

Review

Effects of Animal Venoms and Toxins on Hallmarks of Cancer

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Abstract

Animal venoms are a cocktail of proteins and peptides, targeting vital physiological processes. Venoms have evolved to assist in the capture and digestion of prey. Key venom components often include neurotoxins, myotoxins, cardiotoxins, hematoxins and catalytic enzymes. The pharmacological activities of venom components have been investigated as a source of potential therapeutic agents. Interestingly, a number of animal toxins display profound anticancer effects. These include toxins purified from snake, bee and scorpion venoms effecting cancer cell proliferation, migration, invasion, apoptotic activity and neovascularization. Indeed, the mechanism behind the anticancer effect of certain toxins is similar to that of agents currently used in chemotherapy. For example, Lebein is a snake venom disintegrin which generates anti-angiogenic effects by inhibiting vascular endothelial growth factors (VEGF). In this review article, we highlight the biological activities of animal toxins on the multiple steps of tumour formation or hallmarks of cancer. We also discuss recent progress in the discovery of lead compounds for anticancer drug development from venom components.

Key words: anticancer, apoptosis, animal venoms, cytotoxicity, Hallmarks of cancer.

Introduction

Humans have been using natural substances for their therapeutic properties since the beginning of civilization. Toxins from venomous animals are selective and potent to vital physiological processes in prey animals. As a result, venoms are a veritable mixture of biologically active components, including neurotoxins (i.e. toxins which target the transmission of nerve impulses), myotoxins (i.e. toxins which attack and break down muscle tissue), enzymes and substances which induce pain (e.g. ion channel toxins). Therefore, it is not surprising that research focussed on identifying lead compounds for the development of new therapeutics has long included a focus on animal venoms. Despite this intensive focus, successful transition of venom components to therapeutic agents has been only moderately successful. Examples of therapeutics developed from venoms include captopril (*Bothrops jararaca*), exenatide

(*Heloderma suspectum*) and ziconotide (*Conus magus*). Advanced cancer is a deadly aggressive disease and remains a significant cause of mortality worldwide [1]. Cancer cells are capable of growing (Figure 1) and metastasizing to other regions causing a number of devastating outcomes [2]. Certain snake and arthropod venoms have highly selective toxicity on a variety of cancer cells (Table 1) and have also been used as additional treatments in cancer therapy. For example, the administration of crotoxin (a neurotoxin isolated from *Crotalus durissus terrificus* venom) to advanced cancer patients was reported to minimize the consumption of analgesics indicating an analgesic effect of this neurotoxin [3]. Furthermore, sweet bee venom is applied in pharmacopuncture for patients with chemotherapy-induced peripheral neuropathy [4]. In fact, many venom components such as phospholipase A₂, L-amino acid oxidase, disintegrins,

• **Initiation**

Infectious agents & Carcinogen

❖ Alternate superoxide production

• **Promotion**

1. DNA damage, genome instability & mutation

❖ Alteration of gene expression

2. Modified cell structure & Metabolism alteration

❖ Increases the expression of pro-apoptotic protein
❖ Block ion(s) conductance
❖ Increase in Ca²⁺ influx

3. Angiogenesis

❖ Inhibition of angiogenesis

• **Progression**

1. Immune invasion

❖ Immunomodulation

2. Uncontrolled cell proliferation

❖ Decrease cell proliferation

3. Invasion & Metastasis

❖ Anti-invasive & Anti-adhesive effects
❖ Inhibition of cell metastasis



melittin, polybia-MPI and chlorotoxin have profound effects on cancer development. Therefore, the use of animal toxins with the capacity to exert anticancer effects through multiple mechanisms (Table 2) may be an alternative tool in clinical approaches. This review article examines recent progress in the search for lead compounds for anticancer drug development from the venoms of reptiles and/or arthropods and also shows that each venom component is capable of inhibiting the multiple steps involved in cancer progression or hallmarks of cancer by mechanisms involving cell proliferation, interruption in cell cycle or apoptosis and neovascularization (Figure 2).

Figure 1. Effects of animal venoms or toxins on the pathophysiology of cancer development. ❖ is indicated venom or toxin.

Table 1. Anticancer mechanisms of venom peptides from snake, bee, wasp and scorpion on several types of cancer cells.

