Review Paper:

Snake venom: An emerging anticancer agent

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Abstract

Snake venom consists of different proteins, enzymes, carbohydrates and other bioactive molecules. They are highly toxic in nature and have been recognized for their lethal effects for a long back. However recent studies have revealed the enormous therapeutic potential of snake venom. The crude venom and its enzymatic components including PLA2, SVMP, SVSP, Lectin, LAAO and disintegrin, exhibit anticancer activity through cell lysis, gene expression modulation, cytotoxicity and apoptosis.

This review discusses the anticancer properties of various components of snake venom. Although venom isolation, purification and safety concerns are a challenge, ongoing research shows that snake venom holds great promise for the development of innovative and effective anticancer treatments, requiring further research and clinical trials to combat this disease.

Keywords: Snake venom, Anticancer agent, Cancer therapy, Cytotoxicity.

Introduction

Cancer is considered to be the world's most alarming disease, spreading exponentially as one of the leading causes of mortality and morbidity globally[48]. GLOBOCAN statistics estimate that around 19.3 million cancer cases were diagnosed and 10.0 million deaths occurred worldwide in 2022. Chemotherapy, radiation therapy and surgery are the most commonly used treatments for cancer. An early-stage diagnosed cancer can be curable as small tumors can be easily removed surgically or can shrink in response to radiation and chemotherapy. In surgery, the affected area is surgically removed and, in many cases, for common solid tumors, it is the only curative therapy.

In chemotherapy, the cytotoxic agents are administered orally and intravenously or in combination and those agents result in cytotoxicity of diving and resting cells. Radiation therapy mainly slows down the growth of cancer cells by damaging their DNA or it directly kills the cancer cells (takes days or weeks).

Apart from these methods, there are other conventional methods used for the treatment of cancer which include transplantation (bone marrow and peripheral stem cell), immunotherapy, hormone therapy, gene therapy, photodynamic therapy and cryosurgery. The main objective is to prevent cancer cells from invading, metastasizing, multiplying and killing people[70]. This review highlights the studies reporting snake venom as a noble source of anticancer compounds. Apart from the existing methods, the advent of natural as well as synthetic anticancer compounds has made an effective contribution to cancer management.

Snake venom is a secretion of venomous snakes which consists of different peptides, enzymes, proteins, minerals, carbohydrates and other bioactive molecules. It is a translucent, viscous liquid that can be crystallized by drying. To debilitate and digest their prey, snakes inject their venom via unique fangs into the prey[36]. It is believed that ingestion of snake venom will cause no harm until injected into the blood[86].

Two core components present in snake venom are non-enzymatic and enzymatic. Non-enzymatic components include three finger toxins (3FTx), disintegrin (DIS), Kunitz-type serine proteinase inhibitor (KSPI), defensin (DEF), cysteine-rich secretory proteins (CRiSP), C-type lectins (CTL) and natriuretic peptides (NPs). Enzymatic components comprise of L-amino acid oxidase (LAAO), phospholipase A2 (PLA2), snake venom metalloproteinase (SVMP), snake venom serine protease (SVSP), hyaluronidase, 5'-nucleotidase and acetylcholinesterase[63]. Both enzymatic and non-enzymatic components are reported for their anticancer activity (Table 1).

Also, snake venoms are a vital nominee for the development of novel medicinal agents for many diseases and disorders due to their biodiversity and therapeutic potency [28,31]. So far, many toxins of snake venom have been investigated to treat cancer, thrombosis, arthritis, pain, multiple sclerosis, neuromuscular disorders, cardiovascular and blood disorders, infections and inflammatory diseases and hypertension[55,77].

Anticancer properties of snake venom

Conventional cancer treatments like radiotherapy and chemotherapy are intended to kill cancer cells in large numbers but lack specificity, so they are invariably accompanied by side effects. Cancer cells may develop resistance to chemotherapeutic therapies, which would complicate matters further. Therefore, the goal of anticancer drug discovery has been to find a powerful, non-resistant molecule that is particular to cancer. Numerous publications have explored how snake venom and its various components promotes apoptosis, necrosis, ROS generation and inhibit angiogenesis, cell adhesion, invasion and metastasis in order to decrease cell growth and encourage cell death (Figure 1).

