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Venom-Derived Peptides Targeting Pancreatic Cancer

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Abstract

Pancreatic cancer is a fatal tumor with a 5-year survival rate below 10%. Pancreatic cancer is commonly diagnosed late, with distant metastases. Thus, surgical cures are rare. First-line surgery is often followed by adjuvant chemotherapy. The development of non-surgical pancreatic cancer treatments is very urgent. However, therapeutic resistance continues to affect pancreatic cancer therapy and prognosis. This requires a detailed understanding of therapy resistance processes. Additionally, novel therapeutic methods must be actively investigated as treatments. Pancreatic cancer treatment with natural products has advanced anti-tumor drugs. Several clinical trials have indicated that natural compounds and their derivatives slow pancreatic cancer growth. These effects are achieved by inhibiting angiogenesis, cell migration, and proliferation. Natural products also induce apoptosis and cell death to stop the cell cycle. Animal venom contains bioactive chemicals like amino acids, biogenic amines, nucleotides, inorganic salts, toxic peptides and enzymes that may be medicinal. Recent research has shown that animal venom inhibits many cancer cell types through various pathways. This is done by inhibiting ion channels or binding to cancer cell membrane targets. Animal venom inhibits metastasis and invasion. They also activate intracellular apoptosis and cell cycle arrest pathways. This review article provides insight into the anticancer mechanism of certain venom peptides isolated from various venomous animals targeting pancreatic cancer.

Keywords: Natural Toxins, Venomics, Anticancer Peptides, Apoptosis, Pancreas, Chemotherapy

1. Introduction

Pancreatic cancer is well recognized as a very fatal form of human malignancy, characterized by a notably low 5-year survival rate that is below 10% [1]. Patients with pancreatic cancer are often detected after advanced stages of the disease, sometimes accompanied by distant metastases. Therefore, the chances for successful surgical treatment to achieve a cure are limited [2]. Surgical intervention is frequently used as the first treatment technique, with adjuvant chemotherapy subsequently administered., At the time of diagnosis, only 15-20% of pancreatic cancer patients possess tumors that are operable, rendering surgery the only potential curative option [3]. Around 74% of those diagnosed with pancreatic cancer pass away within the first year of diagnosis. In the last ten years, the incidence of this cancer has steadily increased and is expected to continue rising. Presently, pancreatic cancer is the fourth most common cause of cancer-related deaths in the United States, with projections indicating it may rise to become the second most common cause in the coming decade. Several factors contribute to the poor prognosis for those suffering from this disease. Notably, the resistance of pancreatic cancer cells to traditional therapies, including chemotherapy and radiation therapy, poses a significant challenge [4]. Advancing non-surgical treatment meth-

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ods is critically urgent to improve the effectiveness of pancreatic cancer therapies. However, the persistent challenge of therapeutic resistance continues to substantially affect treatment outcomes and the overall prognosis for patients diagnosed with pancreatic cancer.

The natural environment includes an extensive range of bioactive compounds that possess medicinal properties. The application of natural anticancer drugs has significant promise in combating cancer and producing encouraging outcomes [5]. Venomous animals are important in the exploration and identification of innovative treatment possibilities. They produce different types of venom as a defense mechanism against external threats. Venom inhibits the growth of cancer cells and induces cell death by triggering apoptosis, releasing cytochrome C, and altering protein expression, thereby regulating the cell cycle [6]. The application of snakes and scorpion venoms in the field of medicine, as recently as two decades ago, has demonstrated the advantageous effects of employing venomous animals for the benefit of patients. Research in molecular biology and protein chemistry enables a deeper comprehension of venoms. Currently, a quantity of toxins has been transformed into pharmaceuticals to treat diseases. Lately, there has been an increasing focus on using natural venoms in cancer therapy [7]. Numerous bioactive substances sourced from animals show promise in treating cancer, such as chlorotoxin, which blocks cancer cell invasion; raventoxin, which suppresses HeLa cells; and BJcuL, which curtails the proliferation and growth of tumor cells [8, 9].

2. Pancreatic Cancer

2.1. Incidence, Morbidity and Mortality Rates

Pancreatic cancer (PC) is a deadly and aggressive disease. Presently, it ranks as the tenth most prevalent form of cancer, accounting for only 3% of all new cancer cases, yet it stands as the sixth highest cause of cancer-related deaths, comprising 6% of these fatalities. Forecasts suggest that by 2030, PC is expected to exceed breast, colorectal, and prostate cancers, becoming the second leading cause of cancer-related deaths [10].

There is currently no routine examination program for diagnosing PC. Diagnostic tools are available for patients who have been referred, typically after showing symptoms. The absence of specific symptoms in PC complicates and prolongs the diagnostic process. The rapid tumor growth in PC often results in late-stage diagnosis, with more than 50% of patients already having metastatic cancer at the time of diagnosis [11]. Consequently, therapeutic options are limited, with many patients only receiving palliative care. Only approximately 10% of PC are identified early enough, before metastases appear, to qualify for surgical intervention. Among those who undergo surgery, 90% ultimately die from the disease due to local recurrence or distant metastases, in the absence of additional adjuvant therapy [12]. Nevertheless, surgical resection continues to be the most effective treatment for PC. Combining surgery with chemotherapy and/or immunotherapy provides the best prognosis. While genetic screening may be beneficial for individuals with a familial history of PC, hereditary forms constitute only about 10% of all pancreatic cancer cases [13]. Given this, and the variability in genetic factors, comprehensive population screening is currently deemed neither necessary nor cost-effective [14].

