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Bioactive Components of Snake Venom: Prospects for Cancer Treatment

R.Asha*[1], B.Dinesh[2], Dr.S.Swarnalatha[3], Dr.J.Karthi[4]
*[1, 2] M.PHARM FINAL DEPARTMENT OF PHARMACOLOGY,
[3] PROFESSOR CUM HOD DEPARTMENT OF PHARMACOLOGY,
[4]PRINCIPAL.
PALLAVAN PHARMACY COLLEGE, KANCHIPURAM

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ABSTRACT:
Cancer remains a global health challenge, necessitating the development of novel therapies with improved efficacy and reduced toxicity. Snake venom, a complex mixture of bioactive proteins, peptides, and enzymes, has emerged as a promising source of anticancer agents. These venom-derived components demonstrate diverse anticancer activities, including induction of apoptosis, inhibition of angiogenesis and metastasis, selective cytotoxicity against tumor cells, and immune modulation. Notably, compounds like crotoxin and disintegrins have shown significant preclinical and clinical potential. However, challenges such as toxicity, production scalability, and standardization must be addressed to translate venom-based therapies into clinical use. This review highlights the therapeutic potential of snake venom components in cancer treatment and outlines the mechanisms underlying their anticancer effects.

Keywords: Snake venom, anticancer therapy, crotoxin, apoptosis, angiogenesis inhibition.

I. INTRODUCTION:

Anti-Cancer Drug Development:

Cancer remains one of the leading causes of death globally, despite advancements in treatment methods such as surgery, chemotherapy, and immunotherapy. However, these conventional therapies often have significant limitations, including systemic toxicity, drug resistance, and severe side effects. Consequently, there is an urgent need for novel and more effective treatments with fewer adverse effects.

One promising area of research focuses on natural compounds, with snake venom emerging as a potential source of therapeutic agents for cancer treatment. Snake venom is a complex blend of bioactive molecules—such as enzymes, peptides, and proteins—many of which have demonstrated notable anticancer properties. These venom-derived compounds have shown the ability to trigger cancer cell death (apoptosis), inhibit the formation of new blood vessels (angiogenesis), and prevent the spread of cancer cells (metastasis).

Due to their unique mechanisms of action, snake venom components offer a potentially targeted and efficient approach to cancer therapy. This growing field of research holds great promise in complementing existing cancer treatments and contributing to the development of new, more effective anticancer drugs.

II. SNAKE VENOM:

2.1 Therapeutic Potential of Snake Venom:

Snake venom is a complex mixture of biologically active molecules that have evolved primarily to immobilize and digest prey. It comprises a diverse array of proteins, peptides, enzymes, and small molecules, each serving specific functions—such as disrupting blood clotting, degrading cell membranes, and modulating immune responses. Although its primary role is predatory, venom also functions as a defense mechanism.

In recent years, the broad biological activity of snake venom has attracted considerable interest in medical research, particularly in drug development. Certain venom components have demonstrated promising therapeutic properties, including anticancer, analgesic, anticoagulant, and antimicrobial effects. The unique biochemical characteristics of snake venom—especially its capacity to target specific molecular pathways with high precision—make it a compelling candidate for the discovery of novel treatments for various diseases, including cancer.As research progresses, snake venom continues to emerge as a valuable resource in the development of new and more effective therapeutic agents.

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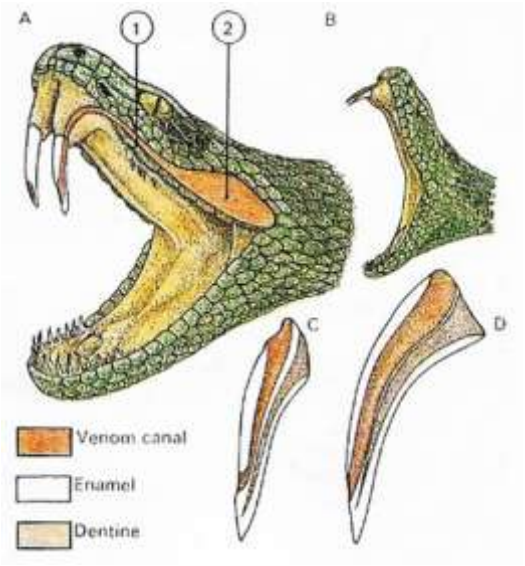

Fig 1: Snake Venom

2.2 Snake Venom in Anti-Cancer Drug Development:

In recent years, snake venom has garnered considerable attention as a promising source of novel therapeutic agents for cancer treatment. The venom of various snake species contains a diverse array of bioactive compounds—such as proteins, peptides, and enzymes—that have demonstrated significant anticancer potential. These compounds operate through several mechanisms, including the induction of apoptosis (programmed cell death), inhibition of angiogenesis (the formation of new blood vessels that support tumor growth), and suppression of metastasis (the spread of cancer to distant organs).

