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Mini review

# Medical application of scorpion venom to breast cancer: A mini-review

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ABSTRACT

Breast cancer is the leading cause of mortality in women worldwide. Today, 1 in 8 women born in the United States will have an invasive cancer in their lifetime. Despite significant attempts, the prognosis of metastatic breast cancer still remains poor. This has compelled scientists to look elsewhere for better therapeutic outcomes. Recent advances in venomic studies have demonstrated some promise in cancer-related ailments. Scorpion venom, a complex cocktail of biogenic amines, proteins, peptides, mucoproteins, organic salts and neurotoxins has shown a potential therapeutic application due to its cytotoxic, apoptogenic, immunosuppressive and antiproliferative properties. This communication reviews the effects of scorpion venom components on breast cancer and their mechanisms.



## 1. Introduction

Breast cancer is considered to be one of the most prevalent and deadliest cancers in women (Jemal et al., 2010). Due to the rapid progression of this disease many attempts have been made to combat its malignancy. Several cancer drugs and adjuvant therapies have shown some promise in the treatment of breast cancer. However, the precarious nature of this pathology has prompted scientists to look elsewhere for better therapeutic measures. Medical applications of animal venoms have been rarely mentioned or utilized in Western medicine. However, traditional medicine such as Unani, Ayurvedic and Chinese medicine have demonstrated some success of animal venoms as a possible therapy for cancer-related illness (Gomes et al., 2010).

Venoms are a cocktail of complex secretory mixtures of proteins, peptides, biogenic amines, mucoproteins, enzymes and non-protein inclusions such as inorganic salts and ions. The properties of snake venom has been widely studied and shown to possess the capability of inducing cytotoxic effects engineered to degrade and destroy unhealthy tissues such as tumors. Due to the different species of snakes, the effects of its venom are based on the potency and type (Sanchez et al., 2010). For instance, viperid snake venom usually contains disintegrin, a compound known to facilitate cell migration, cell adhesion, cell growth, hemostasis and inflammatory responses, and tissue organization (Koh and Kini, 2012). Snake venom is known to constitute hemotoxic constituents which impacts blood functions and cardiovascular systems. They are also known as cytotoxic venoms which target specific cellular sites such as the cell membrane, muscles (respiratory muscles) and other body tissues (Yamazaki and Morita, 2007).

Recently, studies on medical applications of snake venom as a viable alternative to cancer treatment have been reported. Zhang and Wei, 2007 reported that ACTX-6 (98 kDa proteins containing two subunits) from *Agkistrodon acutus* venom induces cell apoptosis. Moreover, a study on the in-vitro effect of BJcuL on adhesion of human ovarian and breast cancer carcinoma cells and viability of these cell lines indicated that BJcuL (a galactose binding lectin from *Bothrops jararacussu*) inhibits the growth of tumor cell

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lines and endothelial cells. BJcuL affect these cells through altering cell adhesion and induction of apoptosis (De Carvalho et al., 2001). The efficacy of using snake venom in treating cancer-related maladies has been modest and encouraging (Yang et al., 2005). However, scorpion venom has shown far more promise in cancer therapy. Several studies (Fu et al., 2007; Mamelak and Jacoby, 2007; De Carvalho et al., 2001) have aimed at scorpion peptides that seem to have antineoplastic activity.

Scorpion venoms are heterogeneous biologically active proteins secreted by scorpions during predatory and defensive contexts (Martin-Eauclaire and Couraud, 1995; de la Vega and Possani, 2005). The venom inhibits voltage-gated ion channels of mammals or insects. It disrupts the mode of operation by binding to sodium ion channels, inhibiting activated channels and neuronal transmission. Also, it has been noted that scorpion venom contains a wide range of pharmacological properties which include antimicrobial, anti-epileptic and channel blocking (Mishal et al., 2013). Scorpion venom has shown anticancer activity on glioma, a type of tumor that targets the central nervous system. BmK AGAP is a sodium channel-specific neurotoxin from *Buthus martensii Karsch* that has been found to induce apoptosis and inhibit the growth of glioma cells (Lyons et al., 2002). Also, Deathstalker scorpion (*Leiuris quinquestriatus*) venom is known to contain a toxin called chlorotoxin, a 36-amino acid peptide which is toxic to insects but not mammalian systems. This toxin is known to block small-conductance chloride ion channels (DeBin and Strichartz, 1991). Glioma cells are sensitive to chlorotoxin due to its expression of glioma-specific chloride ion channel. Chlorotoxin's affinity to glioma cells may serve as a diagnostic tool in the early detection of glioma cancer cells (Lyons et al., 2002). Bengalin is another antiproliferative, cytotoxic and apoptogenic protein in Indian black scorpion venom (*Heterometrus bengalensis*) that acts against human leukemia cells U937 (histiocytic lymphoma) and K562 (chronic myelogenous leukemia) (Gupta et al., 2007).

The purpose of this communication is to review the biomedical action of scorpion venom from different scorpion species on breast cancer and its possible mode of mechanisms.