Toxins/Venoms	Toxin name	Anticancer Mechanisms	Type of Cancer cells
svPLA ₂ s	CC-PLA2-1 & CC-PLA2-2 MVL-PLA2	Inhibition of cell adhesion and migration to fibrinogen and fibronectin Anti-angiogenic effects Increase microtubule dynamicity	Brain microvascular endothelial cells (HBMECs) [11] microvascular endothelial cells (HMEC-1) [13]
Cytotoxins or Cardiotoxins	CTX-I & CTX-II Cardiotoxin III	Apoptotic effect via lysosomal pathway Inhibition of the HGF-induced invasion and migration via HGF/c-Met-dependent PI3K/ Akt, ERK1/2 and NF-κB signalling pathway	Breast cancer cell (MCF-7) Hepatocellular carcinoma (HepG2) Prostate cancer (DU145) Human promyelocytic leukemia cell (HL-60) [18] Human breast cancer (MDA-MB-231) cells [19]
Metalloproteinases	Jararhagin	Inhibition of cancer cell proliferation Increase in apoptosis Increase in caspase-3	B16F10 murine melanoma cells [22]
svLAAOs	OH-LAAO Rusvinoxidase	Apoptosis by oxidative reaction of H ₂ O ₂ causing alteration of gene expression Apoptosis with DNA fragmentation via the activation of caspase-8 and caspase-7	Prostate adenocarcinoma (PC-3 cells) [29] MCF-7 [30]
Disintegrins	Obtustatin Rhodostomin	Specific binding to α1β1 integrin causing the inhibition of tumour cells adhesion and migration Anti-inflammatory effect by blocking the adhesion of activated neutrophils to fibrinogen and attenuating superoxide production	S-180 sarcoma [76] Neutrophils [45]
Bee venom	Lebein Melittin	Inhibition of VEGF-induced neovascularization Apoptosis via mitochondrial pathway Activation of L-type Ca ²⁺ channel Inhibition of inflammatory mediators involved in the MAPK signalling pathway	Human colon cancer cells [43] Human gastric cancer cell (SGC-7901) [77] Human MG63 osteosarcoma cells [50] Lewis lung cancer cell (VEGF-A-hm LLC) [53]
Wasp venom	Polybia-MPI	Pore formation	Prostate and bladder cancer cells [59]
Scorpion venom	Chlorotoxin Bengalin	Inhibition of Cl ⁻ conductance that reduces cancer progression Inhibition of cancer cells migration and invasion via binding activity to matrix metalloproteinase-2 (MMP-2) Activated caspase 9, caspase 3 and induced poly (ADP-ribose) polymerase (PARP) cleavage	Pancreatic cancer cells (PANC-1) [66] Human leukemic cells (U937) and chronic myelogenous leukemia (K562) [75]

Table 2. Comparison of the mechanism(s) behind the anticancer effect(s) of certain animal venoms and toxins.

Animals	Species	Name(s)/Venom components or product	Cellular mechanism(s)	Targeted Hallmarks of cancer
Bee	<i>Apis mellifera</i>	Melittin, pore-forming peptide	Blocks VEGFR2 and the cyclooxygenase-2 (COX-2) mediated MAPK (mitogen-activated protein kinase) signaling pathway [53]	Tumour-promoting inflammation
		bv-sPLA2	Blockade of epidermal growth factor (EGF)-induced signalling [78]	Sustaining proliferative signalling
		Apamin, neurotoxin	Inhibition of vascular smooth muscle cell proliferation and migration by the regulation of Cyclin Dependent Kinase (CDK) [56]	Avoiding immune destruction
		Propolis, Honey bee Product	Inhibits human telomerase [57]	Evading growth suppressors
Scorpion	<i>Heterometrus begalensis</i> <i>Leiurus quinquestriatus</i>	Bengalin	Activation of poly (ADP-ribose) polymerase (PARP) cleavage [75]	Genome instability & mutation
		Chlorotoxin	Binding activity to matrix metalloproteinase-2 (MMP-2) [66]	Resisting cell death
Snake	<i>Crotalus durissus terrificus</i>	Crotoxin, svPLA2	EGFR inhibitor [14]	Sustaining proliferative signalling
				Inducing angiogenesis
	<i>Macrovipera lebetina</i>	Lebein, Disintegrin	Inhibition of VEGF-induced neovascularization [43]	Deregulation cellular energetic
	<i>Naja naja atra</i>	Factor inhibiting glycolysis	Inhibition of glycolysis [79]	Activating invasion & metastasis
	<i>Naja naja atra</i>	Cardiotoxin III, Cytotoxin	Inhibition of the HGF-induced invasion and migration [19]	Evading growth suppressors
	<i>Trimeresurus stejnegeri</i> <i>Bungarus fasciatus</i>	TSV-DM, Metalloproteinase BF-CT, Cytotoxic protein	Inhibition cancer cell proliferation [23] Initiation of cell cycle arrest through cyclin D and CDK down regulation [80]	Evading growth suppressors