What makes snake venom particularly compelling in the context of cancer therapy is its apparent ability to selectively target malignant cells while sparing healthy tissues, potentially reducing the severe side effects often associated with conventional treatments. Venom-derived compounds therefore represent a promising avenue for the development of more targeted and effective cancer therapies, either as standalone agents or in combination with existing treatment modalities.As research into the therapeutic potential of snake venom continues to evolve, it offers the exciting prospect of contributing to the next generation of innovative, precise, and less toxic cancer treatments.

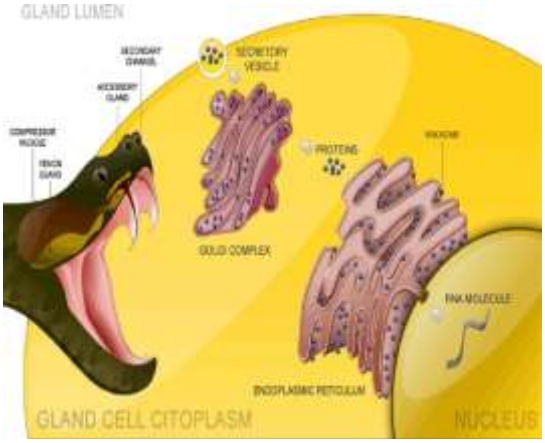

Fig: 2Snake Venom in Anti-Cancer Drug Development

2.3 Snake Venom Components:

Snake venom is a highly complex mixture of bioactive compounds that vary among species but generally include proteins, peptides, enzymes, and small molecules. These components are responsible for the venom's potent effects on prey and have shown significant potential for therapeutic use, particularly in cancer treatment.

2.3.1 Enzymes:

- **Phospholipases (PLA2s):**These enzymes break down phospholipids in cell membranes, compromising cellular integrity and contributing to tissue damage. Some phospholipases also induce inflammation and immune responses, which can be exploited in cancer therapy to selectively target and destroy tumor cells.
- **Snake Venom Metalloproteinases (SVMPs):** SVMPs degrade the extracellular matrix, facilitating venom spread and, in the context of cancer, disrupting tumor architecture. Their ability to break down structural barriers makes them valuable in the study of metastasis and tumor invasion.
- **Serine Proteinases:**These enzymes influence blood coagulation and inflammation and are being investigated for their role in modulating signaling pathways involved in tumor growth and progression.

2.3.2 Peptides:

- **Disintegrins:**Small peptides that inhibit integrins, which are proteins involved in cell adhesion and migration. By interfering with tumor cell attachment and movement,

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disintegrins hold promise as anti-metastatic agents in cancer therapy.

- **Cationic Antimicrobial Peptides (CAPs):** These peptides target cancer cell membranes, leading to membrane disruption and cell death. CAPs are particularly promising for treating drug-resistant cancers due to their ability to bypass traditional resistance mechanisms and induce apoptosis.

2.3.3 Toxins:

- **Neurotoxins:** While primarily known for disrupting nerve function, certain neurotoxins have demonstrated anticancer activity by inducing apoptosis and inhibiting cancer cell proliferation.
- **Cardiotoxins:** Typically affecting cardiac muscle, some cardiotoxins have shown the ability to disrupt cancer cell membranes, leading to cytotoxicity and apoptosis.

2.3.4 Other Bioactive Molecules:

- **Adenosine Phosphates:** These molecules modulate various cellular signaling pathways, influencing tumor cell growth, proliferation, and programmed cell death.
- **L-amino Acid Oxidases (LAAOs):** Enzymes that degrade amino acids and generate hydrogen peroxide—a reactive oxygen species toxic to cancer cells. LAAOs are being studied for their potential to selectively induce oxidative stress in tumors.

2.4 Anticancer Activity of Snake Venom:

Snake venom, a potent biological substance used by snakes for predation and defense, has emerged as a promising source for novel anticancer agents. This potential stems from the diverse array of bioactive molecules present in venom—such as proteins, peptides, enzymes, and toxins—that exhibit selective activity against cancer cells. These components can modulate critical pathways involved in cancer progression, including cell proliferation, apoptosis (programmed cell death), angiogenesis (formation of new blood vessels), and metastasis (the spread of cancer cells).