### 1.1. Effects of BmHYA1 in scorpion venom on breast cancer cells

BmHYA1 is an enzymatic compound found in Chinese red scorpion (*Buthus martensi*) venom. BmHYA1 (hyaluronidase) is a high molecular mass protein shown to negatively impact breast cancer. They are acid-active and neutral compounds known to have the following functions: (1) modulate cell cycle which may include apoptosis; (2) facilitate penetration of anti-cancer drugs: and (3) curtail human breast cancer growth. The capability of BmHYA1 to modulate breast cancer cells happens through a cascade mechanism. Hyaluronan is a non-sulfated glycosaminoglycan polymer located in the extracellular matrix of cancer cells. The elevation of this glycosaminoglycan polymer fosters malignant tumor progression (Zhang et al., 1995; Kosaki et al., 1999). It also serves as a host for tumor survival and metastasis through the modulation and interaction with CD44 cells (Knudson, 1998; Yu and Stamenkovic, 1999). Hyaluronan act as a space-filter that facilitate in cancer cell movement. Hyaluronan binds to CD44 inducing an interaction with the cytoskeleton of the cell. This interaction causes signal transduction pathways to be initiated which in turn promote survival and growth of the breast cancer cells. Hyaluronan has affinity for TGF-β and protects it from cellular proteolytic degradation. Interestingly, it can also activate latent TGF-β via the interaction with CD44 and also has the ability to provide matrix for tumor cells detachment from a basal lamina evading apoptosis (Yu et al., 1997; Henke et al., 1996; Seoh et al., 1999; Kaneko et al., 2000; Tian et al., 2000) and immune-mediated cytotoxic agents.

The complexity associated in deactivating hyaluronan seems impossible. However, some studies have shown that BmHAY1 function as an anticancer agent which is able to modulate cell cycle kinetics. It prevents tumor cell invasion in lymph nodes, and also blocks TNF-mediated cancer cell apoptosis (Chang, 1998). Hyaluronidase degrades hyaluronan at either β-gluconorate-[1 → 3]-N-acetylglucosamine bonds or β-N-acetyl-hexosamine-[1 → 4]-glycosidic bonds (Stern and Jedrzejas, 2006). BmHYA1's ability to induce apoptosis in breast cancer cells shows some promise in the treatment of breast cancer.

### 1.2. Effects of BmK on breast cancer cells

Bmk is a prominent component of Chinese scorpion, *Buthus matensii Karsch*, venom. This Chinese scorpion venom has been an indispensable entity used in Chinese traditional medicine for treating chronic pathologies which include facial paralysis, apoplexy, convulsion, and hemiplegia (Villetti et al., 2001). *B. matensii* neurotoxin has been widely studied in recent times including the biological and physiological function (Zhou et al., 1989), three-dimensional structures (Li et al., 1996) and pharmaceutical properties (Yu et al., 1993; Wang et al., 2001; Ehrenpreis et al., 1969). Li et al. in their recent study reported that clinical incidence of breast cancer is sensitive to Bmk. Their investigation revealed that Bmk: (1) inhibits the proliferation of MCF-7; (2) induces apoptotic activity in MCF-7 through caspase-3 up-regulation; (3) Bcl-2 is down-regulates and prevents cells in Go/G1 phase from progressing in to S-phase (Li et al., 1996). This study elucidates some potential of BmK as an anti-cancer agent on breast cancer cells.

### 1.3. Effects of Androctonus venom on breast cancer cells

Zargan et al., 2011a, reported that scorpion venom from *Androctonus crassicauda* inhibits growth of breast cancer cells, MCF-7. MCF-7 was exposed to different concentrations (10, 25, 50, 100, and 200 μg/ml) of scorpion venoms. The viability and cytotoxicity of the cancer cells were measured by analyzing the lactate dehydrogenase content, nitric oxide production, cell morphology, mitochondria membrane integrity, caspase-3 activity, and DNA inhibition. *A. crassicauda* venom reduced the viability of MCF-7 cells proportionally, in a dosage dependent manner. Also, the lactate dehydrogenase content increased in proportion to the amount of venom it was exposed to, however, cells that were treated with 50 and 100 μg/ml showed the most significance (Zargan et al., 2011a). Moreover, the results of this study revealed increased Caspase-3 activity, a key apoptotic protease (Wimmer et al., 2004; Zaric et al., 2010) and increased quantity of nitric oxide in the treated cells. *A. crassicauda* venom markedly inhibited the mitochondrial membrane potential of the MCF-7 cells, and the analysis of DNA breakage showed that venom concentrations of 50 μg/ml induced DNA breakage. These results suggest a dose-dependent effect of *A. crassicauda* venom on cancer cells (Zargan et al., 2011a). Higher doses induce necrosis to decrease the viability of the cells, while lower doses reduce cell growth by inducing apoptosis. The venom also suppressed proliferation of MCF-7 cells by arresting S-phase of the cell cycle (Zargan et al., 2011a,b,c). Increased nitric oxide in MCF-7 cells after treatment with *A. crassicauda* venom inhibits mitochondrial membrane potential resulting in the release of apoptogenic factors from the mitochondria (Kinsey et al., 2007). This sets off chromatin and DNA condensation, and caspase activation (Zargan et al., 2011a). Nitric oxide has been implicated by other studies as having the ability to induce apoptosis through these mechanisms (Hortelano et al., 1997; Brüne et al., 1998).