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ANTI-CANCEROUS APPLICATIONS OF SCORPION VENOM

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ABSTRACT

The scorpion venom is a potential bio-source and therapeutic tool to design potent drugs against variety of diseases. Scorpion venom had been used as medicinal and therapeutic tool since medieval times in China. Scorpion venom consists of neurotoxins, salts, low molecular weight peptides and different enzymes with high molecular activities. These activities make them novel therapeutic agents. Scorpion venom has anti-proliferative, cytotoxic, apoptogenic and immunosuppressive effects. Therefore, scorpion venom can be used against a vast variety of cancers like, human neuroblastoma, leukemia, glioma, brain tumor, breast cancer, melanoma, prostate cancer, and human lung adenocarcinomas. This review mainly explains the application of scorpion venom for different types of cancers.

Key Words: Anti-cancerous, Scorpion venom.

INTRODUCTION

Scorpions are venomous arthropods members of class arachnids and order scorpion. They are distributed all over the world except Antarctica (Ruming Z *et al.*, 2010). The scorpions belong to the 18 families and about 1500 different species, out of them 50 species are considered as more poisonous (Bawaskar HS and Bawaskar HP, 2012). Among all the families Buthidae is considered as the most fatal, poisonous and medically important family (Michael ES and Victor F, 2003).

Scorpion venom is a cocktail of different peptides including some enzymes like, hyaluronidases, phospholipases, sphingomyelinases (Kunhn-Nentwig L, 2003), acetylcholinesterases, alkaline phosphatases and proteolytic enzymes (Incesu Z, Caliskan F 2005), low molecular weight peptides (less than 10 KDa), ions, neurotransmitters, and amino acids (Possini LD *et al.*, 1999). Some of the low molecular weight peptides are cystine-rich and directly affect the Na^+ , K^+ , Cl^- , Ca^{2+} and ion channels in excitable membranes (DeBin J A *et al.*,

1993). In cellular mitogenesis, these membrane blocker peptides play a major function (Gallagher JD *et al.*, 1996) and control the signal transduction pathways in metastatic cascades (Laniado ME *et al.*, 2001).

The venom peptides are used to cure different diseases like cardiovascular diseases, acute and chronic convulsions, tetanus, subcutaneous nodules, HIV, epilepsy, brain tumor, human leukemia cell lines, male impotency, kidney tumor, prostate tumor, breast cancer, skin cancers, pancreatitis and rheumatism (Chen Y *et al.*, 2012; Gupta D S *et al.*, 2007; Sarzaem A *et al.*, 2012; Song X *et al.*, 2012; Wang WX *et al.*, 2005; Zargon J *et al.*, 2010). Scorpion venom is very effective for the treatment of various types of cancers and contains such peptides that have shown therapeutic potential against various types of cancers (Gomes A *et al.*, 2009). The scorpion venom possesses immunosuppressive, cytotoxic, apoptogenic and antiproliferative effects (Zargan J *et al.*, 2011). These cytotoxic and antiproliferative effects are mediated by inducing targeted apoptosis of cancerous cells (Masuda *et al.*, 1997).

Natural antimicrobial peptides (AMPs) have been isolated from scorpion venom with broad spectrum effects. AMPs are widely expressed and induce diverse effects against bacteria, viruses, fungi and parasites (Boman HG,

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2000). About 34 million people are infected with HIV throughout the globe. But still, no effective vaccine is discovered to eliminate HIV transmission (Anonymous 1). Due to potential anti-HIV activities, five antimicrobial peptides (AMPs) from the scorpion venom have been screened. Three of them (mocoporin-M1, BmKn2 and Kn2-7) exhibited potent anti-HIV activity. Scorpion toxin II is used in spontaneous contraction of muscles in mammals. The venom of *Herders gertschi* has selective activity on ryanodine receptors (RyRs) (Schwartz EF *et al.*, 2009). The regulation of Ca^{2+} ions is carried out through ryanodine receptors (RyRs) for contraction and excitation of cardiac and skeletal muscles (Bers D, 2001). Imperatoxin A (IpTxa) and Maurocalcin (MCA) are peptides, isolated from the scorpion venom *Pandinus imperator* and *Scorpio maurus palmatus* respectively (Esteve E *et al.*, 2003). Therefore these peptides can be successfully used as a probe for translocation in the cell membranes of cardiomyocytes in many cardiovascular diseases (Georgina B *et al.*, 2010). Scorpion venom peptide APAG retards the growth of the intraperitoneal cancerous cells (Li C *et al.*, 2006).