2.4.1 Historical Background and Early Discoveries:

The therapeutic potential of snake venom was first hinted at by Claude Bernard, the father of physiology, whose work laid the foundation for later investigations into venom's medicinal properties. The use of snake venom in cancer treatment was initially reported by Calmette in 1993 through studies on laboratory animals. One key discovery was the venom of Viperalebetinaturnica, which induced apoptosis in ovarian cancer cells by inhibiting the NF-κB and STAT3 signaling pathways. This inhibition prevented the nuclear translocation of p50 and p65 subunits of NF-κB, essential for cancer cell survival. Furthermore, the venom increased the expression of pro-apoptotic proteins such as Bax and Caspase-3, while downregulating the anti-apoptotic protein Bcl-2, enhancing the apoptotic response in tumor cells (Song et al., 2012).

2.4.2 Species-Specific Venom Effects:

Further studies have examined venom from species such as the Indian monocellate cobra (Najakaouthia) and Russell's viper (Viperarusselli), with promising results in models of carcinoma, sarcoma, and leukemia. In in vivo experiments, snake venom increased the lifespan of mice bearing Ehrlich ascites carcinoma (EAC) by improving their impaired antioxidant systems. In vitro studies also demonstrated potent cytotoxic and apoptogenic effects on human leukemia cells (U937/K562), including reduced cell proliferation and morphological signs of apoptosis (Debnath et al., 2007).

2.4.3 Cytotoxins and Cardiotoxins:

Cytotoxins—also known as cardiotoxins—are polypeptides typically consisting of 60–70 amino acids and are found in snakes of the Elapidae family. These molecules are known for their cytotoxicity, hemolytic activity, and potential anticancer properties (Ferrer, 2001). One notable example is Cardiotoxin-3 (CTX-3) from the venom of Najanajaatra (Chinese cobra). CTX-3 has been shown to induce apoptosis in K562 leukemia cells by upregulatingBax and endonuclease G and downregulatingBcl-x. DNA fragmentation analysis confirmed its apoptotic effect (Yang et al., 2006).

Additional studies demonstrated that CTX-3 induces apoptosis via Caspase-12 and the JNK pathway, causing rapid influxes of Ca^{2+} into the cytosol (Yang et al., 2008). Research using HL-60 leukemia cells further confirmed that CTX-3 induces apoptosis through both the endoplasmic reticulum (ER) and mitochondrial pathways, with increased calcium levels leading to cell death (Chien et al., 2008).

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2.4.4 Disintegrins:

Disintegrins are non-enzymatic proteins found in snake venom that show potent anticancer effects by interfering with cell-cell and cell-matrix interactions. These proteins contain the RGD (arginine-glycine-aspartic acid) motif, which allows them to bind to integrins and disrupt processes like tumor cell adhesion, invasion, and metastasis.

- **Salmosin**, a disintegrin from a Korean snake species, effectively suppressed metastatic and solid tumor growth in mice by inhibiting the αvβ3 integrin, a key mediator in melanoma cell proliferation and migration (Kang et al., 1999; Bradbury & Deane, 1993).
- **Contortrostatin (CN)**, a homodimericdisintegrin from the southern copperhead snake, inhibited the adhesion and invasion of human ovarian carcinoma cells (OVCAR-5) and blocked their interaction with extracellular matrix proteins, suggesting strong anti-metastatic potential (Markland et al., 2001).

2.4.5 Phospholipases A2 (PLA2):

PLA2 enzymes hydrolyze the sn-2 ester bond of phospholipids, generating lysophospholipids and free fatty acids with various biological effects (Gao et al., 2005). Snake venom is a rich source of secretory, Ca^{2+} -dependent PLA2 enzymes (Arimura et al., 1989).

- **MVL-PLA2**, isolated from Macroviperalebetina, demonstrated significant anti-integrin activity. In human microvascular endothelial cells (HMEC-1), it inhibited cell adhesion and migration—key steps in metastasis. It also disrupted the actin cytoskeleton and altered αvβ3 integrin distribution. Notably, MVL-PLA2 increased microtubule dynamicity by 40%, potentially interfering with the structural framework necessary for tumor proliferation (Bazaa et al., 2010).