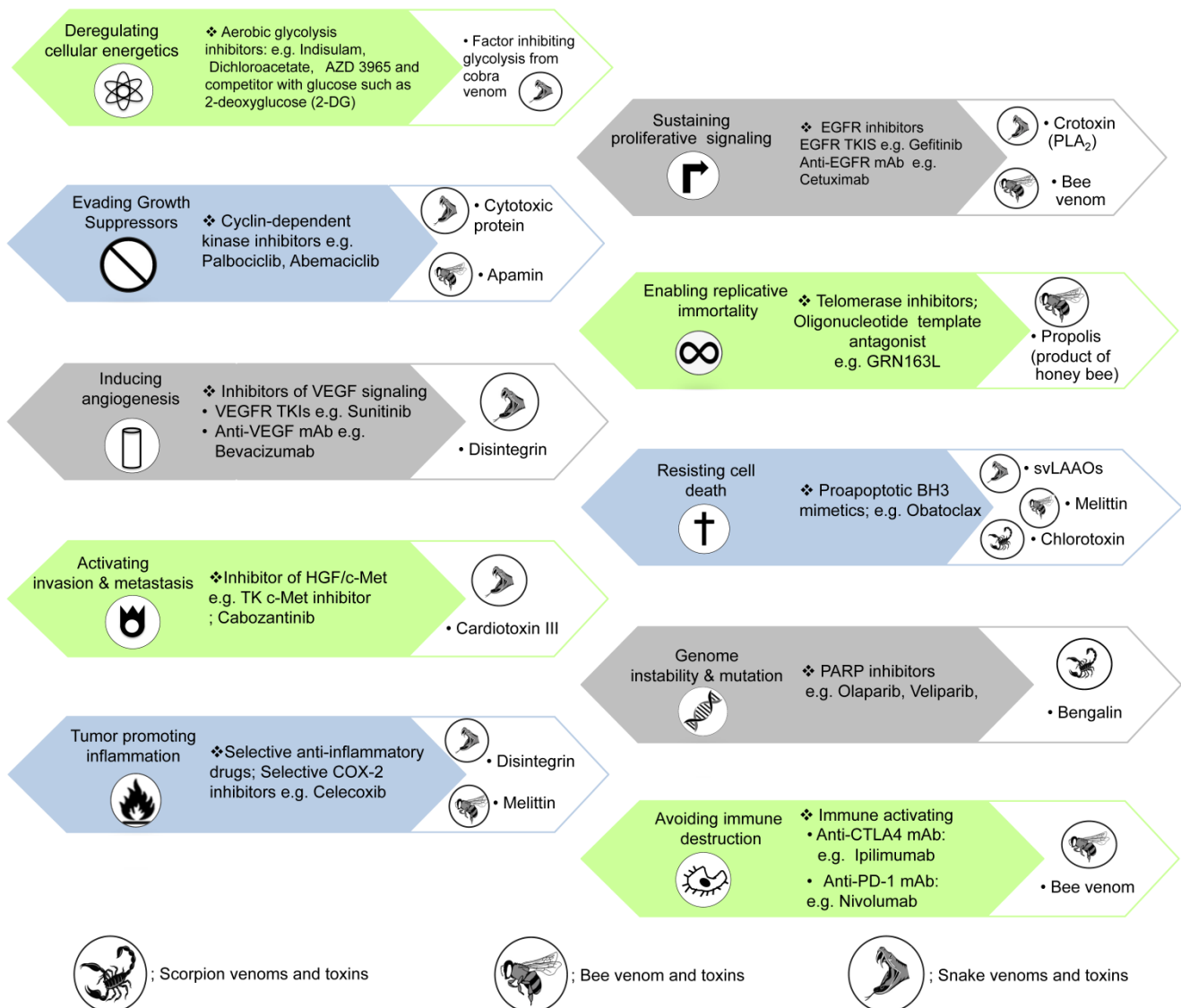


Figure 2. How currently available chemotherapeutic agents [2] and animal venoms/toxins act on the hallmarks of cancer.