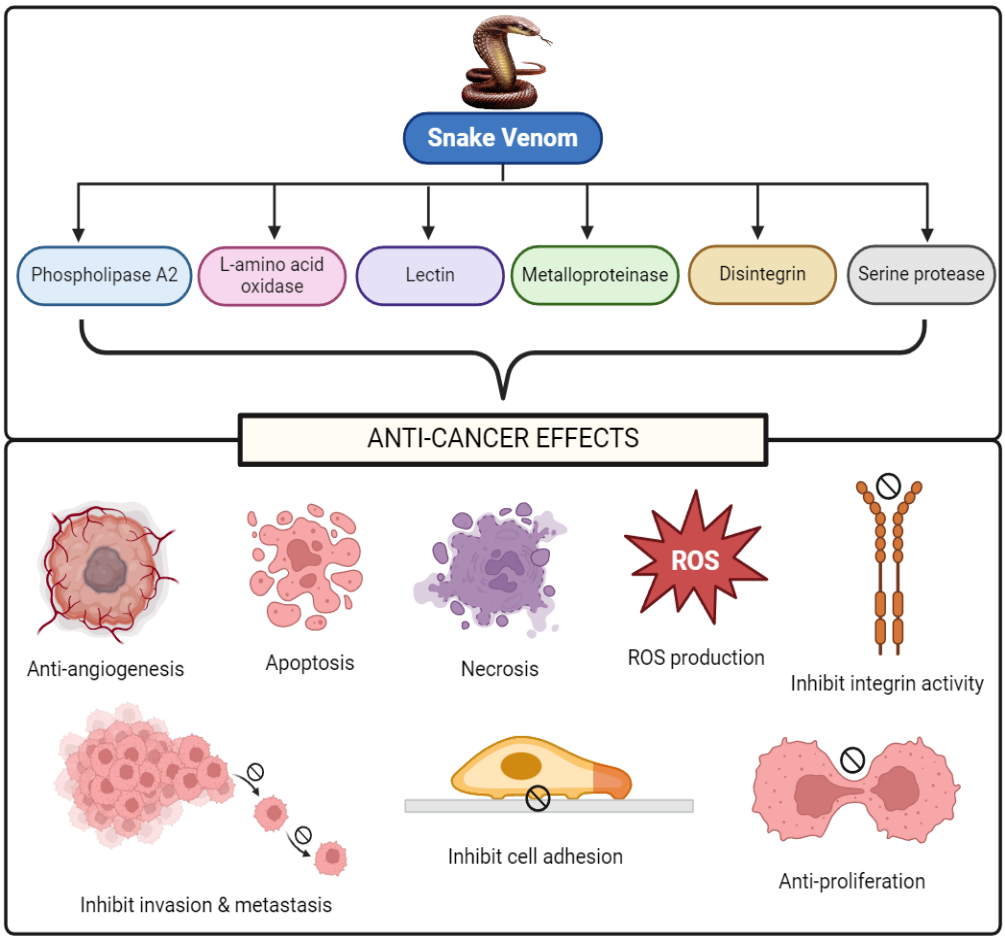

Figure 1: Various component of snake venom addresses significant anticancer effects.

In this situation, proteins from snake venom are attractive candidates for new anticancer drugs. Most mammalian cells respond to the pharmacologically active proteins and peptides of snake venom[20]. Tumor cells are significantly more affected by alteration in cellular metabolism as a result of snake venom cytotoxicity[77]. Claude Bernard, the pioneer of physiology was the first person to recognize the medicinal properties of snake venom. In the 1930s, the first accounts of snake venom to treat cancer came into light.

Since then, several studies have been published that describe the functions, isolations, purifications and structural elucidations of the constituents of snake venom. The thorough structural and functional analysis of snake venoms would aid in the creation of brand-new anticancer medications.

