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## **Medicinal value of animal venom for treatment of Cancer in Humans - A Review**

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### **ABSTRACT**

Since cancer is one of the leading causes death worldwide and there is an urgent need to find better treatment. In recent years remarkable progress has been made towards the understanding of proposed hallmarks of cancer development and treatment. Anticancer drug developments from natural resources are ventured throughout the world. Venoms of several animal species including snake, scorpion, frog, spider etc. and their active components in the form of peptides, enzymes etc. have shown promising therapeutic potential against cancer. In the present review, the anticancer potential of venoms as well as their biochemical derivatives from some vertebrates like snake or frog or some venomous arthropods like scorpion, honey bee, wasps, beetles, caterpillars, ants, centipedes and spiders has been discussed. Some of these molecules are in the clinical trials and may find their way towards anticancer drug development in the near future. The recognition that cancer is fundamentally a genetic disease has opened enormous opportunities for preventing and treating the disease and most of the molecular biological based treatment are cost effective. The search for alternative economical and natural sources for cancer medicines is of utmost need for the future in combating this dreadful disease that is spreading at fast rate in the present era.

**Keywords:** Cancer, animal venom, anticancer drug, medicinal value

## **1. INTRODUCTION**

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

Since cancer is the leading cause of death worldwide, there is an urgent need of finding a better way to treat it. Various therapies have been used for treating cancer such as chemotherapy, radiotherapy, immunotherapy and gene therapy (Baskar *et al.*, 2012). Out of the therapies being used for treatment, chemotherapy remains the predominant option. One of the main obstacles in chemotherapy is that patients eventually get resistant after some time (Lai *et al.*, 2012). Radiotherapy/radiation therapy being an important part of cancer treatment, contributes to almost 40% of curative/ successful treatment for cancer. Its main aim is to decline the multiplication potential of cancer cells (Baskar *et al.*, 2012). But challenge in using radiotherapy for cancer treatment is to increase/maximize effect of radiation doses on cancer cells, while minimizing its effect on surrounding normal cells. Since there are several cases documenting either acute or late radiation toxicity, therefore, it limits the usage of radiation therapy (Barnett *et al.*, 2009).

Immunotherapy for cancer treatment has become a more promising approach in the past decades (Kruger *et al.*, 2007). It is used in the early stage of the tumor development (Geissler and Weth, 2002). Immune targets don't play a significant role in the life or death of the cancer cells since they serve only to direct immune effectors to the tumor cells (Orentas *et al.*, 2012). It mainly focuses on empowering the immune system to overcome the tumor rather than producing widespread cytotoxicity to kill tumor cells.

Surgery, chemotherapy and radiotherapy provide inadequate effect or affect normal cells along with the diseased one. It leads to search for cancer cure from natural products. Anticancer drug developments from natural biological resources are ventured throughout the world. The biodiversity of venoms or toxins made it a unique tool from which new therapeutic agents may be developed. Several animal venoms have been shown to possess a wide spectrum of biological activities which are also effective against cancerous cells.

## **2. SNAKE VENOM**

Venom is nothing but a secretion of venomous animals, which are synthesized in a specific part of their body, called venom gland. It is modified saliva containing a mixture of different bioactive proteins and polypeptides used by an animal for defence or to immobilize its prey (Gomes *et al.*, 2010). Venoms are sub-divided into cytotoxins, cardiotoxins, neurotoxins, and hemotoxins (Ferrer, 2001).

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

Toxins that cause destruction of RBCs are collectively known as Hemotoxins. It targets the circulatory system and muscle tissue of the host causing scarring, gangrene. Cardiotoxins are those compounds which are toxic specifically to heart. It binds to particular sites on muscle cells of the heart preventing muscle contraction (Yang *et al.*, 2005).

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

## 2. 1. Anticancer activity of snake venom

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

Venoms from two viperidae species (*Bothrops jararaca* and *Crotalus durissus terrificus*) acted directly on tumor cells. Their antitumor activity may be due to the indirect phenomenon of inflammatory responses mediated by IL-2, IL-8, TNF- $\alpha$  (Silva *et al.*, 1996).