Hallmarks of cancer

Hallmarks of cancer (Figure 2) are established to describe the biological capabilities acquired during the various steps involved in the development of cancers. The hallmarks of cancer originally included 1) sustaining proliferative signalling, 2) evading growth suppressors, 3) resisting cell death, 4) enabling replicative immortality, 5) inducing angiogenesis and 6) activating invasion and metastasis [5]. In 2011, two emerging hallmarks were proposed to be involved in cellular metabolism and avoiding immune destruction. Additionally, genome instability and mutation as well as inflammation that induces tumours were also labelled as enabling characteristics in the core and emerging hallmarks of cancer [2]. Currently, many studies and clinical trials have demonstrated agents that interrupt each of the biological capabilities necessary for tumour progression (Figure 2). Indeed, modern chemotherapy remains problematic due to a lack of cytotoxic specificity and decline in the patient quality of life from serious adverse effects, e.g. bone marrow suppression, mucositis and chemotherapy-induced peripheral neuropathy. Many animal venoms and toxins contain largely cytotoxic components affecting several kinds of tumour cells [6].

Venom Phospholipase A₂s (PLA₂s) and Cytotoxins

PLA₂ (EC 3.1.1.4) enzymes are the most common phospholipase found in animal venoms especially in snake and bee venoms. Snake venom PLA₂s (svPLA₂s) contribute to a number of pharmacological outcomes including neurotoxicity, myotoxicity, anticoagulation, vascular relaxation and hypotension [7-9]. The biological activities of PLA₂ may be produced either as a consequence of enzymatic activity of PLA₂ or as a consequence of direct interaction of the PLA₂ enzyme with its ligand without any catalytic activation [10]. The hydrolytic activity of the PLA₂ enzyme at the phospholipid membrane induces the release of lysophospholipids (LysoPL) and fatty acids (FAs) resulting in the pharmacological effects within cells such as membrane damage, disruption of membrane-bound protein and functional disturbances of the cellular cascade [10]. These mechanisms can exert antitumour effects. Previous studies have shown that purified svPLA₂s contain antitumour and anti-angiogenic properties [6]. CC-PLA₂-1 and CC-PLA₂-2, two secreted PLA₂s purified from *Cerastes cerastes* venom, caused dose-dependent inhibition of human brain microvascular endothelial cell adhesion and

migration [11]. 'MVL-PLA₂', an acidic Asp49 PLA₂ from *Macrovipera lebetina* venom exhibited anti-integrin activity by the inhibition of adhesion and migration of human tumour and microvascular endothelial cells [12, 13]. Crotoxin was reported to display anti-proliferative activity through the regulation of epidermal growth factor receptor (EGFR) on the squamous carcinoma cells [14]. Abolition of enzymatic activity by 4-BPB (p-bromophenacyl-bromide) failed to attenuate the antitumour effects, indicating the antitumour effect is independent of the catalytic property of venom PLA₂ [12, 15]. Many studies have shown that the enzymatic activity of venom PLA₂ is not responsible for the cytotoxic and myotoxic activities, and other mechanisms such as interaction with a specific receptor may be involved [10]. The antitumour effects of an acidic PLA₂ from the venom of *Bothrops jararacussu*, BthA-I-PLA₂, was thought to induce apoptosis in breast adenocarcinoma, human leukemia T and Erlich ascetic tumour cell lines [16]. Additionally, cytotoxins or cardiotoxins from elapid venoms also induce membrane damage and necrotic cell death. These effects are mediated via the direct interaction of these toxins with cell membrane phospholipids resulting in membrane pore formation [17]. Two cobra venom cytotoxins, CTX-I and CTX-II, possess significant anticancer activity mediated via a lysosomal pathway and entry of cathepsin to cytosol with a minimum effect on normal cells [18]. Moreover, cardiotoxin III, isolated from *Naja naja atra* venom also shows anti-invasive and antimetastatic activities via the suppression of hepatocyte growth factor (HGF) induced c-Met phosphorylation in human breast cancer cells [19].