Early research on the suppressive effect of simple snake venoms on tumor cells produced dubious results. Pain alleviation for patients with terminally malignant tumors was the primary clinical outcome of the mixture made from snake venom[48]. Modern high throughput screening technologies have made it possible to identify and isolate novel therapeutic compounds from biotoxins like the snake venoms that have demonstrated potential for fighting against cancer. Growing knowledge of molecular mechanisms is helping in this direction as well. Numerous studies have examined the tumor-suppressing effect of snake venoms and several of them are currently undergoing phase I and phase II clinical trials[77].

Molecular Aspects of snake venom: The components of snake venom encourage cell death and prevent cell multiplication. Snake venom acts on mammalian cancer cells via various pathways by causing cell membrane damage, increasing calcium ion influx, altering the expression of proteins that regulate the cell cycle, causing cytochrome C release, inhibiting the synthesis of nucleic acids to prevent cell proliferation, preventing thrombin-induced metastasis, inhibiting platelet action to prevent fibrin formation and inducing cancer cell apoptosis to control tumor size[77].

As mentioned in figure 2, some other mechanisms of action are: ROS- dependent DNA damage (mainly by LAAO and PLA2), extracellular matrix-integrin signalling blockade (mainly by SVMP, disintegrin and C- type lectin), prevention of cancer cell invasion, migration and proliferation (mainly by LAAO, C-type lectin, Phospholipase A2, disintegrin and snake venom metalloprotease) and apoptosis activation via intrinsic or extrinsic pathways (mainly by PLA2 and LAAO)[13]. The anticancer activity of crude venom and its components, reported in recent years is mentioned in table 1.

Table 1
Anticancer properties of different components of venom and their mechanism

S.N.	Venom Component	Enzymatic/ Non-enzymatic	Snake species	Cancer type	Anticancer mechanism
1.	Phospholipase A2	Enzymatic	*Crotalus durissusterrificus*	Oral	Antineoplastic effect[24]
				Breast	Apoptosis[3]
			BothropsMoojeni	Colon, Mucoepidermoid	Cytotoxicity[33]
			Bothropsjararacussu	Breast	Antitumor and antimetastatic effects[27]
			Bungarus fasciatus	Breast, Lung	Cytotoxicity[85]
			Bothrops jararaca	Promyelocytic leukemia, liver	Cytotoxicity[18]
			Bothropspauloensis	Breast	Apoptosis[7]
2.	L- amino acid oxidase	Enzymatic	*Crotalus adamanteus*	Ovarian	H_2O_2 mediated cytotoxicity[87]
			Crotalus adamanteus	Colon	Cytotoxic and pro-apoptotic activity[62]
			Bothropsmoojeni	Leukemia	ROS production, apoptosis and differential DNA methylation[14]
			Bothropsjararacussu	Liver	Cytotoxic, genotoxic and induce oxidative stress[52]
			Bothropsjararacussu	Breast	Cytotoxicity and apoptosis[17]
			Cerastes vipera	Liver, Lung, Colon, Prostate, Breast	Antiproliferative and cytotoxic effect[71]
			Calloselasmarhodostoma	Leukemia	Apoptosis[23]
3.	Lectin	Non-enzymatic	*Macroviperalebetina*	Melanoma	Inhibit cell adhesion, migration and invasion[41]
			Daboia russelii	Lung	Induces cytoskeletal damage and apoptosis[65]
			Bothropsleucurus	Melanoma	Cell death by necrosis[6]
			Macroviperalebetina	Fibrosarcoma, Melanoma, Colon, Leukemia, Ovarian	Inhibits adhesion, migration, invasion and angiogenesis of tumor cells[74]
			Bothropsjararacussu	Breast, Ovarian	Inhibits tumor cell and endothelial cell growth[26]
4.	Metalloproteinase	Enzymatic	*Bothropsleucurus*	Malignant glioblastoma, Mammary carcinoma	Cytotoxicity[34]
			Bothrops jararaca	Melanoma	Cytotoxicity[22]
			Crotalus viridis	Osteosarcoma	Detachment of cell[49]
5.	Disintegrin	Non-enzymatic	*Crotalus durissuscollilineatus*	Breast	Cell migration inhibition[64]
			Macroviperalebetina	Melanoma	Apoptosis[40]
			Crotalus viridisviridis	Urinary bladder, Fibrosarcoma, Skin melanoma, Colon, Breast	Anti-metastatic activity[50]
			Crotalus scutulatusscutulatus	Urinary bladder, Skin	Inhibits cell adhesion and migration[51]
			Bothropscolombiensis	Urinary bladder carcinoma, Melanoma	Inhibits cell adhesion and migration[72]
6.	Serine protease	Enzymatic	*Crotalus durissuscollilineatus*	Breast, Liver	Inhibits ion channel[12]
7.	Crude	Enzymatic and Non-enzymatic	*Bitis arietans, Cerastes gasperettii, Echiscoloratus, Echispyramidum*	Ileocecal, Breast	ROS mediated apoptosis[2]
			Naja haje	Hepatocellular	Inhibits proliferation[47]
			Viperaraddeikurdistanica	Breast	ROS mediated apoptosis[53]