2.2. Causes and Risk Factors

Age is strongly correlated with the development of PC, with those becoming most at risk in the 60-70 age range. Some patients with a family history of PC may experience an earlier onset of the disease, known as 'genetic anticipation', showing symptoms two decades earlier than their affected relatives. Also smoking significantly increases the risk of developing PC. Research indicates that smokers have to acquire a PC ten years earlier than non-smokers. Male smokers under the age of 50 are particularly susceptible to this increased risk [15]. Evidence suggests that nicotine, found in cigarettes and other tobacco products, elevates the risk of developing PC. Additionally, nicotine has been observed to hasten the transformation from healthy cells to cancerous pancreatic cells in animal stud-

ies. Furthermore, nicotine is implicated in increasing both the quantity and aggressiveness of metastatic cancer cells [16]. Another lifestyle factor believed to influence PC is dietary choices and obesity. An established correlation exists between elevated BMI and increased susceptibility to developing PC [17]. Other variables like age, chronic pancreatitis, and additional comorbid conditions have a significant impact on the likelihood of developing PC [18].

2.3. Types of Pancreatic Cancer

Pancreatic cancer (PC) is divided into two main categories: tumors of the endocrine pancreas, which cause islet cell cancer, and tumors of the exocrine pancreas, which lead to pancreatic ductal adenocarcinoma (PDAC) and acinar cancer. PDAC is the predominant and most aggressive form, constituting approximately 90% of all PC cases. Before PC is diagnosed, pancreatic duct epithelial cells develop precursor lesions called pancreatic intraepithelial neoplasia (PanIN). There are three stages of PanIN—PanIN-1, PanIN-2, and PanIN-3—each representing increasing levels of severity [19]. Over time, these non-invasive PanINs advance in severity and grade, eventually evolving into invasive neoplasia that progresses to PDAC.

PDAC is believed to originate from the neoplastic transformation of ductal epithelial cells. The stepwise model suggests a progressive transition from dysplasia to malignancy, characterized by the presence of precursor lesions that may be seen under a microscope. These precursor lesions include pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms, and mucinous cystic neoplasms. The majority of people exhibit a purely somatic process in this phenomenon, however around 10% of patients diagnosed with PDAC possess an inherent susceptibility to developing malignancies due to genetic predisposition. A small portion of this inclination may be attributed to variations in well-established genes with substantial penetrance. including genetic conditions such as ovarian and hereditary breast cancer, as well as Lynch syndrome, which are associated with the development of pancreatic tumors exhibiting distinct phenotypic characteristics. The genesis of PDAC cells, which undergo progression through increasing grades of cytological atypia, may be derived from several sources such as morphology, genetic [19], expression investigations, and organoid models [20].

Histologically, pancreatic ductal adenocarcinomas (PDACs) consistently arise from the ductal epithelium, undergoing a process that starts with low-grade dysplasia and progresses to high-grade dysplasia. This sequence of changes transitions the normal pancreatic ductal epithelium to low-grade and subsequently high-grade dysplastic pancreatic intraepithelial neoplasms (PanINs), culminating in invasive adenocarcinoma. Accompanying these pathological transitions are genetic alterations. For instance, KRAS activating mutations may occur in what appears to be histologically normal ductal epithelium. Initial somatic changes linked to KRAS oncogene activation and telomere reduction are observable in low-grade PanINs. As high-grade PanINs accumulate, there is a marked inactivation of crucial tumor suppressor genes that regulate the cell cycle, such as TP53, cyclin-dependent kinase inhibitor 2A (CDKN2A), and SMAD4. Invasive adenocarcinomas are characterized by an increased presence of structural and copy number variations, encompassing complex processes such as chronotherapies and polyploidization. The extracellular matrix (ECM) forms a sophisticated framework of molecules that provide structural and biochemical support to cells across various tissues and organs [20].

3. Current treatment of pancreatic cancer

3.1. Surgery

At now, surgical excision is the only therapeutic option that has the potential to cure the condition. The surgical treatment for pancreatic ductal adenocarcinoma (PDAC) might include the complete or partial removal of the pancreas, depending on the tumor's size and location. However, this approach depends on early detection and diagnosis of the disease, making it impractical for the majority of patients [21]. For patients eligible for surgical resection, the actual five-year cure rate remains exceedingly low, ranging from 3% to 5% [22].

3.2. Chemotherapy

The custom chemotherapeutic treatment for pancreatic cancer mostly revolves around the use of gemcitabine therapy, which may be combined with one or more other drugs. FOLFIRINOX therapy provides an alternative treatment choice for individuals, especially those who are younger and in better physical condition. This combined therapy offers a greater overall survival rate for individuals with pancreatic cancer, but it comes with the drawback of increased toxicity and a significantly poorer side effect profile compared to gemcitabine [23]. The chemotherapeutic medicines currently in use are mentioned in **Table 1**. These therapies include gemcitabine, which is currently considered the most effective treatment option, along with various combination medications that have also been developed.

4. Venom Peptides

Venom comprises a diverse array of components that synergistically interact to subdue prey or defend against potential predators. The development of venom and its administration machinery has occurred independently throughout numerous phyla over millions of years. This evolutionary process has been driven by the need to defend against predation and facilitate the capture and digesting of prey. The phenomenon of multiple convergent evolution has resulted in the emergence of a wide array of distinct components observed in many venomous animals. This phenomenon leads to the emergence of an extensive and largely collection of pharmacologically active compounds that undergo evolutionary changes to exhibit bioactivity and possess the capacity to be utilized as therapeutic interventions for various diseases [29, 30]. Venom constituents are typically classified into three principal categories: proteins, low molecular weight organic chemicals, and inorganic compounds. It is widely recognized that proteins and peptides account for around 95% of venom's dry weight, while the remaining elements are of lesser significance [31].