The anticarcinogenic activities of Indian monocellate cobra and Russell's viper venom were studied in carcinoma, sarcoma and leukemia models. Under *in vivo* experiments it was found that the sublethal doses of the Indian Elapidae (monocellate cobra) and viperidae (Russell's viper) venom caused cytotoxicity on EAC cells; it increased the life span of EAC cell containing mice and reinforced its antioxidant system. (Debnath *et al.*, 2007).

Cardiotoxin-3 (CTX-3), a basic polypeptide of 60 amino acid residue present in *Naja naja atra* venom has been reported to possess anti cancer property. It induces apoptotic cell death accompanied by upregulation of both Bax and endonuclease G, and down regulation of Bcl-x in K562 cells which was confirmed by DNA fragmentation (Yang *et al.*, 2006).

drCT-1 is a heat stable, 7.2 kDa protein toxin isolated from Indian Russell's viper (*Daboia russelli russelli*) venom and is supposed to possess anti-proliferative, cytotoxic, and apoptotic property. Another protein toxin isolated from Indian Russell's viper (*Daboia russelli russelli*) venom drCT-2 which also possessed antineoplastic activity (Gomes *et al.*, 2007). Disintegrins also possess the ability to inhibit tumor behaviour both *in vitro* and *in vivo*. RGD (Arg-Gly-Asp) containing disintegrins are non-enzymatic proteins that inhibit

cell-cell interactions, cell-matrix interactions, and signal transduction. Salmosin, a disintegrin isolated from Korean snake venom, effectively suppressed growth of metastatic tumor as well as solid tumor in mice (Kang et al., 1999).

The lipolytic enzymes, phospholipase, with anticancer potentials present in cobra venom hydrolyse the fatty acyl ester at the sn-2 position of membrane phospholipids (Braganca and Khandeparker, 1966). Phospholipase B in the venom of the Australian elapid snake was cytotoxic to cultured rhabdomyosarcoma cells (Bernheimer, 1987). Phospholipase A2 (PLA2), isolated from *Bothrops newweidii* venom produced cytotoxic activity on B16 F10 melanoma cells (Daniele et al., 1997).

Contortrostatin (CN) is a homodimeric disintegrin found in southern copperhead snake venom. Its anticancer effect was studied on OVCAR-5 (human epithelial carcinoma cell line of ovary) cells. CN effectively blocks the adhesion of OVCAR-5 cells to several extracellular matrix proteins and inhibits tumor cell invasion through an artificial basement membrane (Markland et al., 2001).

LAAOs (L-amino acid oxidase) are dimeric flavoprotein that contains a non-covalently bound FAD as a co-factor (Pawelek et al., 2000). LAAOs isolated from *Ophiophagus hannah* venom decreases thymidine uptake in murine melanoma, fibrosarcoma, colorectal cancer and Chinese hamster ovary cell line that also showed reduction in cellular proliferation (Cura et al., 2002). Also, LAAO isolated from *Agkistrodon acutus* snake venom showed accumulation of tumor cell at sub-G1 phase of cell cycle. Crotoxin is a cytotoxic PLA2 compound isolated from a South American snake, *Crotalus durissus terrificus* venom (Faure et al., 1993). Crotoxin displays cytotoxic activity against a variety of murine and human tumor cell line in vitro (Rudd et al., 1994). According to recent study, snake venom extracted from *Walterinnesia aegyptia* (WEV), alone or in combination with silica nano-particles can decrease the proliferation of human breast carcinoma cell line (MDAMB-231). In this study, decreased expression of Bcl-2 and enhanced activation of caspase-3 has been found when breast cancer cell line was treated with WEV along with nano-particle and also showed significant reduction in actin polymerization and cytoskeletal rearrangement but it was not the case with non-cancer cell line (Al-Sadoon et al., 2012).

### **3. SCORPION VENOM**

Scorpion venoms are a complex mixture of a large variety of molecules and they play an important role in defence and prey capture. In contrast to spider and snake venom, scorpion venom usually displays low levels of enzymatic activity (Gwee et al., 2002). They contain mucopolysaccharides, phospholipases, hyaluronidases, low molecular weight molecules such as serotonin, histamine, histamine releasing peptides, inorganic salts, mucus, and many basic small proteins called neurotoxins (Muller, 1993). The latter have specific interaction with ion channels, making scorpion venom capable of binding specifically to certain types of cells; such as cancer cells. Therefore this is a type of venom holds molecules that are of interest to the pharmaceutical industry in terms of drug design and development.