Snake Venom Metalloproteinases (SVMPs)

Metalloproteinases are major components in venoms of snakes of the families Crotilidae and Viperidae [20]. SVMPs cause coagulation factor activation, inhibition of platelet aggregation as well as hemorrhagic and fibrinolytic activities [20]. Anticancer activities of SVMPs involve pro-inflammatory effect and apoptotic activity. A purified SVMP from *Bothrops jararaca*, Jararhagin, interrupted cancer cell adhesion and exhibited a potent cytotoxic effect on melanoma cells [21] via an increase in caspase-3 and anti-proliferative activities [22]. A metalloproteinase from *Trimeresurus stejnegeri* venom, TSV-DM, inhibited cancer cell proliferation and induced morphological changes on ECV304 cells [23].

Snake Venom L-Amino Acid Oxidases (svLAAOs)

LAAOs are flavoenzymes found in several organisms. These enzymes catalytically deaminate L-amino acid to the corresponding α -keto acid with the concomitant release of ammonia (NH_3) and hydrogen peroxide (H_2O_2) [24]. Snakes of families Viperidae, Crotalidae and Elapidae contain 1-9% LAAOs in their venoms [25]. Most svLAAOs contribute to a number of pharmacologic effects including platelet aggregation, antimicrobial activity, edema, hemolytic or hemorrhage effects, cytotoxicity and apoptosis [25, 26]. Previous research has postulated that LAAOs initiate cell death or apoptotic activity by oxidative reaction of H_2O_2 causing alteration of gene expression [27]. Accumulated oxidative stress from H_2O_2 in the cell surface then triggers apoptosis, which can be abolished by antioxidants, catalase or specific H_2O_2 scavengers [25, 28] resulting in the inhibition of svLAAO-induced apoptosis. Mechanisms behind svLAAO-induced apoptosis of cancer cells may involve the inhibition of metastasis in the host cells by preventing platelet aggregation and activation of phagocytic cells including the interruption of tumour cell adhesion [6, 81]. 'OH-LAAO', a purified L-amino acid oxidase from king cobra (*Ophiophagus hannah*) venom displays a specific antitumour activity on human breast adenocarcinoma cell lines by inducing cell apoptosis via both intrinsic and extrinsic pathways, which can be indicated by the enhancement of caspase-8 and -9 activities. OH-LAAO also induced the alteration of gene expression in 178 genes for which at least 27 genes may be involved in the cytotoxic and apoptotic effects [27]. The immunohistochemical staining on the PC-3 tumour xenograft section showed a marked increase of apoptotic cells among OH-LAAO-treated nude mice [29]. Rusvinoxidase, a novel LAAO isolated from the venom of *Daboia russelii russelii*, also caused changes in cell morphology, membrane integrity, shrinkage of cells and apoptosis with DNA fragmentation on human breast cancer (MCF-7) cells through the activation of caspase-8 that subsequently activated caspase-7 [30].

Disintegrins from snake venoms

Integrins are heterodimeric transmembrane proteins associated by non-covalent bond of α - and β -subunits (e.g. $\alpha\text{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha\nu\beta_5$). Integrins play many important roles to promote major mechanisms of tumour development including cell-extracellular matrix interaction, cytoskeleton organization, signalling transduction, epithelial cell adhesion, growth, proliferation, invasion and