Natural products possess a significant chemical variety, rendering them a promising reservoir of medicinal compounds. The continuing growth of identifying possible anticancer chemicals from animal sources is evident. Animals possess a diverse array of poisons and venom that protect themselves from environmental factors. Venoms have diverse therapeutic uses in the management of cardiovascular disorders, autoimmune conditions, neurological disorders, and cancer. Multiple investigations have documented the potential of venom proteins and peptides as medicines with anticancer properties [32–34]. The venom derived from different animal sources, including snakes, bees, scorpions, beetles, wasps, ants, caterpillars, and spiders, possesses anticancer effects **(Figure 1)**.

5. Mechanism of action of venom peptides as an anticancer-based therapy

5.1. Apoptosis

Apoptosis is pivotal in the anti-tumor activities of various scorpion venoms and associated toxins. This programmed cell death follows two separate pathways: intrinsic and extrinsic. The intrinsic pathway entails increased permeability of the mitochondrial membrane, leading to the release of cytochrome c. The release of cytochrome c is controlled by the inhibitory action of Bcl-2 and the stimulatory action of Bcl-2-associated X (Bax), which facilitates the release of cytochrome c. Subsequent to this release, caspases are activated, starting with caspase-9. Caspase-9 activates further downstream processes, including the cleavage of procaspase-3, which then activates caspase-3, leading to cell cytotoxicity [35]. The extrinsic apoptosis pathway is activated by the elevated expression of Fas ligand (FasL) [36], which attaches to the Fas receptor—a member of the cytotoxicity-inducing receptor family located on the cell membrane [37]. Caspases-3 and 7 target various substrates, such as poly ADP-ribose polymerase (PARP), lamin, caspase-activated DNase inhibitor (iCAD), and the protein 8-related to XK (XKr8). These caspases execute the cleavage of these substrates, influencing critical apoptotic processes such as nuclear condensation, DNA frag-

Table 1: **The current chemotherapeutic drugs used to treat advanced and metastatic PC.**

Drug	Class	Reference
Gemcitabine	Nucleoside analogue	[24]
5-Fluorouracil as adjuvant	Cytotoxic	[25]
[Gemcitabine + cisplatin	Platinum-containing anticancer drug	[24]
Gemcitabine + erlotinib	Nucleoside analogue + tyrosine kinase inhibitor	[26]
Gemcitabine as adjuvant	Nucleoside analogue	[27]
Gemcitabine + capecitabine (GEM-CAP)	Pro-drug of 5-fluorouracil	[28]
FOLFIRINOX*	Combination therapy	[23]

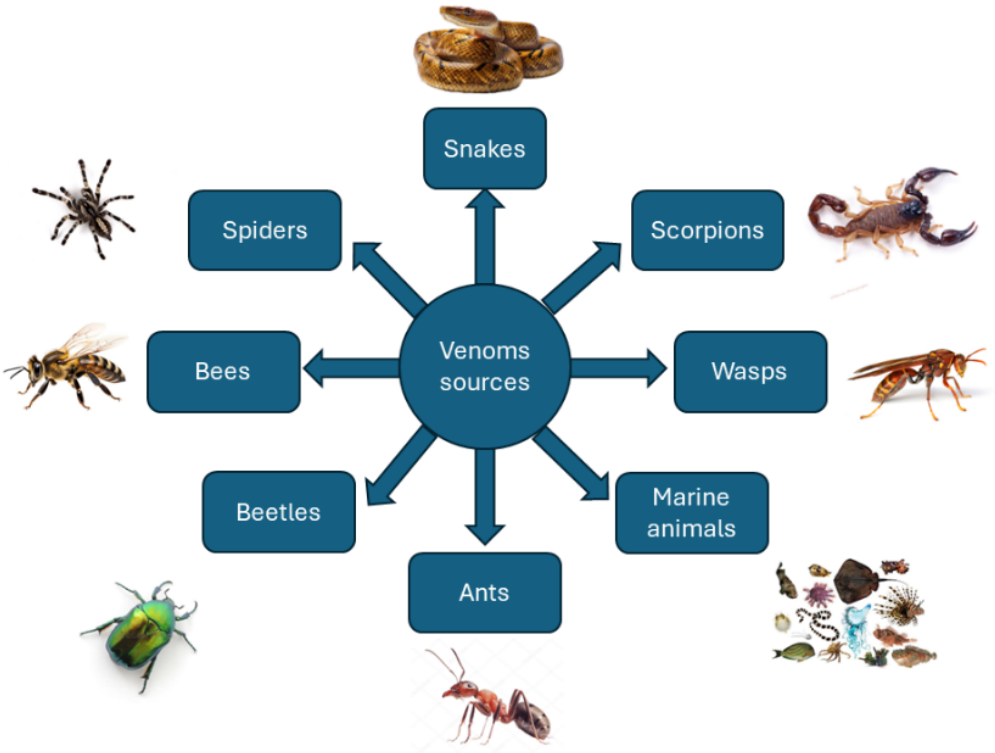

Figure 1: **Venoms derived from different venomous animals.**

mentation, membrane blistering, and the exposure of phosphatidylserine [38] **(Figure2)**.