#### **3. 1. Scorpion venom in cancer therapy**

Around 250 bioactive proteins and peptides have been characterized from approximately 1500 scorpion species, besides those that have already shown great anti-tumor

activity and are under research (Possani *et al.* 2000). The most studied peptides are the long chain toxins composed of 60-70 amino acid residues cross-linked by disulfide bridges. These peptides activate mainly Na<sup>+</sup> channels (Goudet *et al.*, 2002). Short chain toxins with 30-40 amino acids residue cross linked by three disulfide bridges form another polypeptide family, acting mainly upon K<sup>+</sup> or Cl<sup>-</sup> channels; ion channels are fundamental for cellular activities and scorpion venom proteins act upon these channels are extremely important in the defense against predators and in prey capture (Goudet *et al.*, 2002).

One of the most active principles found in scorpion venom is Chlorotoxin (Cltx), a peptide isolated from the species *Leiurus quinquestriatus*; Cltx 36 amino acids with four disulfide bonds, and inhibits chloride influx in the membrane of glioma cells (Soroceanu *et al.*, 1999). This peptides bind only to glioma cells, displaying little or no activity at all in normal cells. The toxin appears to bind matrix metalloproteinaseII (MMP-2) (Deshane *et al.*, 2003; Veiseh *et al.*, 2007), an extracellular matrix enzyme that inhibits gelatinase activity. MMP-2, a proteinase involved in tumor invasion, is especially up-regulated in gliomas and related cancers, but is not expressed in normal brain cells (Deshane *et al.* 2003). Cltx binds effectively to MMP-2 endogenously expressed by glioma cells (Deshane *et al.*, 2003; Veiseh *et al.*, 2007), and exposure results in loss of gelatinase activity, disruption in chloride channels currents, reduction in both MMP-2 and chloride channel expression and internalization of chloride channels (Deshane *et al.*, 2003; Veiseh *et al.*, 2007; McFerrin and Sontheimer, 2006; Soroceanu *et al.*, 1998).

A serine proteinase-like protein named BMK-CBP, isolated from the venom of Chinese red scorpion (*Buthus martensii* Karsch) bind with the cancer cell line MCF-7 and the cell binding ability was dose dependent (Gao *et al.*, 2008).

A homogenous Hyaluronidase, (a virulent factor of beta-hemolytic streptococci), named BmHYA1, was purified from Chinese red scorpion (*Buthus martensii*) which could hydrolyse hyaluronic acid into relatively smaller oligosaccharides and modulated the expression of CD44, cell surface markers in breast cancer cell lines MDA-MB 231 (Feng *et al.*, 2008).

Charybdotoxin (CTX), a 37 amino acid neurotoxin from the venom of the scorpion *Leiurus quinquestriatus* hebraeus, induced blockage through Ca<sup>2+</sup> activated K<sup>+</sup> channels, caused a slight depolarization in human breast cancer cells and thereby arrested the cells in the early G1, late G1, and S phases and accumulated cells in the S phases (Ouadid-Ahidouch *et al.*, 2004).

Bengalin, a high molecular weight protein isolated from Indian Black scorpion (*Heterometrus bengalensis*) venom showed anticancer activity on U937 and K562 cells. Bengalin elicited loss of mitochondrial membrane potential (MMP) which commenced cytochrome c release in the cytosol, decreased heat shock protein (HSP) 70 and 90 expression. This showed that Bengalin might provide putative molecular mechanism for their anticancer effect on human leukemic cells which might be mediated by mitochondrial death cascade (Gupta *et al.*, 2008).

#### 4. HONEY BEE VENOM

Bee venom contains a variety of peptides, including melittin, apamin, adolapin, the mast-cell-degranulating peptide, enzymes (phospholipase A2) biologically active amines (i.e. histamine, epinephrine), and a non peptide components with pharmaceutical properties.

#### 4. 1. Anticancer agents in bee venom

Bee venom has been widely used in the treatment of tumors. Several cancer cells, including renal, lung, liver, prostate, mammary gland as well as leukemia cells can be targets of bee venom peptides such as melittin and phospholipase A2.