			Pseudocerastespersicus	Lung	Caspase dependent apoptosis[76]
			Viperalatifii	Liver	Apoptosis[59]
			Ophiophagus hannah	Pancreatic	Inhibits angiogenesis[46]
			Naja najaoxiana	Breast, Hepatocellular, Prostate	Apoptosis[31]
			Montiviperaxanthina	Colon, Breast, Osteoblastic, Osteosarcoma	Cytotoxicity[88]
			Walterinnesiaaegyptia	Breast	Apoptosis[4]
			Viperalebetinaturanica	Ovarian	Apoptosis[79]

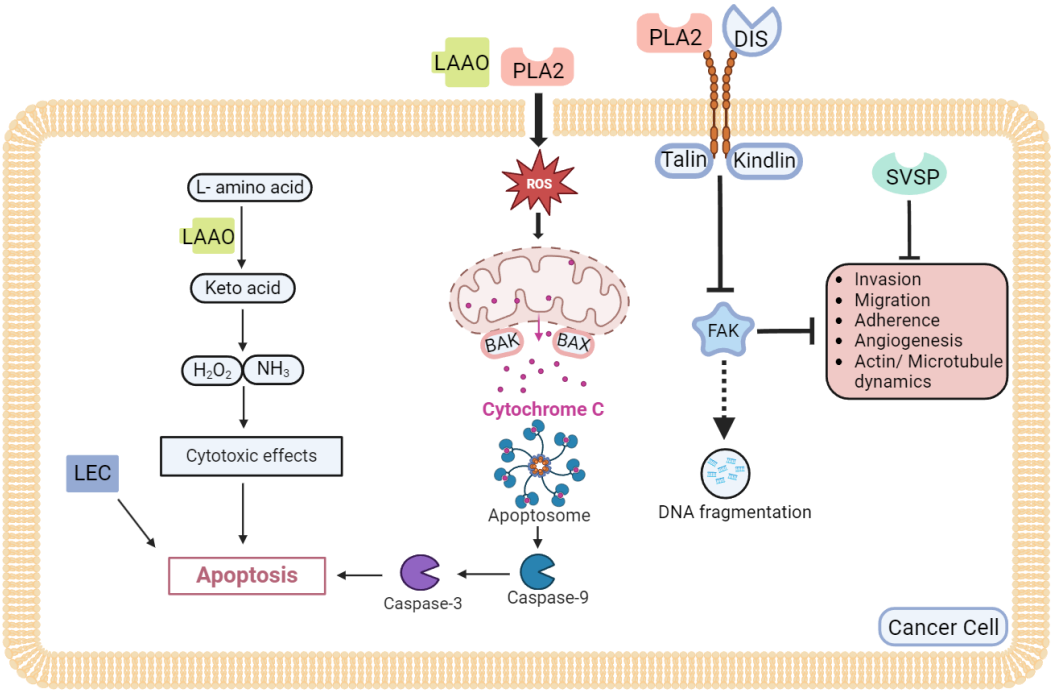

Figure 2: Mechanism occurring during snake venom toxin-mediated anticancer effect.