5.2. Cell cycle arrest

The cell cycle includes a sequence of cellular processes that end in the replication of DNA and the division of cells, ultimately leading to the production of two daughter cells. Throughout the process of the cell cycle, numerous regulatory systems are in operation to ensure the accurate division of cells. The term used to refer to these are cell cycle checkpoints. The G phase is situated in the gap. The progression from the G2 phase to the M phase in the cell cycle is primarily regulated by the cyclin-dependent kinase 1 (CDK1)/Cyclin B complex. The inhibitory role of p21, a strong inhibitor of cyclin-dependent kinase, is essential for lowering CDK1 activity and inducing cell cycle arrest during the G2/M phase, thus impeding the development of cancer cells. Venom, toxins, or specific isolated fractions demonstrate the ability to halt cell cycle progression at various stages, including G0/G1, G2/M, and G1/S [20].

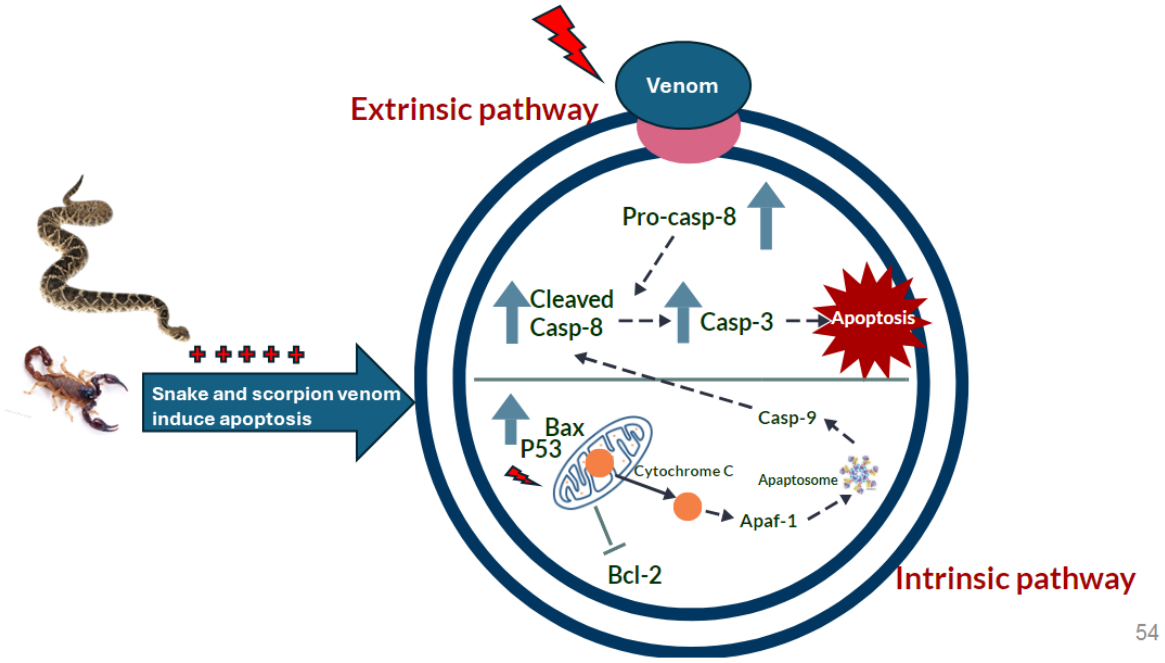

Figure 2: **Illustration depicting the mechanisms of apoptosis:** The extrinsic pathway is initiated when venom binds to specific receptors, activating caspase 8. In the intrinsic pathway, the release of cytochrome c from mitochondria prompts the formation of the apoptosome, leading to the activation of caspase 9. Both caspase 8 and 9 catalyze the activation of other downstream caspases, including caspase 3, which results in cellular death. Cytochrome c is released through increased mitochondrial membrane permeability in the intrinsic pathway. The inhibition of Bcl-2 curtails the release of cytochrome c, while the enhancement of Bax, a regulator of apoptosis, facilitates this release. The activation of caspase 9 follows, which then cleaves procaspase-3, resulting in the activation of caspase-3 and subsequently inducing apoptosis.

5.3. Angiogenesis inhibition

Angiogenesis is the formation of new blood vessels, a process commonly seen in solid tumors. Cancer cells often display increased levels of growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), both of which significantly contribute to neovascularization. A key mechanism of venom involves its capacity to inhibit the expression of VEGF [39].

5.4. Disruption of plasma membrane and ion channel modulation

At the cellular membrane level, cancer cells differ from normal cells in two key ways: a more pronounced net negative charge and a greater number of microvilli, which increase the surface area of the cells. In standard mammalian cells, anionic molecules like phosphatidylserine (PS) and phosphatidylethanolamine (PE) are situated in the inner membrane, while zwitterionic phospholipids are found in the outer membrane [40, 41]. During the transformation from a normal cell to a cancer cell, there is a loss of asymmetric phospholipid distribution across the cell membrane. This modification leads to the movement of some phosphatidylserine (PS) and phosphatidylethanolamine (PE) to the outer membrane layer, increasing the net negative charge. The enhanced negative charge is further intensified by the upregulated expression of anionic molecules, including O-glycosylated mucins (high molecular weight glycosides with negatively charged saccharides), gangliosides, and heparin sulfates, which are more concentrated on the outer membrane layer.