2.4.6 L-Amino Acid Oxidases (LAAOs):

LAAOs are dimericflavoproteins containing FAD (flavin adenine dinucleotide) as a cofactor (Pawelek et al., 2000). These enzymes catalyze the oxidative deamination of amino acids, producing hydrogen peroxide—a reactive oxygen species with cytotoxic effects on tumor cells.

- LAAOs from Ophiophagushannah (king cobra) venom inhibited thymidine uptake and reduced cell proliferation in various cancer cell lines, including murine melanoma, fibrosarcoma, colorectal cancer, and CHO cells (Cura et al., 2002).
- LAAOs from Agkistrodonacutus venom caused cell cycle arrest in the sub-G1 phase and induced apoptosis in A549 human alveolar epithelial cells via the Fas signaling pathway (Kang et al., 1999).

2.5 Crotoxin: A Cytotoxic Protein with Potential in Cancer Therapy:

Crotoxin is a potent cytotoxic phospholipase A_2 (PLA_2) compound derived from the venom of Crotalusdurissusterrificus, a South American rattlesnake (Faure et al., 1993). This venom-derived protein has demonstrated significant cytotoxic activity against various murine and human tumor cell lines in vitro, particularly those expressing high levels of epidermal growth factor receptor (EGFR) (Rudd et al., 1994). Its selective toxicity toward EGFR-overexpressing tumors underscores its potential as a targeted therapeutic agent, especially in cancers characterized by elevated EGFR expression.

2.5.1 Preclinical Evidence:

In vivo studies have further confirmed the antitumor potential of crotoxin. Daily intramuscular administration in mice bearing Lewis lung carcinoma led to an 83% reduction in tumor volume (Newman et al., 1993). Similarly, a 69% tumor growth reduction was observed in the MX-1 human mammary carcinoma model. However, crotoxin exhibited comparatively lower efficacy in HL-60 leukemia cells, with only a 44% inhibition of growth, suggesting a preferential effect on solid tumors.

2.5.2 Clinical Evaluation:

A Phase I clinical trial was conducted to evaluate the safety and therapeutic potential of crotoxin in humans with solid tumors unresponsive to conventional treatment. The trial involved daily intramuscular administration of crotoxin for 30 days, at doses ranging from 0.03 to 0.22 mg/kg. A total of 35 treatment cycles were administered across 23 patients. The study reported no treatment-related fatalities, and some patients experienced disease stabilization or partial responses, depending on the carcinoma type.

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2.5.3 VRCTC-310: A Crotoxin-Based Combination Therapy:

Building on crotoxin's therapeutic promise, a novel compound—VRCTC-310—was developed by combining crotoxin with cardiotoxin, a basic amphipathic peptide also derived from snake venom. A Phase I clinical trial assessed the safety, pharmacokinetics, and mechanism of action of VRCTC-310 in 15 patients with refractory malignancies. Participants received daily intramuscular injections for 30 days. The maximum tolerated dose (MTD) was established at 0.017 mg/kg, supporting progression to Phase II clinical trials (Costa et al., 1997).

2.6 Mechanisms of Anticancer Activity:

Snake venom contains a variety of bioactive molecules that exert anticancer effects through multiple mechanisms. These include inducing apoptosis, inhibiting angiogenesis and metastasis, exerting selective cytotoxicity, and modulating the immune system.

2.6.1 Induction of Apoptosis:

One of the primary mechanisms by which snake venom exerts its anticancer effect is through the induction of apoptosis (programmed cell death). Several venom components, such as phospholipases A_2 (PLA_2s) and specific peptides, activate the intrinsic apoptotic pathway, leading to caspase activation and cellular disassembly. For instance, venom from the Indian cobra (Najanaja) contains elements that trigger apoptotic signaling and suppress tumor cell proliferation.

2.6.2 Inhibition of Angiogenesis:

Tumor growth is highly dependent on angiogenesis—the formation of new blood vessels to supply nutrients and oxygen. Snake venom proteins, including disintegrins and metalloproteinases, inhibit angiogenesis by preventing endothelial cell adhesion and tube formation. Disintegrins found in the venom of the Russell's viper (Daboiarusselii) have shown potent anti-angiogenic activity, thereby restricting tumor vascularization and slowing cancer progression.