Phospholipase A2 (PLA2): Phospholipase A2 is a lipid digesting enzyme involved in inflammatory human diseases and also the major component in some snake envenomation and has a key role in lipid membrane metabolism and in diet lipid catabolism[78]. It produces a product from hydrolysis, arachidonic acid, which displays prominent biological activities[39]. PLA2 has 14 cysteine residues which together form 7 disulfide linkages and 120 amino acids. It causes the 2-acyl ester bond to hydrolyze in a calcium-dependent manner, releasing lysophospholipids and free fatty acids. Additionally, PLA2 has the ability to cause membrane phospholipids to hydrolyze and to release some bioactive substances.

It is essential for a number of biological processes including cell division and signaling, anticoagulant, antiplatelet and hemolytic effects as well as harmful processes like cardiotoxicity, neurotoxicity, cytotoxicity, hypotensive and pro-inflammatory effects[58]. Phospholipases have been shown to have anticancer and anti-angiogenic properties including acidic and basic PLA2s and synthetic peptides derived from PLA2 homologues[15]. Purified PLA2 from *Cerastes cerastes* and *Macrovipera lebetina transmediterranea* venom was reported to inhibit the angiogenesis, migration and adhesion of cancerous cells[8,89].

An *in-vitro* study reported that Nigexin, a component of *Naja nigricollis* PLA2, shows notable cytotoxicity in cell cultures of several cancer types including neuroblastoma, epithelial and leukemia cancers[21]. Using various enzyme concentrations, the *Bothrops jararacussu* acidic PLA2 (BthA-I-PLA2), has exhibited anticancer effects on breast adrenocarcinoma, Erlich ascitic tumor and leukemia T and the predicted cause of the anticancer activity is due to apoptosis by speeding up the phospholipids turnover[69]. Neutrophils function as the initial line of defence at the site of damage, carrying out defence mechanisms such as phagocytosis, the generation of reactive oxygen species (ROS) and the creation of inflammatory mediators like cytokines[83]. A study found that BaTX-II, an Asp49 PLA2 isolated from *Bothrops atrox*, caused neutrophils to produce hydrogen peroxide[75].

There are several processes involved in tumour angiogenesis[32,35] and each one could be a target for the creation of anti-angiogenic and anti-metastatic treatments.

Numerous investigations have indicated that integrin signalling plays essential roles in controlling angiogenesis[1]. Integrins are trans-membrane proteins, hetero-dimeric in nature and are responsible for cell-cell as well as cell-matrix interactions. A significant integrin-dependent tyrosine phosphorylated protein is called focal adhesion kinase (FAK).

Several cancer-promoting pathways linked to FAK have been responsible for the development of colorectal cancer[43]. According to previous research, PLA2 of *Macrovipera lebetina* inhibits migration by targeting integrin proteins, in addition to abolishing adhesion of endothelial cells and angiogenesis[9]. The antitumor efficacy of the PLA2 isoform from *Bothrops moojeni* venom (BmPLA2) against human rhabdomyosarcoma (RD) and colorectal adenocarcinoma (Caco-2) cell lines was reported in some recent studies[33].

L-amino acid oxidase (LAAO): LAAO is a dimeric flavoenzyme that catalyses the oxidative deamination of L-amino acids into alpha-keto acids, hydrogen peroxide and ammonia through an intermediary amino acid. It is found in wide range of organisms like bacteria, algae, fungi, snakes and, mainly exists in homodimeric form with a cofactor which can be either flavin mononucleotide or flavin adenine dinucleotide[30]. The study of LAAO of snake venom is pharmacologically important as it possesses diverse functions such as apoptosis induction, cytotoxicity, substrate preference, activation or inhibition of platelet aggregation, hemolysis, bactericidal activity, edema, hemorrhage induction and on the basis of these functions, it has been characterized[15].

In this review, we have discussed the apoptotic property of this enzyme causing cell death of onco-cells. In the process of apoptosis, L-amino acid of snake venom origin unchains complex processes like apoptosis of vascular or endothelial cells causing hemorrhage[30]. Similarly, several authors have reported this enzyme causing apoptosis in various cell lines such as human promyelocytic leukemia cells (HL-60), human embryonic cells (293T), human monocytic cells (MM6), human leukemia T cells and rat lymphocytic leukemia cells (L1210). The apoptotic impact was attributed to H_2O_2 produced by the oxidative process in the experiments used to assess the cytotoxic activity of LAAO.