Certain venom peptides are known as host defense peptides. The positive charge of AMPs and

the negative charge of cancer cells enhance electrostatic interactions, thus elevating their selective toxicity towards cancer cells. Additionally, the interaction between the hydrophobic amino acids of amphiphilic antimicrobial peptides and the phospholipid bilayer of cell membranes facilitates their integration into the membrane structure [41]. Upon attachment to the cell membrane, peptides initiate cytotoxic actions through mechanisms such as pore formation, disruption of the membrane, or breaking down membrane lipids via micelle formation. Concurrently, cationic peptides enhance the transmembrane potential, thus facilitating greater membrane permeabilization. Another cytotoxic mechanism involves the voltage-activated opening of ion channels. Ion channels significantly influence cancer pathophysiology through various mechanisms. The role of calcium (Ca^{2+}), sodium (Na^{+}), and potassium (K^{+}) channels in the growth of cancer cells is crucial, as they regulate numerous essential signaling pathways that control cell survival and membrane potential. Furthermore, these channels contribute to cancer-specific traits like resistance to growth inhibitors, evasion of apoptosis, perpetual proliferation, and metastatic capability [42].

The anticancer properties of venoms effectively inhibit or block key cancer characteristics. Composed of intricate bioactive peptides with a substantial protein content of varying lengths, these venoms demonstrate considerable activity, stability, and a broad spectrum of pharmacological actions. Venoms from venomous creatures have diverse biological effects, particularly in modulating ion channels related to sodium (Na^{+}), potassium (K^{+}), chloride (Cl^{-}), and calcium (Ca^{2+}), as well as inhibiting proteases [43, 44], and anticancer activity [45] **(Figure 3)**.

6. Anti-cancer activity of snake venom

The venom produced by snakes consists of complex combinations of proteins, peptides, and other bioactive compounds. These compounds are generated by the venom gland of snakes and subsequently injected by their distinctive fangs to incapacitate and attack their prey. Snakebite envenoming poses a significant public health concern, as it poses a hazard to human life. However, snake venoms have been acknowledged as a promising source of physiologically active drugs [46, 47]. The components of venom can be categorized into two main groups: enzyme components and non-enzyme components. L-amino acid oxidases (LAAO), Phospholipase A2 (PLA2), metalloproteases (SVMP), 5'-nucleotidases, acetylcholinesterases, serine proteases (SVSP), and hyaluronidases are among the enzymatic snake venoms. Disintegrins (DIS), Kunitz peptides, three-finger toxins (3FTx), C-type lectins (CTL), cysteine-rich secretory proteins (CRiSP), and natriuretic peptides (NP) are examples of non-enzymatic components [48] **(Figure 4)**.

The impact of two integrin antagonists, recombinant disintegrins mojastin 1 and viridistatin 2, on the human pancreatic cancer cell line BXPC-3, was significant. Both recombinant disintegrins effectively impeded crucial aspects of the metastatic process, such as adhesion, cell proliferation, migration, and survival by inducing apoptosis. These proteins represent promising therapeutic candidates for the treatment of pancreatic cancer [49]. Crude venom from Ophiophagus hanna exhibited cytotoxic action, which resulted in the induction of apoptosis and a reduction in the activity of migration [50].

Snake venom also exhibits anticancer activities against various other cancers. For instance, the L-amino acid oxidase (LAAO) extracted from Ophiophagus hanna has shown inhibitory effects on the proliferation of human breast cancer and lung adenocarcinoma cell lines, with IC50 values recorded at 0.04 μg/mL and 0.05 μg/mL, respectively [51]. Additionally, the venom from Vipera raddei kurdistanica has demonstrated cytotoxic effects and the ability to trigger apoptosis in breast cancer cells [52]. The mechanisms and effects of different snake venoms are summarized in **Table 2.**

7. Anti-cancer activity of Scorpion venom

Scorpions are predatory arachnids of medicinal significance that are classified under the phylum Arthropoda. A comprehensive record reveals

Table 2: Snake venoms against various cancer types and their mechanisms of action

Scientifc name	Common name	Anti-cancer compounds	Mode of action	Ref.
Bungarus fasciatus	Banded krait	Cathelicidin-BF	Suppresses the proliferation of B16F10 and B16 cells.Top of Form	[53]
Bothrops jararacussu	Golden lancehead	BJcuL (lectin)	Halts the development and endothelial cells and growth of tumor cells, and causes erythrocytes to clump together	[54]
Vipera lebetina obtuse	West Asian bluntnosed viper	Obtustatin	It exhibits antiangiogenic properties in cancer cells. Top of Form	[55]
Agkistrodon rhodostoma	Malayan pit viper	Rhodostomin	Impedes the interaction between integrins and extracellular matrix (ECM) proteins, which is essential for the proliferation of cancer cells	[56]
Bothrops atrox	Common lancehead	Batroxobin	Blocks the spread and metastasis of cancer cells	[57]
Vipera lebtina turanica	Turan bluntnosed viper	Snake venom toxin	Restricts the growth of cancer cells by causing arrest in the G2-M phase. It inhibits an anti-apoptotic transcription factor, NF-$\kappa\beta$, and significantly reduces the translocation of the p50 nucleus.	[58]
Macrovipera lebetina	Blunt-nosed viper	Lebectin	Obstructs migration, adhesion, and invasion of tumor cells, and inhibits angiogenesis.	[59]
Eristicophis macmahoni	Asian sand viper	Eristostatin	Prevents the colonization of melanoma cells in the liver and lung.	[60]
Vipera palEastinae	Palestine viper	Viperistatin	The interaction between integrins and the extracellular matrix is crucial for the migration and invasion of cancer cells. This interaction inhibits the adhesion and movement of cancer cells.	[61]
Agkistrodon acutus	South American rattlesnake	Cromatine	Prevents attachment of skin melanoma and human urinary cancer cells to fibronectin.	[62]
Macrovipera lebetina	Blunt-nosed vipe	MVL-PLA2	Exhibits angiogenesis inhibition and triggers changes in the actin cytoskeleton	[63]
Agkistrodon controtrix	Southern copper-head snake	Contortrostatin	Inhibits platelet aggregation, blocks cancer cell growth, adhesion, migration, and angiogenesis.	[64]
Bothrops leucurus	Whitetail lance- head	Leucurogin	It exhibits antiangiogenic effects in cancer cells	[65]
Bothrops leucurus	Whitetail lance- head	Leucurolysin-B	Exhibits cytotoxic effects on MCF7, U87, UACC, T98, RT2, and EAC cancer cell line	[66]
Echis carinatus	Indian saw-scaled viper	Vicrostatin	Prevents the migration of human umbilical vein endothelial cells.	[67]
Crotalus viridis	Prairie rattlesnake	Viridistatin 2	Suppresses proliferation, migration, adhesion, and promotes apoptosis, thereby reducing survival in human pancreatic carcinoma (BXPC-3) cells.Top of Form	[49]
Crotalus tzab can	Yucatan Neotropical Rattlesnake	Tzabcanin	Blocks the adhesion of melanoma (A-375) cells and lung cancer (A-549) cells to vitronectin.	[68]
Ophiophagus Hannah	King cobra	Ophiophagus hannah venom	Demonstrated inhibitory effects on tumor cell-induced angiogenesis.Top of Form	[50]