In recent study scientists reported that bee venom can induce apoptosis in cancer cells (in human leukemic U937 cells), the key regulators in bee venom induced apoptosis are Bcl-2 and caspase-3 through downregulation of the ERK and Akt signal pathway (Moon *et al.*, 2006).

Melittin, a water soluble toxic peptide derived from bee venom of *Apis mellifera* was reported to have inhibitory effects on hepatocellular carcinoma. Melittin inhibits tumor cell metastasis by reducing motility and migration via the suppression of Rac-1 dependent pathway, suggesting that melittin is a potent therapeutic agent for hepatocellular carcinoma (Liu *et al.*, 2008). Melittin prevents liver cancer cells metastasis through inhibition of the Rac-1-dependent pathway.

The main target of non-steroidal anti-inflammatory drugs action is Cyclooxygenase (COX). COX-2 has been implicated in mammary carcinogenesis. The bee venom can inhibit COX-2 expression and block pro-inflammatory cytokines (TNF-alpha, IL-1 beta) production, thus prevent breast cancer (Nam *et al.*, 2003). Inhibition of COX-2 activity and proinflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) production by water soluble sub-fractionated parts from bee (*Apis mellifera*) venom.

#### 5. BEETLE VENOM

Many of the Blister beetles (Coleoptera :Meloidae) produce toxic defensive secretions which upon contact with the skin cause blistering. One such toxin is cantharidin which has been extracted from *Mylabris caraganae*, the dried bodies of which have been used in Chinese Folk Medicine since the 13<sup>th</sup> century for the removal of warts (Galvis *et al.*, 2013) and forever 2000 years for the treatment of cancer.

##### 5. 1. Beetle venom in cancer treatment

Cantharidin is a monoterpene derived from the bodies of several types of blister beetle, including *Mylabris phalerata* and *M. cichorii* (Chinese blister beetles) and this compound is stored in the beetle hemolymph and making up about 5% of body dry weight (Galvis *et al.*, 2013). Cantharidin has been found to inhibit the growth of human leukemic cells *in vitro* (Rauh *et al.*, 2007).

In contrast to other chemotherapeutic agents, cantharidin acts as leukemia progenitor and stem cells (Dorn *et al.*, 2009).

Several derivatives of cantharidin also retard the growth of prostate, oral, colon, cervical, gall bladder cancer cell lines (Efferth *et al.*, 2005; Liu and Chen, 2009; Fan *et al.*, 2007; Fan *et al.*, 2004; Wang *et al.*, 2000; Peng *et al.*, 2002; Chen *et al.*, 2005; Kok *et al.*, 2005; Hill, Stewart *et al.*, 2007; Hill, *et al.*, 2007).

Research has also shown that cantharidin is an inhibitor of phosphoprotein phosphatase 1 and 2A which results in DNA damage and apoptosis (Li *et al.*, 2010). Cantharidin, a potent and selective PP2A inhibitor, induces an oxidative stress-independent growth inhibition of

pancreatic cancer cells through G2/M cell cycle arrest and apoptosis. These enzymes are involved in regulation of metabolism and the initiation of signal transduction in cells resulting in cell division. Thus cantharidin may represent a small molecule able to switch cancer cells division and carcinogenesis off/on as well as to probe the key regulatory role of PPA2 in cell metabolism (Galvis *et al.*, 2013).

Huang *et al.*, 2007 (Huang *et al.*, 2007) showed that growth inhibition and killing of human colorectal cancer cells by cantharidin was both time- and dose-dependent. The cantharidin exposure reduced CDK1 kinase activity which led to failure of the cells to progress from G2 to M phases in the cell cycle. In addition, the colorectal cells were killed by apoptosis which was induced through the mitochondrial and death receptor pathways and activation of caspases 8, 9 and 3.

Recently, a number of papers have been published showing that cantharidin, apart from inhibiting PP1 and PP2A, has multiple effects on cancer cells. Another study by Huang *et al.*, 2013 (Huang *et al.*, 2013) on metastasis of human bladder carcinoma cells, showed that exposure to cantharidin blocked the gene expression, protein levels, and activities of the matrix metalloproteinase -2 (MMP-2) and/or MMP-9. These enzymes are associated with invasive properties of many cancers so that cantharidin had an antimetastatic effect possibly by targeting the p38 and JNK1/2 MAPKs pathway of the bladder cancer cells.