It is found that even at low concentration of LAAO, there is high apoptosis induction in numerous mice cell lines[80]. LAAO from snake venom catalyses the oxidative deamination reaction that transforms L-amino acid into α-keto acid, resulting in the production of hydrogen peroxide and ammonia[61,66]. This hydrogen peroxide played major role in cytotoxic effect of the enzyme to host cells[10,23,38]. Glycan molecules present on the enzymes help in its attachment, to the cell surface providing H_2O_2 to the cell and lead to apoptosis[45,84]. According to early 3-D structural investigations of the viperid *Calloselasma rhodostoma*, histidine 223 of LAAO played key role in enzyme catalysis help in the removal of a proton from α-amino group in the zwitter ion form[19].

Lectin: Lectin is a polyvalent carbohydrate binding protein of non-immune origin, found in many vegetal and animal species and is known to influence cancer cells growth[16]. Snake venom lectin is a homodiamer protein with molecular mass of 16 kDa, which generally contains 135 amino acids[25]. Lectins, with an inhibitory concentration of 50% acts as an effective growth inhibitor in pancreatic (CFPAC-1) and renal (Caki-1 and A-498) cancer cell lines[67]. BJcuL's (a lectin purified from *Bothrops jararacussu* venom) cause cytotoxicity in tumor cells by changing cell adhesion property and triggering apoptosis in MKN45 and AGS gastric cancer cells. BJcuL may stimulate actin disintegration, speed up cellular detachment from the extracellular matrix and compete with extracellular matrix glycoproteins for attachment to the cell surface.

Lebecetin, a C-type lectin isolated from *Macrovipera lebetina* venom, has shown to exhibit anti-integrin action. It prevented many tumor cell lines from adhering to diverse adhesion substrates via integrin-mediated mechanisms. The migration, adhesion and invasion of malignant cells could all be prevented by this protein[73]. Researchers demonstrated BlL, a galactoside-binding lectin derived from *Bothrops leucurus* venom, to have cytotoxic effect against tumor cells and to induce apoptosis in K562 cells.

Snake venom metalloproteinases (SVMP): SVMP is an important group of compounds found mostly in crotalid venom and viperid venom. SVMP can cause bleeding by altering blood coagulation or interacting with the major extracellular matrix constituents collagen, laminin and fibronectin[15]. SVMP are also referred to as zinc-proteases, multidomain proteins that have the capacity to produce physiologically active by products by autoproteolysis[44]. SVMPs are categorized as belonging to -the mature P-I class, which only has a metalloprotease domain, the P-II class, which has a metalloprotease domain followed by a disintegrin domain, the P-III class, which is a metalloprotease with disintegrin-like and cysteine-rich domains, or the P-IV class, which is a heterotrimeric class of SVMPs and has an additional snake C-type lectin-like (snaclec) domain[15].

MDC (metalloprotease/disintegrin-like/cysteine-rich) proteins are a subclass of high molecular weight SVMPs. The intricate bleeding process caused by these enzymes has prompted research into the interaction between the disintegrin domain and the major blood coagulation factors including platelets and integrins[5]. It has been demonstrated that several groups of matrix metalloproteases/ADAMs participate in the development of new vasculature during tumor progression. These multidomain proteins play a role in cell-cell and cell-extracellular matrix adhesion as well as cancer cell growth[15]. Because of their structural resemblance to mammalian MMPs (ADAM) and SVMPs (low and high

MMPs) including disintegrins, snake venom components have drawn attention from scientists as possible agents for treating animal malignancies[82].

Disintegrins: Disintegrins are a group of synthesized or naturally occurring nontoxic and non-enzymaic low molecular weight (5–10 kDa) RGD-containing peptides and are crucial components in the majority of viperid and crotalid venoms. These substances are initially distinguished by their capacity to engage with the integrins IIb3, 51 and 3lls, which are articulated by a variety of cells including those implicated in tumor growth and proliferation[37]. Based on binding studies, integrins and their subtypes have been identified as the main functional adhesion receptors on tumor cells. A research shows that salmosin, a disintegrin isolated from the venom of a Korean snake, causes apoptosis by directly binding to integrin and competing with the extracellular matrix[42].