migration [31]. Disintegrins (MW 5-10 kDa) are a family of nontoxic and non-enzymatic RGD-containing peptides (Arg-Gly-Asp sequence) in the venoms of vipers, crotalids, elapids, and colubrids [32]. Peptides containing the RGD domain (disintegrins and metalloproteinases) were proven to have antitumour effects involving angiogenesis and cancer metastatic dissemination both *in vitro* and *in vivo* [33]. A number of purified disintegrins have been demonstrated to have potential interaction with integrins and to abolish cancer development [34]. Mechanisms behind antitumour activity of disintegrin include inhibition of cell adhesion, attenuation of cancer cell migration, invasion and antimetastatic activity [34, 35]. Jerdostatin, a purified disintegrin from *Protobothrops jerdonii* venom [36], and obtustatin, a disintegrin from *Vipera lebetina obtuse*, were found to bind to $\alpha_1\beta_1$ causing blockages of adhesion and cell migration in *in vitro* studies including inhibition of angiogenesis in the *in vivo* experiments [34, 37]. Contortrostatin is a disintegrin from *Agkistrodon contortrix contortrix* was reported to display a potential binding activity on many types of integrins, e.g. $\alpha\nu\beta_3$, $\alpha_5\beta_1$, $\alpha\text{IIb}\beta_3$ and $\alpha\nu\beta_5$ [34] causing the interruption of tumour growth *in vitro* and blockage of metastasis and neovascularization *in vivo* [38, 39]. In addition, recombinant contortrostatin initiated and displayed antitumour and antiangiogenic activities on a breast carcinoma model following administration by liposomal encapsulation [40]. The purified disintegrin from a Korean snake (*Agkistrodon halys brevicaudus*) venom, 'salmosin', inhibited cell proliferation and also induced cell cycle arrest resulting in active apoptosis [41]. A previous animal study showed that salmosin was able to inhibit tumour-induced angiogenesis without toxic activity on normal function of pre-existing blood vessels [42]. Lebein, a heterodimeric disintegrin isolated from *Macrovipera lebetina* venom was recently reported to have anti-angiogenic activity through the inhibition of Vascular Endothelial Growth Factor (VEGF)-induced neovascularization [43]. Major limitations in translating the possible use of disintegrins into the clinic are their instability and limited bioavailability. However, administration of salmosin by integrating the salmosin gene complex into cationic liposomes has produced promising results [44]. This approach has not only shown that salmosin can exert antiangiogenic activity but also demonstrates the feasibility of this approach in other anticancer gene therapies [44]. Furthermore, anti-inflammatory effects are likely to be important mechanisms behind the anticancer effects of disintegrin. This effect has been investigated where purified disintegrin, 'rhodostomin', from the venom of *Calloselasma*

rhodostoma displayed anti-inflammatory effects by blocking the adhesion of activated neutrophils to fibrinogen and decreasing superoxide production [45].

Bee and wasp venoms

Phospholipases, hyaluronidases and mastoparans are found in bee and wasp venoms [46]. Bee venom induces membrane lysis and inhibits tumour cell proliferation, and also promotes cancer cell apoptosis by an increase in reactive oxygen species (ROS) and a rise in intracellular Ca^{2+} . Previous studies showed that bee venom also evoked the attenuation of mitochondrial membrane potential, which activates the release of cytochrome C and caspase-3, resulting in DNA fragmentation [47, 48]. Moreover, bee venom secretory PLA_2 (bv-s PLA_2) and phosphatidylinositol-(3,4)-bisphosphate synergistically inhibited cell proliferation by a mechanism involving the maturation of immunostimulatory human monocyte-derived dendritic cells [49]. Melittin, a pore-forming peptide from *Apis mellifera* (Western honey bee) venom exerts neoplastic activity on many types of cancer cell lines. In human osteosarcoma cells, melittin ($> 0.075 \mu\text{M}$) induced apoptosis by activating the L-type Ca^{2+} channel leading to an increase in intracellular Ca^{2+} which was fully abolished by pre-treatment with a Ca^{2+} chelating agent, BAPTA (1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetra-acetic acid) [50]. Anti-proliferative effects of melittin proportionally involve the inhibition of calmodulin binding activity, which appears to be a major intracellular target [51]. Many *in vivo* studies have demonstrated that administration of melittin is capable of minimizing tumour size suggesting the presence of antitumour activity in this peptide [52, 53]. Melittin significantly inhibited tumour cell metastasis and tumour cell growth in nude mice by reducing cell motility and migration by the suppression of the Rac1-dependent pathway [54]. These data suggest that bee venom and melittin could be of potential use in cancer treatment. However, reports have indicated that administration of melittin in high doses may cause hepatic injury and haemolysis [51]. Recently, vascular endothelial growth factor-melittin fusion protein (VEGF165-melittin fusion protein) displayed inhibitory effects on the development of human hepatocellular carcinoma cell lines and inhibited tumour growth *in vivo* [55]. In addition, apamin, a neurotoxin from bee venom inhibited vascular smooth muscle cell proliferation and migration by the regulation of Cyclin Dependent Kinase (CDK) [56]. Besides melittin, apamin and bee venom, 'propolis', a product of honey bees also produces inhibitory effects