Other effects of cantharidin have been studied in human breast cancer cells by Shou *et al.*, 2013 (Shou *et al.*, 2013). They reported that cantharidin resulted in apoptosis and reduced growth, adhesion and migration of the cancer cells. The reduced adhesion resulted from repression of cell adhesion to platelets through down regulation of the  $\alpha 2$  integrin adhesion molecule on the surface of the cancer cells. The repression of the  $\alpha 2$  integrin occurred through the protein kinase C pathway probably due to PP2A inhibition.

Finally, most important for therapeutic use of cantharidin, Dang and Zhu, 2013 (Dang and Zhu, 2013) have tackled the problems of toxicity, insolubility and short half-life in circulation of this drug by designing cantharidin solid lipid nano particles as drug carriers which can be given orally.

One analogue, norcantharidine, also reduced the production of molecules that promote tumor cell adhesion and metastasis. It is believed to suppress protein phosphatase, increase oxidative stress within cancer cells, down regulate the gene STAT3 and activate the Bax genes that induce cell apoptosis by up-regulating the MAPK/ERK and p53 pathway genes (Sagawa *et al.*, 2008).

Cantharidin stopped the production of P-gp, a membrane transport protein that creates chemotherapeutic drug resistance in a hepatoma cell lines (Zheng *et al.*, 2008).

## **6. WASP VENOM**

Scientists from the institute for Biomedical Research (IRB Barcelona) have carried out successful in vitro tests using wasp venom to kill cancer cells. The peptide from wasp venom has the ability to form pores in the cell plasma membrane, penetrate into the cell and finally, cause its death either by necrosis or by triggering apoptosis. However, this powerful natural weapon can not only damage tumor cells but also affect healthy cells. As such, the researchers designed a means of transporting the peptide to the tumor and making it accumulate in a specific and controlled manner. The system consists of a decorated carrier polymer with two

components: a peptide that is bound to a tumor cell receptor and the cytotoxic peptide of the wasp venom.

In vitro experiments show that the substance is adequately distributed within the tumor cells and causes their death, while healthy cells, such as red blood cells, are not affected (Moreno *et al.*, 2014).

### 6. 1. Anticancer agents in wasp venom

Wasp venom contains Polybia MPI (from venom of the social wasp *Polybia paulista*) which shows anti tumor activity (Wang *et al.*, 2008b). Polybia MPI is able to target non polar lipid cell membrane, forming ion permeable channels, leading to depolarization, irreversible cytolysis and finally cell death (Matsuzaki *et al.*, 1997). It has been shown that Polybia MPI can significantly inhibit the proliferation of tumor cells and associated endothelial cells by membrane disrupting.

Fujiwara *et al.*, 2008 (Fujiwara *et al.*, 2008) isolated and determined the structure of anti cancer molecule from the outer envelope of the social wasp *Vespa simillima*. A biologically active quinone, 7,8-seco-para-ferruginone exhibited a growth inhibitory effect on rat liver cancer cells. The authors suggest that the cytotoxic activity is related to the morphological changes that induce apoptosis of the cells exposed to this molecule.

NVP(1), a 6.6 kDa protein isolated from the venom of *Nidus vespae*, inhibited proliferation of HepG2 hepatoma cells in the concentration of 6.6µg/ml. in addition NVP(1) promoted apoptosis of HepG2 cells as indicated by nuclear chromatin condensation. This protein could arrest cell cycle at G1 stage and inhibit the mRNA expression of cyclinB, cycline E, cyclin D1. NVP(1) increased p27 and p21 protein expression but suppressed cdk2 protein expression. The extra-cellular-signal-regulated-kinase (ERK) was activated, indicating that NVP(1) inhibits proliferation HepG2 through ERK signalling pathway, through activation of p27 and p21 and reduction of cdk2expression (Wang *et al.*, 2008).

