

Scorpion Toxins and its Applications

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ABSTRACT

Scorpion venoms consist of neurotoxins. Animal venom and toxins are the potential bioresource and therapeutic tool in biomedical applications. Chinese, believing scorpion venom have powerful analgesic properties. Scorpion venom has been used as traditional and folk therapy in various pathophysiological conditions. Scorpion venom is a complex mixture of salts, neurotoxins, peptides and proteins. Scorpion toxins have antiproliferative, cytotoxic, apoptogenic, and immunosuppressive properties. These properties make scorpion toxin as useful agents for therapeutic application. This article reviews focused on the application of scorpion toxins in therapeutic and agriculture

Keywords: Antiepileptic, Analgesic, Glioma, Scorpion toxins.

INTRODUCTION

Medical applications of venoms and toxins have been mentioned in Ayurvedic, unani, chinese and homeopathic system of medicine (1). Venom is the secretory product of venomous animals. Venoms are complex mixture of number of proteins, peptides, enzymes, toxins and non protein inclusions. Toxins are chemically pure toxic substances. Scorpion toxins exhibit a wide range of biological properties and actions. It also has toxicity, pharmacokinetic and pharmacodynamic characteristics (2). Scorpion and its toxins have been used to cure epilepsy, rheumatism, and male impotency since medieval times (3). The purpose of this article is to review biomedical applications of scorpion toxins including the analgesic, antiepileptic, pain management, brain tumor, autoimmune diseases, glioma and protein Engineering. The structure and characteristics of toxins are also discussed.

Scorpion toxins: Scorpion toxins are proteins found in the venom of scorpions. Scorpion toxin's molecular function is to inhibit ion channels. Their toxic effect may be mammal or insect specific. It acts by binding to sodium channels, inhibiting the inactivation of activated channels and blocking neuronal transmission. Toxins are isolated from the venom of different species of scorpion based on their pharmacological action and structural properties of peptide family.

Application of scorpion toxins: Venoms are rich source of several bioactive compounds that possess therapeutic potentials. Scorpion venoms contain several small molecular weight peptides having wide pharmacological activities such as anti-epileptic, antimicrobial and channel blocking.

1) Anticancer activity of scorpion toxins: Cancer, despite the all out efforts from developed countries still causes one in five deaths. Surgery, chemotherapy and radiotherapy provide inadequate protection. It affects

normal cells along with cancer cells. The search for cancer cure from natural product has been practiced for over a century. Scorpion toxins have shown therapeutic potential against cancer.

Scorpion toxin for glioma: A glioma is a type of tumor in the brain or spine. The most common site of gliomas is the brain (4). It is called a glioma because it arises from glial cells. The scorpion toxins are used to treat cancer patients by injecting fluorescent scorpion toxin into cancerous tissue to show tumor boundaries. *BmK AGAP* is sodium channel-specific neurotoxins from *Buthus martensii* Karsch. *BmK AGAP* toxin induced apoptosis and inhibited growth of glioma cells (5). Chlorotoxin is a 36-amino acid peptide found in the venom of the deathstalker scorpion (*Leiurus quinquestriatus*), which blocks small-conductance chloride channels (6). Chlorotoxin is toxic to insects but non toxic to the mammalian system (7). Glioma cells have been shown to express a glioma-specific chloride ion channel (GCC) that is sensitive to chlorotoxin (CTX). Chlorotoxin is specifically bind to glioma cells. Chlorotoxin may serve as glioma-specific markers with diagnostic and therapeutic potential (5). Chlorotoxin helps to early detection of glioma cancer cells could save lives.

Scorpion toxin for leukemia: Leukemia is a type of cancer of the blood or bone marrow characterized by an abnormal increase of immature white blood cells called "blasts". Bengalin is a high molecular weight protein isolated from the Indian scorpion (*H. bengalensis*). Bengalin possessed antiproliferative, cytotoxic and apoptogenic activity against human leukemic cells U937 (histiocytic lymphoma) and K562 (chronic myelogenous leukemia). Bengalin provide a putative molecular mechanism for their anticancer effect on human leukemic cells mediated by mitochondrial death cascade (8).

Scorpion toxin for breast cancer: Breast cancer is a cancer originating from breast tissue, most commonly from the

inner lining of milk ducts (9) Breast cancer may be invasive or noninvasive. Invasive means it has spread from the milk duct or lobule to other tissues in the breast. Noninvasive means it has not yet invaded other breast tissue. A hyaluronidase(BmHYA1), was purified from the venom of Chinese red scorpion (*Buthus martensi*).The human breast cancer cell line of MDA-MB-231 is an aggressive cancer cell line that supposedly contains much hyaluronan. Hyaluronidase reduces human breast cancer. It may provide a new class of anti-cancer therapeutics and without toxic side effects (10).