on human telomerase leading to failed leukemic cell growth [57]. Furthermore, the venom of the Brazilian wasp (*Polybia paulista*) displayed cytotoxic, genotoxic and mutagenic activities on human cancer cells [58]. These activities replicate the effect of phospholipases, mastoparan and hyaluronidase on cell membrane function and permeability causing the interaction between DNA and other toxic compounds [58]. An antimicrobial agent purified from Brazilian wasp venom, 'polybia-MPI' or MPI including its modified analogue 'MRI-1', significantly inhibited tumour growth *in vitro* and *in vivo* via pore formation [59, 60].

Scorpion venoms including purified or synthetic toxins from scorpion venoms

Envenoming by scorpions causes a broad range of symptoms, from local pain to deadly symptoms [61]. However, the scorpion's body parts and venoms have been used as traditional medicine for many diseases. Scorpion venoms contain mucopolysaccharides, free amino acids, phospholipases, hyaluronidases, amines and nucleotides [61]. The non-disulfide-bridged scorpion venom peptide has become a crucial substance to initiate pharmacologic activities including antibacterial, antifungal, antimalarial, antiviral and anticancer activities [62, 63]. Scorpion venom and toxins exhibit antitumour activities both in cell lines and animal models [46]. Specific interaction with ion channels seems to be the major mechanism behind anticancer effects of scorpion toxins. Chlorotoxin (CITx), from the venom of *Leiurus quinquestriatus*, and its synthetic compound, 'TM601', inhibited cancer progression by the attenuation of Cl^- conductance and angiogenesis [61]. CITx blocked migration of glioma cells [64] and inhibited aggressive metastatic breast cancer cells [65]. In pancreatic cancer cells (PANC-1), CITx inhibited cell migration and invasion by binding activity to the matrix metalloproteinase-2 (MMP-2) [66]. Additionally, CITx promoted efficacy and increased bioavailability of certain clinical chemotherapies, e.g., doxorubicin [67] and cisplatin [68]. Moreover, gene encoded peptides such as Bm-12 [69] and Gst-BmKCT [70] also reduced Cl^- conductance and metastasis of glioma cells in both *in vitro* and *in vivo* studies. The potassium channel blocking peptide Margatoxin (MgTx), from the venom of *Centruroides margaritatus* blocked human lung adenocarcinoma cell proliferation and decreased tumour volume in mice [71]. The calcium-activated potassium channel (BKca-channel) blockers, 'Iberitoxin' (IbTx) and 'Charybdotoxin' (ChTx) were also reported to inhibit the proliferation and migration of glioma [72] and melanoma cells [73], respectively. Furthermore, anticancer effects of

Heterometrus bengalensis venom and its purified substance 'Bengalin' were reported to decrease cancer cell proliferation and enhance apoptosis in leukemic cell lines [74] by the activation of caspase-9, caspase-3 and induced poly (ADP-ribose) polymerase (PARP) cleavage [75].

Conclusion

The clinical use of many chemotherapeutic agents can induce a number of significant adverse effects leading to unsatisfactory clinical outcomes. In addition, it has been reported that application of specifically targeted cancer therapy may promote cancer development by residual functional capabilities and lead to the adaptation or resistance of tumour cells to chemotherapy. As a result of these, anticancer agents from natural resources appear to be promising tools for cancer therapy. This review demonstrates that animal venom peptides and certain animal products exert antitumour effects by interfering with multiple processes or hallmarks of tumour development. Venom peptides, especially svLAAOs, disintegrins or melittin are anticipated to prevent adaptive resistance caused by specific inhibition of targeted therapy, potentially involving mutation or remodelling of cancer growth. Although a number of venom components have been shown to have a promising effect on tumour development, further pre-clinical and clinical studies are required to prove the efficacy and safety of these anticancer peptides. We envisage that the natural potential of these toxins can be exploited to produce clinically useful agents, as well as diagnostic tools for cancer assessment.

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Competing Interests

The authors have declared that no competing interest exists.

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