## 7. ANTS AND CENTIPEDE VENOM

Ants and centipedes are well known for producing very potent toxins. Using the SVR (a transformed endothelial cell line) angiogenesis assay, which is extensively used to screen angiogenesis inhibitors (Bai *et al.*, 2003), the researchers found that solenopsin A, a primary alkaloid from the fire ant *Solenopsis invicta*, exhibits antiangiogenic activity. Scientists investigated the ability this toxin has of inhibiting a series of kinases involved in this process.

Regarding centipede venom, there is a published study reporting its antitumoral action (Sonoda *et al.*, 2008). It was shown that a synthetic compound, Manb (1-4) [Fuca (1-3)] Glcb 1-Cer, (glycosphingolipid-7) which was identified in the millipede *Parafontaria laminata armigera* had an antiproliferative effect on melanoma cells. This compound suppresses the activation of the focal adhesion kinase (FAK)-Akt pathway as well as the activation of the extracellular signal regulated kinase (Erk) 1/2 pathways, both involved in melanoma cell proliferation.



## 8. CATERPILLAR VENOM

There are few studies reporting antitumoral potential of caterpillar venom. Cecropins are group of peptides that were first isolated from the hemolymph of the giant silk moth *Hyalophora cecropia*. This peptide has been used as a potent anti-cancer agent against a variety of tumor cell lines (Chen *et al.*, 1997; Moore *et al.*, 1994; Suttman *et al.*, 2008). The mechanism of action of this peptide against tumor cells appears to involve the formation of the pores in the membrane of these cells (Chen *et al.*, 1997).

Moore *et al.*, 1994 (Moore *et al.*, 1994) showed that cecropins are active against several mammalian lymphomas and leukemias *in vitro* and a preliminary *in vivo* study showed that cecropin B increases the survival time of mice bearing murine ascitic colon adenocarcinoma cells.

Suttman *et al.*, 2008 (Suttman *et al.*, 2008) showed that cecropin A and B inhibit the viability proliferation of bladder cancer cells, but with no effect on fibroblasts. The selective antitumor action mechanism of these peptides depends on disruption of target cell membrane resulting in irreversible cytolysis and cell destruction. Both peptides may offer novel strategies for the treatment of bladder cancer cells with limited cytotoxic effects on benign cells.

## 9. SPIDER VENOM

Spider venoms are a rich source of bioactive compounds with therapeutic potential. The venom of the spider *Macrothele raveni* potently suppresses cell growth in the myelogenous leukaemia K562 cell line in a dose and time-dependent manner with an IC (50) of 5.1µg/mL. The results indicate that the venom of the spider *M. raveni* potently and selectively suppresses the growth of K562 cells by inducing apoptosis via caspase 3 and caspase 8 mediated signalling pathways (Liu *et al.*, 2012).

A study was done to examine the effects of antitumor activity of the venom from the spider *Macrothele raveni* (Araneae, Hexathelidae) on the human breast carcinoma cell line, MCF-7. The spider venom affected cell viability in a dose- and time dependent manner as observed by [3H]-methyl thymidine incorporation assay. Cytotoxicity changes in MCF-7 cells caused by the spider venom at concentrations of 10, 20, and 40 µg/mL were determined by lactate dehydrogenase release assay. Flow cytometry showed that the spider venom induced apoptosis and necrosis of MCF-7 cells at these concentrations. MCF-7 cells treated with spider venom were accumulated on the G2/M and G0/G1 phases. In addition, Western blotting analysis indicated that one of the pharmacological mechanisms of spider venom was to activate the expression of p21. *In vivo* examination of the inhibition of tumor growth in nude mice by the spider venom (at concentrations of 1.6, 1.8, and 2.0 µg/g mice) revealed that tumor size significantly decreases compared to controls by 21 days of treatment and at all points of analysis thereafter for 7 weeks ( $p < 0.01$ ) (Davies *et al.*, 2002).

Hyaluronidases found in the venom of some spiders could be used to increase tissue permeability thus facilitating penetration of some drugs or even employed directly as anti tumor agents (Csoka *et al.*, 2001; Girisk and Kemparaju, 2007; Matsushita and Okabi, 2001).