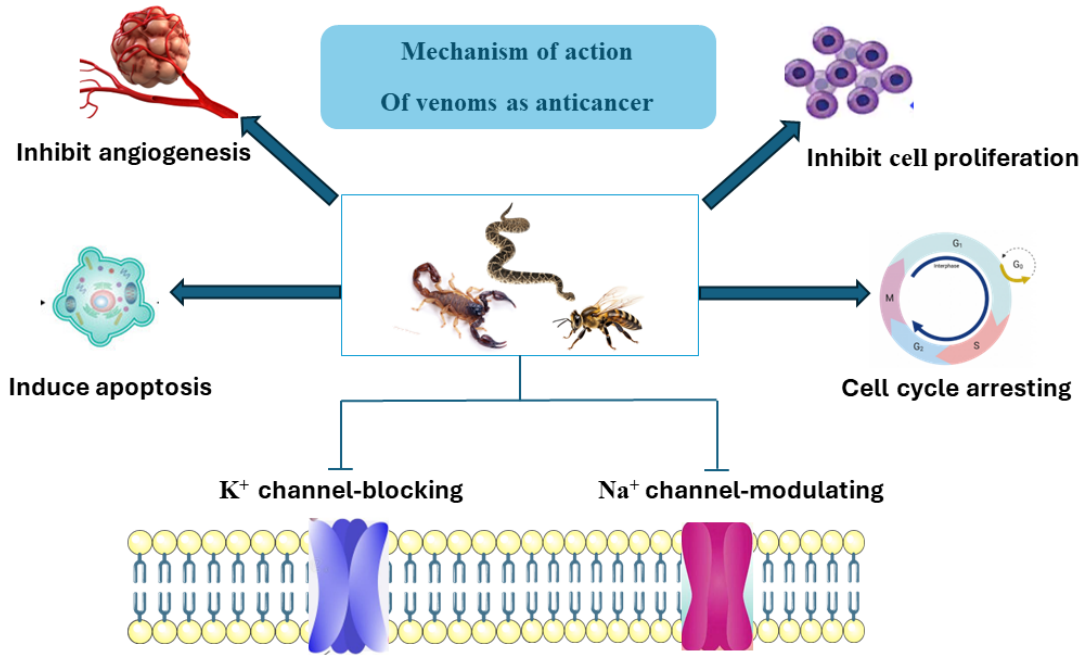

Figure 3: Mechanism of action of venoms as anticancer agents.

the existence of three distinct scorpion families, namely Scorpionidae, Hemiscorpiidae, and Buthidae [69]. The scorpion has a set of venom glands situated in the terminal portion of its tail, known as the telson. These glands are accompanied by a pair of ducts that are positioned towards the tip of a curved spine. This spine serves the purpose of penetrating the integument or skin of prospective prey [70]. The consequences of a scorpion sting may exhibit significant variability, ranging from localized discomfort or inflammation to severe clinical manifestations, perhaps leading to death. The degree of scorpion envenomation is correlated with the existence of neurotoxins inside the venom [71]. Peptides generated from scorpion venoms can be classified into two distinct groups: disulfide-bridged peptides (DBPs), including neurotoxins, and non-disulfide bridged peptides (NDBPs), which exhibit anti-cancer, immunomodulatory, and antibacterial properties, DBPs has been extensively conducted, primarily driven by the medical significance associated with envenomation, scorpion venom composition illustrated in **Figure 5** [72].

Most DBPs express cross-linking through 3-4 disulfide bridges and possess the ability to selectively interact with ion channels. DBPs constitute the primary component of scorpion venom and have been identified as peptides that participate in interactions with ion channels. Natural venom components have been primarily influenced by DBPs, which are neurotoxins. Neurotoxins can obstruct or alter specific ion channels, leading to autonomic stimulation. Additionally, α-toxins can induce a substantial discharge of catecholamines. The combination of these two occurrences has the potential to initiate a series of physiological responses that may lead to the development of tachycardia, heart failure, and ultimately, mortality [73]

The majority of non-disulfide bridged peptides (NDBPs) identified in scorpion venom exhibit characteristics of antimicrobial peptides. These peptides possess amphipathic properties and typically assume an α-helical conformation The peptides have been found to show changes in their structural shape in response to environmental

