and twist activity (Tang et al., 2011).

Phospholipases A (2) is the enzyme that hydrolyzes the sn-2 acyl ester bond of various phospholipids to produce free fatty acids and lysophospholipids (Gao et al., 2005). Snake venom is a chemically complex mixture of various active proteins or peptides belonging to Ca^{2+} dependent

secretory PLA (2) (Arimura et al., 1989). A group of scientists reported that the PLA (2) from *Macrovipera lebetina* venom exhibits anti-integrin activity. In their study, done on HMEC-1 (human micro vascular endothelial) cells, MVL-PLA (2) has shown inhibition of cell adhesion and migration; also the actin cytoskeleton and distribution of $\alpha v \beta 3$ integrin were disturbed. MVL-PLA (2) also reported increase in microtubule dynamicity by 40% (Bazaa et al., 2010).

LAAOs are dimeric flavoprotein that contains a non-covalently bound FAD as a co-factor (Pawelek et al., 2000). LAAOs isolated from *Ophiophagus hannah* venom decreases thymidine uptake in murine melanoma, fibrosarcoma, colorectal cancer and Chinese hamster ovary cell line that also showed reduction in cellular proliferation (Cura et al., 2002). Also, LAAO isolated from *Agkistrodon acutus* snake venom showed accumulation of tumor cell at sub-G1 phase of cell cycle. It also induced apoptosis via Fas pathway in A549 cells (human alveolar epithelial cell line) (Kang et al., 1999).

Since, we are all aware of high cytotoxic property of snake venom or toxins, its effect on non-cancerous cell line is still controversial with some groups suggesting it is harmless to non-cancer cell line while other mentioning its cytotoxic effect on non-cancer cell line also. But now, people have found out solution to this also by combining the components obtained from snake venom with nano-particle and allow it for targeted delivery to the diseased site. According to recent study, snake venom extracted from *Walterinnesia aegyptia* (WEV), alone or in combination with silica nano-particles can decrease the proliferation of human breast carcinoma cell line (MDA-MB-231). In this study, decreased expression of Bcl-2 and enhanced activation of caspase-3 has been found when breast cancer cell line was treated with WEV along with nano-particle and also showed significant reduction in actin polymerization and cytoskeletal rearrangement but it was not the case with non-cancer cell line (Al-Sadoon et al., 2012).

Crotoxin is a cytotoxic PLA2 compound isolated from a South American snake, *Crotalus durissus terrificus* venom (Faure et al., 1993). Crotoxin displays cytotoxic activity against a variety of murine and human tumor cell line in vitro (Rudd et al., 1994). Crotoxin induced cytotoxic effects appear to be highly selective towards cell line expressing high density of epithelial growth factor receptor. Antitumor efficacy in vivo using daily intra muscular administration of crotoxin has been demonstrated on Lewis lung carcinoma (Newman et al., 1993) with 83% growth inhibition, and MX-1 human mammary carcinoma with 69% growth inhibition. Lower activity was observed in HL-60 leukemia cells with 44% growth inhibition suggesting that crotoxin might have high specificity towards solid tumor. In phase I clinical trial, crotoxin was administered intra-muscular for 30 days in patients with solid tumor refractory to conventional therapy at doses ranging from 0.03-0.22 mg/kg. A total number of 35 cycles of crotoxin administration was evaluated in 23 patients. No death was observed in this study. Patients with different types of carcinomas responded in different way resulting in the reduction of disease. The therapeutic

response obtained in some patients was quite promising and deserved additional development of this compound under phase 2 clinical trial with a recommended dose of 0.14 mg/m² (Cura et al., 2002).

VRCTC-310 is a natural product produced by combining two purified snake venom, a non-covalent heterodimer crotoxin, and a basic amphipathic peptide cardiotoxin. A phase I study was performed to evaluate the mechanism tolerated dose (MTD), safety profile, and pharmacokinetic data with VRCTC-310. 15 patients with refractory malignancies were given intramuscular injection daily for 30 days continuously. MTD was found to 0.017 mg/kg and recommended for phase II studies with dose range of 0.017 mg/kg (Costa et al., 1997).

According to a news published in a journal (Popular science), an Irish company is using American rattle snake venom to test its anti-cancer potential. They isolated a protein from rattle snake venom that causes malignant cancer cell to commit suicide. This company has developed a venom-derived drug called CB24 and started testing it on humans in October'11. That drug has already been tested in mice and human cell lines with great success.

Conclusion and Future Prospects

Above description makes it clear that different components of the venom are being used for clinical trial and they can be used as a natural therapeutic agent against cancer. Since there is controversy about the cytotoxic effect of the venom on normal cells, therefore its effect on normal cells should be evaluated. Tagging of the venom with nanoparticles for targeting the cancer cells can be one of the best therapeutic approach for the treatment of cancer.

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