Disintigrins like Contortrostatin, Eritostatin, Rhodostomin, Obtustatin, Trigramin, Salmosin, Triflavin, Albolabrin and Echistatin have also shown the ability to potentially suppress tumor cells[15]. Disintegrins have the ability to interact with the extracellular matrix and are crucial in the development of angiogenesis and the metastatic spread of cancer.

This peptide has been shown to prevent the spread of ovarian cancer both *in vitro* and *in vivo* as well as the enlistment of blood vessels in tumors[15]. It prevents angiogenesis, invasion and migration of cancer cells[81].

Snake Venom Serine protease (SVSP): SVSPs are complex and versatile enzymes and mainly act on hemostasis[12]. They are widely distributed in viperid venoms, primarily in the form of monomeric glycoproteins between 26 and 67 kDa[68]. SVSPs have demonstrated tremendous promise for the therapeutic and diagnostic usage of coagulant diseases. A study demonstrated that collinein-1, an SVSP that was isolated from the venom of *Crotalus durissuscollilineatus*, decreased the viability of MCF7, human breast cancer cell line[12]. Markland[54] showed that crotalase, a serine protease, reduces the proliferation of B16 melanoma cells in a test tube but has no cytotoxic or cytostatic effects on cells when administered to living organisms and it does not appreciably prolong animal survival.

The venom of *Macrovipera lebetinatransmediterranea*, a snake native to Tunisia, contained a unique PIVL inhibitor (Kunitz-type serine proteinase inhibitor) and has the capacity to precisely suppress trypsin function and ability to inhibit integrin allowing it to prevent tumour cells from adhering, migrating and invading[60].

Similarly, Vipegrin, a non-enzyme protein is another Kunitz-type serine proteinase inhibitor isolated from Russell's viper and impedes trypsin's catalytic activity. Vipegrin is cytotoxic to MCF7 human breast cancer cells and restricts its invasive property[11].

Development of anticancerous medicines from snake venom

Celtic Biotech (Ireland) is the only company developing novel candidate therapies from snake venom for the treatment of solid cancers and pain in humans. They have formulated CB24 (Crotoxin, a heterodimeric cytotoxic phospholipase complex protein) from venom of a South American rattlesnake *Crotalus durissus terrificus* and furthermore searching the anticancer possibilities of Cardiotoxin (CB-6, a therapeutic protein derived from cobra venom), CTC310 (combination of CB-24 and CB-6), Crotalin (CB-CDV) and Crotamine (CB-5, another anti-tumour peptide from the Viperidae family). The company has completed part II of phase I clinical trial of lead candidate CB24. In pre-clinical research, it was found to be highly toxic to several tumor cell types and in early clinical studies, a sizable fraction of cancer patients showed stabilized illness, partial responses and even complete responses. These product candidates, which are derived from specialized receptor binding proteins discovered in snake venom, may help cancer patients to increase survival, experience better quality of life and spend less money on therapy[29,56,57].

Conclusion

Crude venom and its components *viz.* PLA2, LAAO, lectin, SVMP, disintegrin, SVSP and several elements from snake venom have been recognised for their anticancer activity and some of them are being tested in clinical trials. This review briefly discussed specific anticancer compounds of snake origin and their mechanism of action at cellular, molecular and nuclear level. The mechanistic behaviour of snake venom compounds is directly or indirectly leading to lipid damaging activity and DNA damaging activity which in turn causes apoptosis. Various enzymatic compounds (PLA2, SVMP, SVSP and LAAO) and non-enzymatic compounds (disintegrin and lectins) of snake origin, act for the disruption of cytoskeleton of cells, which may be the possible reason to exploit them as anticancer agents.

In some studies, reffering to melittin (from honeybee venom) and chlorotoxin (from scorpion venom) labelled with nanoparticles showed improved specificity, stability and therapeutic efficacy against cancer. Consequently, the snake venom toxins tagged with nanoparticles can be better approach to target the cancer cells. There is still a need for more preclinical and clinical research to prove the safety and effectiveness of snake venom anticancer peptide.

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