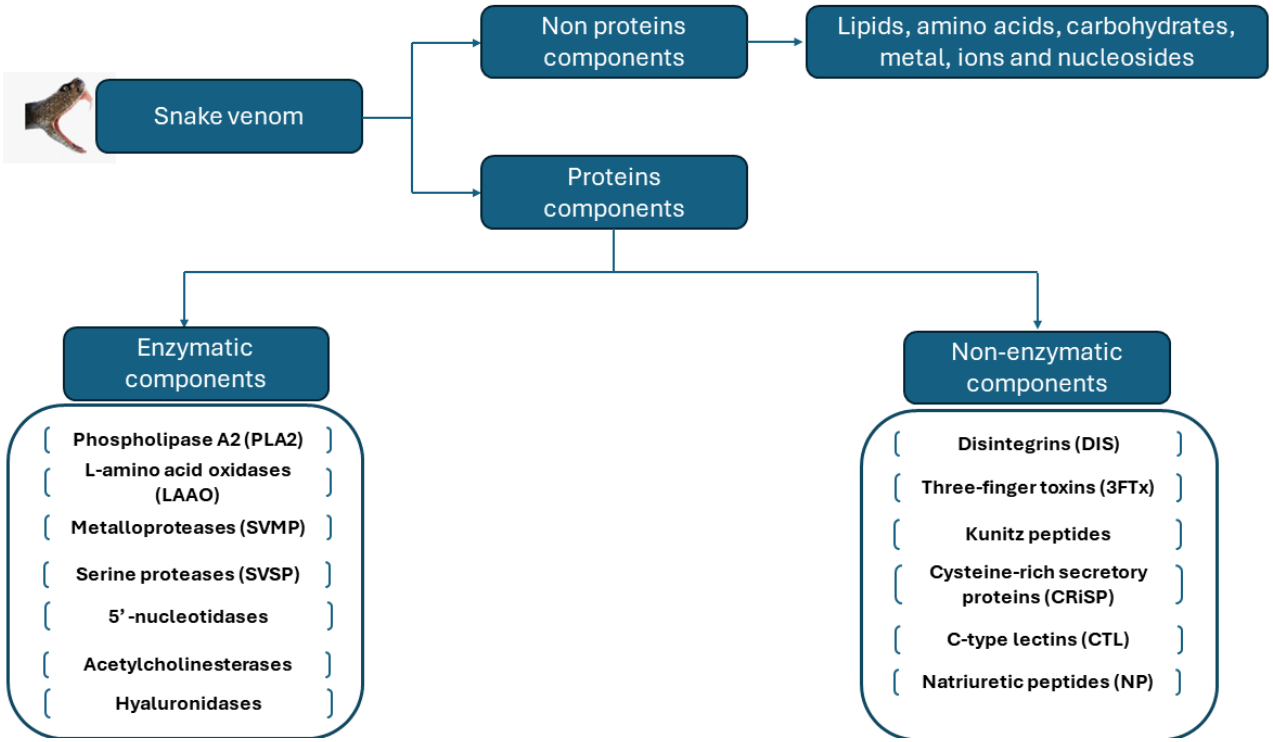

Figure 4: Flow chart illustrates the composition of snake venom. Snake venom is classified into two primary categories based on its constituents: enzyme components and non-enzyme components. Enzymatic snake venoms encompass a variety of types, including L-amino acid oxidases (LAAO), Phospholipase A2 (PLA2), serine proteases (SVSP), metalloproteases (SVMP), 5'-nucleotidases, hyaluronidases and acetylcholinesterases. Examples of non-enzymatic components include, three-finger toxins (3FTx), cysteine-rich secretory proteins (CRiSP), disintegrins (DIS), Kunitz peptides, natriuretic peptides (NP) and C-type lectins (CTL).

conditions. This ability enables them to interact with bacterial membranes more effectively, hence contributing to their antibiotic effectiveness. Beyond their antimicrobial properties, NDBPs exhibit a range of additional activities, including insecticidal, antifungal, antiviral, antimalarial, hemolytic, anti-proliferative, immunomodulatory effects and bradykinin-potentiating [73, 74].

Anti-microbial peptides (AMPs) that are produced from scorpion venom often have a small size with a relatively low number of amino acids (ranging from 13 to 56 aa). These peptides possess a positive charge, varying from +1 to +7, and are characterized by the presence of hydrophobic regions. The NDBP-class of scorpion AMPs has been observed to have a diminished capacity for resistance development in bacteria. This finding serves as additional evidence supporting the poshemolyticsibility of these molecules as a basis for the creation of innovative peptides aimed at targeting infectious diseases [74].

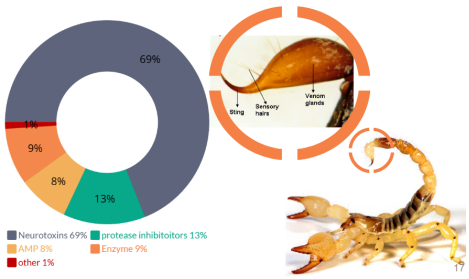

Figure 5: Composition of scorpion venom. The scorpion venom consisted of 69% neurotoxins, 13% protease inhibitors, 8% anti-microbial peptides (AMP), 9% enzyme and 1% others).

Chlorotoxin (CTX) is a peptide consisting of 36 amino acids, sourced from the venom of the

scorpion Leiurus quinquestriatus. It blocks low-conductance chloride channels in the colon's mucosal lining.