2.6.3 Inhibition of Metastasis:

Metastasis—the spread of cancer cells to distant sites—is a leading cause of cancer-related mortality. Snake venom compounds such as disintegrins and metalloproteinases interfere with cell adhesion, migration, and invasion by degrading components of the extracellular matrix. This disruption prevents cancer cells from infiltrating nearby tissues and establishing secondary tumors.

2.6.4 Targeted Cytotoxicity:

Some venom-derived peptides exhibit selective toxicity toward cancer cells while sparing healthy cells. This specificity reduces systemic toxicity—a major limitation of conventional chemotherapy. Toxins from species like the King cobra (Ophiophagushannah) and common krait (Bungaruscaeruleus) have demonstrated preferential cytotoxicity against tumor cells, making them strong candidates for targeted cancer therapy.

2.6.5 Immunomodulation:

Snake venom also possesses immunomodulatory properties. Certain venom components can activate or suppress immune cell functions, influencing the body's ability to detect and destroy cancer cells. For example, peptides from the Bamboo pit viper (Trimeresurusgramineus) can modulate immune responses, offering potential applications in cancer immunotherapy by enhancing T-cell or macrophage activity against tumors.

2.7 Research and Preclinical Studies:

Numerous in vitro and in vivo studies support the anticancer potential of snake venom components. Peptides such as batroxobin**,** isolated from Bothropsasper, have shown efficacy in inhibiting tumor cell proliferation and inducing apoptosis. Other venom-derived molecules have demonstrated synergistic effects when used in combination with standard cancer treatments, improving overall therapeutic outcomes in preclinical models.

2.8 Clinical Trials and Challenges:

Although the therapeutic potential of snake venom is promising, several challenges must be addressed for clinical translation:

- **Toxicity and Safety:** The potent bioactivity of venom components necessitates rigorous evaluation to determine safe and effective dosing.
- **Complexity and Standardization:** Venom is a complex mixture of many compounds, and isolating specific therapeutic agents requires advanced purification and characterization methods.

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- **Production and Scalability:** Large-scale production of venom-derived molecules for clinical use remains a hurdle, though advances in recombinant biotechnology and synthetic biology may offer viable solutions.

III. DISCUSSION:

Snake venom comprises a diverse array of biologically active molecules including enzymes (phospholipases A_2, metalloproteinases, serine proteinases), peptides (disintegrins, cationic antimicrobial peptides), and toxins (neurotoxins, cardiotoxins). These components contribute to venom's complex biological activity and have been repurposed for therapeutic applications, particularly cancer treatment.Venom-derived enzymes like phospholipases A_2 disrupt tumor cell membranes and induce inflammation, while metalloproteinases degrade extracellular matrix proteins, inhibiting tumor invasion and metastasis. Peptides such as disintegrins interfere with integrin-mediated cell adhesion, effectively preventing metastasis and angiogenesis, which are critical for tumor growth and spread.

One of the most studied venom components, crotoxin, a phospholipase A_2 from Crotalusdurissusterrificus, exhibits selective cytotoxicity against tumors overexpressing EGFR, demonstrating notable antitumor efficacy in both preclinical and Phase I clinical trials. Furthermore, combination therapies such as VRCTC-310, which combines crotoxin with cardiotoxin, have shown promise in enhancing therapeutic outcomes.Mechanistically, snake venom components induce apoptosis through intrinsic pathways involving caspase activation, inhibit tumor angiogenesis by preventing endothelial cell adhesion and migration, and suppress metastasis via extracellular matrix degradation. Additionally, venom peptides modulate immune responses by influencing T-cells and macrophages, suggesting a role in cancer immunotherapy.

Despite these promising findings, the clinical translation of venom-derived therapies faces significant hurdles. The inherent toxicity of venom components demands careful dose optimization and safety assessment. Moreover, venom complexity challenges the isolation and standardization of individual therapeutic agents. Production at scale remains difficult, though advances in biotechnology offer potential solutions.

IV. CONCLUSION:

Snake venom represents a rich and largely untapped reservoir of bioactive molecules with significant potential for cancer therapy. Its components exhibit multifaceted anticancer mechanisms, including targeted cytotoxicity, apoptosis induction, and inhibition of tumor progression processes such as angiogenesis and metastasis. Preclinical and early clinical studies validate the promise of venom-derived compounds like crotoxin and disintegrins as effective anticancer agents. However, addressing challenges related to safety, standardization, and scalable production is essential for their successful integration into mainstream cancer treatment. Continued research and technological advancements will be pivotal in realizing the full therapeutic potential of snake venom-based anticancer drugs.

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