Scorpion toxin for Brain tumor: A brain tumor is an intracranial solid neoplasm. Tumor is defined as an abnormal growth of cells within the brain or the central spinal canal. The scorpion venom peptide, chlorotoxin shows promise as an imaging agent for brain surgery. Chlorotoxin is an example of an elaborated cystine knot. Cystine knot contains an extra disulfide bond. Chlorotoxin is specifically bind to brain tumor cells (5). Chlorotoxin is conjugated with fluorescent dye can be used as a 'tumor paint' to delineate the margins of brain tumors and hence facilitate their surgical removal (11). This selective cancer cell targeting probably occurs via binding to the extracellular matrix protein, which is overexpressed in brain cancer cells (12). Chlorotoxin may serve as brain tumor-specific markers with diagnostic and therapeutic potential.

Scorpion toxin for Skin, lung, cervical, esophageal and colon cancer: Chlorotoxin is a non invasive screening tool for early detection of Skin, lung, cervical, esophageal and colon cancers. Chlorotoxin is conjugated with iron oxide nano particles through a polyethylene glycol linker could successfully attach to both drug and targeting ligands. The target nanoparticles demonstrated preferential accumulation and increased cytotoxicity in tumor cells. Further, in vivo models these nanoparticles were retained within the tumors. It was suggested that this multifunctional nanoparticle system may find potential application in cancer diagnosis and treatment (13).

2) Scorpion Toxins for Analgesic : An analgesic (painkiller) is any member of the group of drugs used to relieve pain. Several Asian scorpions are commonly employed in Chinese medicine to treat chronic pain, including *Buthus martens* Karsch (BmK). BmK dIT-AP3 toxin showed peripheral antihyperalgesia and antinociception in carrageenan induced inflammation in rats (14). BmK AS, another toxin also induces peripheral antihyperalgesia and antinociception in carrageenan-induced inflamed rats, possibly by modulating the sodium channel in nociceptors (15). BmK AS1 toxin produced an antinociceptive effect on the rat peripheral nervous system and spinal cord, this effect was attributed to the modulation of tetrodotoxin-resistant and tetrodotoxin-sensitive sodium channels in peripheral and central neurons (16).

3) Scorpion Toxins for Antiepileptic Effects: Epilepsy is one of the most common neurological disorders, and affects 40 to 50 million people throughout the globe (17). The chronic application of antiepileptic drugs (AEDs) is widely used to treat epileptic seizures (18). Many patients

suffer from serious side-effects when chronically treated with AEDs, such as chronic toxicity, cognitive impairment, sedation and teratogenesis (60). Therefore, new AEDs for the treatment of epilepsy need to be developed (19). *Buthus martensi* Karsch (BmK) is an Asian scorpion of the Buthidae family, whose venom has been used for treatment of neurological diseases such as epilepsy. Especially its tail has been used in Chinese traditional medicine to treat several neuronal diseases, such as several types of paralysis, apoplexy and epilepsy (20).Several toxins have been isolated and characterized from *Buthus martensi* Karsch venom, including α and β neurotoxins, that present an antiepileptic effect in rats (21). BmK IT2 modulates Na^+ channels in the hippocampus and constitutes an attractive tool for studies on this pathology (22). BmKAEP (anti-epilepsy peptide) is a neurotoxin. It is a β -toxin, a Na^+ channel inhibitor. Several studies have shown that BmKAEP can inhibit coriaria lactone-induced epilepsy in rats (23).

4) Scorpion Toxins for Cardiovascular Effects: Cardiovascular diseases are the main cause of death in modern life. Several toxins, isolated from different venom sources, act on all cardiovascular system levels, e.g. integrins and desintegrins that disrupt blood coagulation cascade. A toxin from *Androctonus australis garzonii* venom that is able to induce atrial natriuretic peptide secretion and BmK I toxin from *Buthus martensi* scorpion venom, that is able to modulate cardiac contraction (24, 25). Margatoxin (MgTX) is a peptide from *Centruroides margaritatus*, which selectively inhibits Kv1.3 voltage-dependent potassium channels. It increases the time necessary to conduct action potentials in the cell in response to a stimulus. Acetylcholine (ACh) plays a key role in activation of nicotinic and muscarinic ACh-receptors. Margatoxin influences nicotinic ACh-receptor agonist-induced norepinephrine release. Upon activation of muscarinic ACh receptors with bethanechol, Margatoxin-sensitive current was suppressed. Kv1.3 affects the function of postganglionic sympathetic neurons. It was concluded that Kv1.3 influences sympathetic control of cardiovascular function (26).