Research indicates that CTX can attach to several proteins including membrane type-1 MMP, matrix metalloproteinase-2 (MMP-2), CLC-3 chloride ion channels and tissue inhibitor of metalloproteinase-2. The activation of MMP-2 is critical for the invasion and migration of pancreatic cancer cells. A fusion protein, M-CTX-Fc, was created by linking the CTX peptide to the amino terminus of the human IgG-Fc domain without a hinge domain. This fusion protein specifically targets PANC-1 cells in vitro, showing a dose-dependent decrease in MMP-2 secretion. Internalization of M-CTX-Fc into PANC-1 cells has been observed, with chlorpromazine (CPZ) treatment reducing this internalization, suggesting that the process relies on clathrin.

[73].

Previous research has shown that crude scorpion venom and particular peptides (such as IbTX, charybdotoxin, margatoxin, AGAPSYPU2, ClTx, Smp43, and Smp24) are effective in attacking cancer cells, in vitro and in vivo. These compounds demonstrate a wide range of modes of action. Significantly, a certain peptide has effectively advanced through both phases I and II clinical studies [39, 75] (Table 3).

8. Anti-cancer activity of bee venom

Bee venom consists of an assortment of bioactive amines, peptides, proteins, and small molecular compounds with therapeutic properties. These include substances like apamin, alpine, melittin, mast-cell-degranulating peptide, various enzymes, and non-peptide elements [58]. Bee venom has been utilized in the management of numerous conditions, including rheumatism, arthritis, pain, cancers, and dermatological issues. Extensive research has confirmed the anticancer effects of bee venom, highlighting its capabilities to trigger apoptosis, demonstrate cytotoxic effects, induce necrosis, and inhibit the proliferation of cancer cells [79].

Melittin, which forms approximately 40-50% of the dry weight of bee venom, is a major component. Melittin has been widely researched for its anticancer effects and is considered a viable alternative to conventional cancer chemotherapy. Both phospholipase A2 and melittin can selectively target a range of cancer cells, including those in the prostate, mammary gland, liver, kidney, and lungs.

[80].

Bee venom substantially inhibited the growth of the human pancreatic cancer cell lines PANC-1 and AsPC-1. This inhibition occurred by inducing cell cycle arrest and apoptosis, while also reducing cell migration. More precisely, bee venom caused an arrest in the S phase and enhanced the regulation of protein expression for cyclins and cyclin-dependent kinases (CDKs). Additionally, it activated the p53-p21 signaling pathway [81].

Bee venom triggers apoptosis in lung cancer cells (A549 and NCI-H460) through the enhancement of death receptor 3 expression and suppression of the NF-κB pathway. Further research has highlighted the anticancer effects of bee venom on colon cancer cells, demonstrating that the stimulation of death receptors and suppression of NF-κB contribute to cancer cell death regulation. Moreover, bee venom has a pronounced apoptotic effect on human breast cancer cells (MDA-MB-231), notably causing protein degradation, denaturation, and DNA fragmentation within these cells [82].

9. Conclusion

The use of several chemotherapeutic drugs in clinical settings might result in various notable side effects, ultimately leading to unsatisfactory clinical outcomes. Furthermore, there have been reports indicating that the implementation of pancreatic cancer therapy that is specifically designed to target the disease may potentially facilitate the progression of cancer through the preservation of functional abilities, hence resulting in the tumor cells adapting or developing resistance to chemotherapy. Consequently, anticancer drugs derived from natural resources have great potential as effective tools for cancer treatment. This review shows that animal venom, especially that of snakes, scorpions, and bees, has antitumor properties by affecting various processes or char-

Table 3: Crude scorpion venoms against various cancer cell lines and their mechanisms of action

Scorpion species	Cell line	Cell death	Mechanism of action	Ref.
Androctonus crassicauda	HCT-8,HCT-116, MDA-MB-231, SH-SY5Y, MCF-7	Apoptosis	Arrest of cells in the S phase, increased production of iNOS, elevated expression of Caspase-3, and DNA fragmentation.	[76]
Androctonus amoreuxi	PC-3, MCF-7	Apoptosis	Suppression of Bcl-2 activity / Increased expression of C-3	[39]
Rhopalurus junceus	MDA-MB-468, A549,MDA-MB-231Hep-2,NCI-H292, HT-29, SiHa, U-937, K-562	Apoptosis, Necrosis	Elevated levels of p53, Bax, Caspase-3, 8, and 9, with a decrease in Bcl-2 in HeLa cells (favoring apoptosis over necrosis), while a decrease in p53 expression in A549 cells did not impact Bax levels but lowered Bcl-2 (favoring necrosis over apoptosis).	[77]
Buthus martensii Karsch	HeLa,MCF-7, SMMC-7721	Apoptosis	Enhances p21 activity, increases C-3 expression, inhibits Bcl-2, and causes cell arrest in the G1 and S phases.	[78]
H.liangi	KYSE-510	Apoptosis	Expression of C-3 and p21	[31]
H.bengalensis Koch	K-562, U-937	Apoptosis	Arrests cells in the Sub-G1 phase.	[35]
C.limpidus limpidus	HeLa	N/A	N/A	[78]
O.doriae	MCF-7, SH-SY5Y	N/A	Suppresses cell proliferation and DNA synthesis, induces mitochondrial depolarization, activates Caspase-3, and reduces antioxidant activities.	[76]

acteristics of tumor growth. Venom peptides are expected to hinder the development of adaptive resistance by selectively inhibiting targeted therapy, which may involve altering or restructuring cancer growth. While certain venom components have demonstrated potential in influencing the development of pancreatic cancer, additional preclinical and clinical investigations are necessary to establish the effectiveness and safety of these anticancer peptides. It is expected that the natural properties of these toxins can be used to generate therapeutic drugs with clinical applications, as well as diagnostic instruments for the evaluation of cancer.

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