Scorpion venom for human neuroblastoma

It has been demonstrated that the venom of *Odontobuthus doriae* induces swelling, inhibition of neurite outgrowth, irregular shape, rupture of membrane and release of cytosolic contents in the human neuroblastoma cells. Moreover, scorpion venom increases platelet aggregation (Gadwalkar *et al.*, 2006), also possesses phospholipases and proteolytic enzymes. Lactate dehydrogenase (LDH) level in treated cells is considerably high as compared to normal cancerous cells. So it induces more apoptogenic and cytotoxic effects. The uncontrolled proliferation is the hallmark of cancerous cells. Stoppage of DNA replication and induction of cell death are the two basic components to design therapeutic agents against cancers. Scorpion venom induces DNA fragmentation, which might be due to acute necrosis that elevates caspase-3 sharply (Gadwalkar *et al.*, 2006). It also inhibits the DNA synthesis by bromodeoxyuridine (BrdU) incorporation.

Scorpion venom for leukemia

Scorpion venom contains various peptides which can be used to treat many types of malignancies. The scorpion venom component III (SVC III) selectively acts against human leukemia Jurkat cell line and THP-I cells. Scorpion venom component III (SVC III) exhibits its effect by modulating the NF- κ B signalling pathway. Nuclear factor κ B (NF- κ B) is very important transcriptional factor and plays important role in proliferation, production of immunocytes, development of T and B lymphocytes and in cell apoptosis (Hayden MS *et al.*, 2006). Various studies have been shown that there is close relationship between NF- κ B and hematopoietic malignancies like leukemia,

lymphoma and multiple myeloma due to the aberrant activation of NF- κ B signalling pathways. The blocking of NF- κ B signalling pathway cease down the uncontrolled proliferation of cancerous cells (Escárcega RO *et al.*, 2004). The scorpion venom component SVC III arrests the cell cycle and inhibits the cell proliferation at G1 phase by suppressing the production of cyclin D1 protein. BmBKTx derived from the scorpion venom, suppresses the breakdown of the tumor suppressor protein p53. Another peptide isolated from the scorpion venom is "Bengalin". It retards the growth of the human leukemia cell lines U937 (histocytic lymphoma) and K562 (choronic myelogenous leukemia) and renders them towards apoptosis. Bengalin provides a destructive mechanism against leukemia cell lines by mediating mitochondrial death cascades. Bengalin is also used to cure the osteoporosis in females.

Scorpion venom for glioma

The scorpion venom is very useful against glioma cells. Venom contains a peptide called "Cholorotoxin" with 36 amino acids (Gelly J C *et al.*, 2004). Cholorotoxin specifically binds to the glioma cells but not with human neurons, astrocytes and fibroblasts (Jacoby DB *et al.*, 2010; Lyons SA *et al.*, 2002). As the glioma cells display an up regulation of chloride ion channels, cholorotoxin blocks the conductance of chloride channels (Shen S *et al.*, 2005).

Cholorotoxin has been synthetically produced called TM601. It specifically retards the growth of glioma cell lines and it can also be used as a "tumor paint" to delineate the tumor margins (Veiseh M *et al.*, 2007). Cholorotoxin selectively acts against the glioma cells. This selective targeting of cancerous cells is probably due to the binding to the extra cellular matrix proteins. These extra cellular proteins are over expressed in glioma or cancerous cells (Kesavan K *et al.*, 2010).

Scorpion venom for brain tumor

Scorpion venom is also very effective against brain tumor. The scorpion venom peptide Cholorotoxin is also used as imaging agent in brain surgery. Cholorotoxin possesses cystine knot (cystine rich amino acids) with extra disulfide bond. So it specifically binds to the brain tumor cells. Cholorotoxin is conjugated with fluorescent dye to display the tumor lines and makes surgical removal easier (Veiseh M *et al.*, 2007).

The selective targeting of cholorotoxin is probably due to its binding with extra cellular matrix proteins, which are over expressed in cancerous cells. Cholorotoxin can also be used as noninvasive screening tool for the early detections of cancer cell lines. Cholorotoxin when conjugated with iron nano-particles through a linker could successfully be used for the targeting of drugs and ligands. These target nono-particles show preferential increased accumulation and cytotoxicity (Biswas A *et al.*, 2010)].