5) Scorpion toxins that potentiate erectile function: Penile erection is a neurovascular phenomenon that depends upon neural integrity, functional vascular system and healthy cavernosal tissue (27, 28).Toxins are purified from scorpion venom have shown efficiency in promoting priapism and erection in different experimental models (29). Crude venom from the scorpion *Tityus serrulatus* causes relaxation in rabbit and human cavernosal smooth muscle in vitro (30,31). Other scorpion venoms from *Androctonus australis* and *Buthus judaicus* have also been reported to cause relaxation of rabbit corpus cavernosum. (32).

6) Scorpion venom for autoimmune diseases: Autoimmune diseases arise from an inappropriate immune response of the body against substances and tissues normally present in the body. The treatment of autoimmune diseases is typically with immunosuppression—medication which decreases the immune response. Scorpion-derived peptides blockers of

Kv1.3 channels in effector memory T cells may have use in the treatment of multiple sclerosis, rheumatoid arthritis, bone resorption and other autoimmune diseases. Kaliotoxin KTX is a neurotoxin derived from the scorpion *Androctonus mauretanicus*(33). KTX is a potent immunosuppressive agent (34). Therapeutic properties of Kaliotoxin(KTX) is immunosuppressive and symptomatic neurological effects determined using experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis. A polypeptide toxin OSK1 extracted from scorpion *Orthochirus scrobiculosus*. Its potency is drastically enhanced in blocking one class of voltage-gated potassium channels, Kv1.3, which is a pharmacological target for immunosuppressive therapy (35).

7) Scorpion toxin in antimalarial drugs: *Plasmodium falciparum* is a protozoan parasite, which cause malaria in humans. It is transmitted by the female *Anopheles* mosquito. Antimalarial drugs are used for the treatment and prevention of malaria infection. Meucin-24 and Meucin-25 was first identified from venom gland of scorpion *Mesobuthus eupeus*. Which selectively kill *Plasmodium falciparum* and inhibit the development of *Plasmodium berghei*, both are malaria parasites. Meucin-24 and Meucin-25 do not harm mammalian cells. These two venom-derived proteins are used for the development of anti-malarial drugs (36).

8) Scorpion Toxins as Natural Scaffolds for Protein Engineering: Protein engineering is a process that increases stabilities of proteins through artificial selection and evolution (37). The core of protein engineering is an appropriate protein scaffold (38). A protein scaffold is a peptide framework that exhibits a high tolerance of its fold for modifications (39). Extraordinary thermal and biological stability of cystine-knot miniproteins provides an attractive scaffold for the development of peptide-based diagnostics. Scorpions produce a variety of toxins associated with a small number of protein scaffolds. Toxin U₁-liotoxin-Lw1a isolated from scorpion *Liocheles waigiensis* venom, which have DDH fold. U₁-LITX-Lw1a has potent insecticidal activity across a broad range of insect pest species. It is providing a unique structural scaffold for bioinsecticide development (40). Toxin scaffolds opened a new door to design minimized proteins expressing new functions.

9) Scorpion toxin provide safe pesticide: Scorpions have powerful venom which is complex poisonous peptides. Michael Gurevitz isolates the venom constituents of the Israeli yellow scorpion. He developed genetic methods for producing and manipulating the desired toxins in bacteria. Genetically engineered toxins penetrate into insects and attack their nervous systems, leading to paralysis and death. These toxins are highly active against some insects like leaf-eating moths, locusts, flies and beetles and have no effect on beneficial insects like honeybees or on mammals like humans (41).

10) Scorpion toxin provide safe Insecticide: Scorpions have toxins that are superbly adapted to killing insects. Scorpion toxin genes are also used to kill insect pests by creating hypervirulent fungus in the insect through gene

insertion. St. Leger produces the insect-killing fungus (*M. anisopliae*). Synthetic scorpion gene is inserted into the *M. anisopliae* fungus. Fungus will produce the scorpion toxin only when it is in the blood of the insect and it will never produce under any other circumstances. Then he tested the infectivity of the transgenic fungus against mosquitoes, caterpillars and the coffee borer beetle. He determined that scorpion toxins are highly specific to pest species (42).

CONCLUSION

Scorpion venom is a goldmine for insecticidal and therapeutic agents. Scorpion venom is made up of neurotoxins and other proteins that can cause paralysis or death. The toxin's molecular function is to inhibit ion channels. Scorpion toxins are used in insecticides, vaccines, and protein engineering scaffolds. The toxins are now used to treat cancer patients by injecting fluorescent scorpion toxin into cancerous tissue to show tumor boundaries. Scorpion toxins have immense therapeutic properties and certainly can be proved to be a boon for mankind possibly in cancer prevention and therapy.

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