## 10. TOAD VENOM IN CANCER TREATMENT

The anticancer activities of crude toad skin extracts was tried with Chan Su, a traditional Chinese medicine prepared from the dried white secretions of the auricular and skin glands of toad (*Bufo bufo gargarizans*). Chan Su –induced apoptosis in T24, human bladder carcinoma cell line . Chan Su treatment was coupled with a down-regulation of anti –apoptotic bcl-2 and bcl-X(S/L) expression and an up-regulation of pro-apoptotic bax expression. It induced proteolytic activation of caspase 3 and caspase 9 (Ko *et al.*, 2005).

Bufadienolides, is one of the active constituents of Chan Su preparation. A new bufadienolide named 16- $\beta$ -acetoxy-bufarenogin was recently isolated from Chan Su which showed *in vitro* cytotoxicity against HeLa cell line (Qiao *et al.*, 2008).

The skin extract (TSE) from common Indian toad (*Bufo melanostictus* Schneider) possessed significant antineoplastic activity on EAC cells and human leukemic cell lines U937 and K562 cells. The cell growth inhibition due to TSE was established by G1 phase arrest in cell cycle of leukemic cells (Das *et al.*, 1998; Giri and Gomes, 2004).

Bufalin, another bufadienolides from Chan Su, has anticancer property against leukemia as well as melanoma cells. Bufalin arrested the growth of ML1 cells preferentially on G2 phase and U937 cells at the S and G2 phase of the cell cycle. Further, an increase in bufalin concentration noticeably inhibited DNA synthesis and topoisomerases II activity of cancer cells (Hashimoto *et al.*, 1997).

A non-hemolytic defensin, Brevinin 2R, has been isolated from the skin of the frog *Rana ridibunda*. It exhibited pronounced cytotoxicity towards malignant cell, including T cell lymphoma, B cell lymphoma, colon carcinoma, fibrosarcoma, breast adenocarcinoma, lung carcinoma as compared to primary cells including peripheral blood mononuclear cell, T cell and human lung fibroblast. Brevinin 2R caused over expression of pro-apoptotic molecules in these cancer cells. It also led to decrease in mitochondrial membrane potential and increase in reactive oxygen species without changing caspase activities. Autophagosome have been detected upon Brevinin 2R treatment suggesting that autophagy due to Brevinin 2R treatment was activated by lysosomal mitochondrial death pathway (Ghavami *et al.*, 2008).

Cinobufagin, isolated from *Bufo siccus*, showed *in vitro* inhibitory effects on five types of human cancer cells (Chen *et al.*, 1998). The cytotoxic activity of Bufalin and cinobufagin on prostate cancer cell line was associated with constant increase in  $Ca^{2+}$ , leading to apoptosis (Yeh *et al.*, 2003).

## 11. DISCUSSION

Animal venoms have been evolving along with the defence mechanisms presented by their enemies and preys, in a quick and effective manner, thus providing both defence against predators as well as prey capture which resulted in a large repertoire of molecules that binds to specific targets. Research regarding venom has become a very exciting field of study because of the recent advances in genomic and proteomic technologies such as venomous systems genome project (Menez *et al.*, 2006) and the development of methods to screen venoms (Escoubas, 2006; Favreau *et al.*, 2006) allowing better alternatives and means to study the pharmacologically active substances in animal venom found so far. Venoms from these animals may hold the promises for curing many types of malignancies, especially upon

analyzing results from studies which shows complete remissions of tumor cells after treatment with the bioactive molecules derived from venoms from different animal sources.

## 12. CONCLUSIONS

The purpose of the present review is to focus on the use of animal venom as potential source of alternative medicine in the treatment of cancer which in the present decade is considered to be a life threatening human disease. The possibility of using the biomolecules derived from the animal venom in biotechnological processes lead modern researchers to expect that these derivatives are one of the promising sources of natural bioactive compounds. Studies with the animal venoms have contributed significantly to the development of the Biomedical Sciences. Several bioactive molecules such as peptides and enzymes derived from the animal venoms can exert important pharmacological potentialities in human physiology which in turn can be an effective tool for correcting the genomic alterations as noticed in cancerous cells. Further research in this field is of prime need to identify the main venom components and their specific targets in cell-culture so that these animal venoms can be clinically used for the treatment of human cancer in future. In this review a brief overview of the recent progresses in this field of research has been discussed regarding the active molecules obtained from several animal venoms which can be clinically used in the treatment of cancer patients which in the present era is a global burden for human survival.

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