Scorpion venom for breast cancer

Scorpion venom contains a substance called as hyaluronidase (BmHYA1) which specifically acts against breast cancer cell lines by inhibiting the effect of hyaluronan (Sariego J, 2010). Hyaluronan is important for the metastasis of cancer thus hyaluronidase (BmHYA1) inhibits its effects (Feng L *et al.*, 2008). It has been demonstrated that the venom of *Odontobuthus doriae* not only induces apoptosis in cancerous cells but also inhibits the synthesis of DNA in human breast cancer cells (MCF-7) [17]. ICD-85 is also venom derived peptide and showed potential anticancerous effects against breast cancer (Koochi MK *et al.*, 2009). It has been shown that ICD-85 exhibit anticancerous and cytotoxic effects against other types of cancers like HeLa cell lines HL-60, Vero and MDA-MB231 (Mirakabadi ZA *et al.*, 2008). ICD-85 inhibits the HeLa cell lines by apoptosis when compared to normal LK cells.

Scorpion venom for prostate cancer

Prostate cancer is the major cause of death in men. It has been revealed that polypeptide extract from the scorpion venom PESV is potent against androgen independent-prostate cancer cell lines (Zhang YY *et al.*, 2009). Hormone refractory prostate cancer (HRPC) remained a challenge but the finding of new promising agent is important against androgen independent prostate cancer (Kan SF *et al.*, 2007)[42]. A polypeptide extract from scorpion venom (PESV) has been isolated from *Buthus martensi Karsch* (Bmk). PEVS is a peptide with 50-60 amino acids and has antiproliferative, cytotoxic and apoptosis-induced activities against Human Umbilical Vein endothelial Cell (HUVEC), inhibition of neovascularization, suppression of tumor growth of S180 sarcoma and H22 hepatocellular carcinoma in mice (Zhang WD *et al.*, 2005).

Scorpion venom for pancreatitis

Pancreatitis is the swelling of the pancreas and its surrounding tissues. It occurs due to the leakage of pancreatic enzymes through vesicles. These vesicles contain proteinaceous enzymes that cause inflammation. Vesicles allow cell membrane to get open, release proteins and transport them out without affecting the rest of the cell contents. These proteins are called as Vesicle Associated Membrane Proteins, or VAMPs. VAMP2 and VAMP8 cause pancreatitis. It has been observed that the scorpion venom efficiently breaks these VAMPs and eliminates the ability of vesicles to release proteins and cargo them out (Fletcher *et al.*, 2010). Scorpion venom peptides are also very effective for lung, cervical, esophageal, colon and skin cancers.

Scorpion venom for melanoma

Peptide TRAIL (TNF-related apoptosis-inducing ligand) isolated from scorpion venom is used to induce apoptosis in melanoma cells by potassium channel inhibitor TRAM-34 (Quast S A *et al.*, 2012). The death ligand TRAIL induces apoptosis via TRAIL-R1/DR4 and TRAIL-R2/DR5 (Lemke J *et al.*, 2010). TRAIL shows a particular targeting against cancer cells while normal cells mostly remain unaffected. TRAIL specifically down regulates the TRAIL receptors, initiator caspases and proapoptotic Bcl-2 proteins in melanoma cells (Kurbanov BM *et al.*, 2007). TRAIL causes the depolarization of the mitochondrial membrane potential ($\Delta\psi_m$) and mitochondrial outer membrane permeabilization (MOMP), resulting in release of mitochondrial factor such as cytochrome c, AIF (apoptosis-inducing factor) and SMAC (second mitochondria-derived activator of caspases) which ultimately inhibits the melanoma cell proliferation and induces its death by apoptosis (Norberg E *et al.*, 2010).

Scorpion venom for Human Lung Adenocarcinoma

Scorpion venom contains some enzymes like, phospholipase A2, acetylcholinesterase, alkaline phosphatase and proteolytic enzymes with strong cytotoxic and gelatinolytic activities (Pessini A C *et al.*, 2001). Monoamine oxidase inhibitory activities of venom peptides from *Mesobuthus gibbosus* have been observed. The proteolytic enzymes cause, necrosis, hemolysis and gangrene (Almeida FM *et al.*, 2002). Identification of these proteases is very important in the treatment of different cancers. When proteases from *Mesobuthus gibbosus* is applied on the human lung adenocarcinoma (A549) cell lines then considerable decrease in the cancerous cell lines have been observed. Hence these peptides have strong proteolytic and gelatinolytic activities against human lung adenocarcinoma.

CONCLUSION

It has been elaborated that scorpion venom is an immense sea with a lot of therapeutically important peptides. Indeed scorpion venom peptides possess potential anti-proliferative, cytotoxic and apoptogenic effects against different types of cancers. It seems that this bio-source has been specifically produced possibly to prevent different types of cancers and cancer therapy. Florescent labeled scorpion venom peptides have now been introduced into the cancerous patients to visualize the boundaries of cancerous tissues. Many of peptides are not yet discovered and a lot of research is required to reveal other therapeutically important peptides from scorpion venom.

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