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**INTRODUCTION POTENTIAL OF SCORPION VENOM (CHLOROTXIN)
FOR THE TREATMENT OF VARIOUS DISEASE**

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ABSTRACT

Chlorotoxin is a small 36 amino-acid peptide identified from the venom of the scorpion *Leiurus quinquestriatus*. Initially, chlorotoxin was used as a pharmacological tool to characterize chloride channels. While studying glioma-specific chloride currents, it was soon discovered that chlorotoxin possesses targeting properties towards cancer cells including glioma, melanoma, small cell lung carcinoma, neuroblastoma and medulloblastoma. It is rich in neurotoxins, enzymes, enzyme inhibitors, histamine, lipids and different salts from which peptides demonstrate a great potential against a variety of diseases. Therefore, it is motivating to use these properties for the treatment of cancer, cardiovascular diseases, diabetes, AIDS, apoplexy, influenza H5N1, paralysis, epilepsy, malaria, measles, severe combined immunodeficiency, fever blisters and diabetes. Scorpion venom has shown the presence of 100,000 bioactive compounds but only 1 % of these have been purified, isolated and characterized by

HPLC and mass spectroscopy etc. For the production of high-quality antivenom with specific antibodies, gentler electrical stimulation is a better method as compared to manual production. Recombinant DNA technology has facilitated the identification of new components. Some important medicinal compounds isolated from scorpion venom include HsTX1 (from *Heterometrus spinnifer*), mucroporin-M1 (from *Lychas mucronatus*), chlorotoxin and charybdotoxin (from *Leiurus quinquestriatus hebraeus*). *B. leptochelys* venom has shown the presence of at least 148 components. Six novel long-chain peptides were isolated from the scorpion *Buthus martensi* Karsch venom. Abdullah bayrami displays a proliferative effect on MCF-7 cells and also shows antimicrobial potential. A new toxin derived from the venom of *Liocheles waigiensis* [U1-liotoxin-Lw1a (U1-LITX-Lw1a)] displays significant insecticidal action.

Keywords: Scorpion venom, Toxins, Cell channels, Disease treatment, Drug formation

INTRODUCTION

Scorpions are famous all over the world for their poisonous sting, which is highly painful and causes a lot of health issues, including severe pain, inflammation, hypertension, cardiac arrhythmia; it may also lead towards muscle paralysis or even death in children. Their venom has been reported to show significant hazardous effects on health [1] as it inhibits the functioning of Na⁺/K⁺ ATPase pump and may cause the failure of the nervous system [2]. Management of poisoning is one of the biggest challenges faced by health care professionals globally [3]. There are reports of the treatment of numerous diseases through the venom of some poisoned species e. g., lionfish spine poison extract [4] and snake venoms [5-7]. Scorpion's venom also finds applications in the diagnosis of various diseases, including tetanus, epilepsy, chronic

and acute convulsion [8]. Scorpions (about 1500 species) are known as one of the ancient species which have been living on the earth since 400 million years ago. They are the causes of approximately 1.2 million stings and 3250 human deaths every year throughout the world [9]. In Saudi Arabia (especially in the northwest region), there is highly prevalence of scorpion stings in Riyadh [10]; about 25 species of snakes are proved to be highly toxic in this country [11]. The most toxic venom belongs to the genus "Androctomus" which also exists in KSA [12]. The common outdoor activities and hot climatic conditions result in the common exposure of local residents to scorpion attacks [10].

Potential Therapeutic Application Of Scorpion Venom [13]

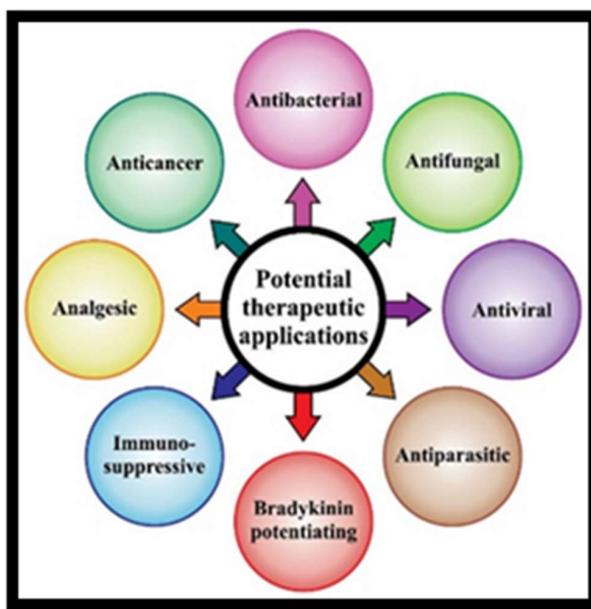


Figure 1: Potential therapeutic application of scorpion venom

The scorpion venom can interfere with the ion channel operating mechanisms in the body and result in the blockage of the normal neurotransmitter signalling path. Despite of its negative effects, it is also beneficial for human beings as it can be used for the cure of various deadly diseases [13], including cancer, [14] blood and pancreatic cancers [15] and is also useful for the synthesis of toxin-neutralizing vaccine [16]. It has also been reported that the scorpion venom selectively attacks on cancerous cells without showing any interaction with healthy cells. Its application results in the rupture of normal architecture of cancerous cells and also decreases cell proliferation [17]. Current studies were performed to review the chemical nature of scorpion venom and its potential therapeutic applications.

MATERIALS AND METHODS

Review studies were performed on the chemical nature [18] and therapeutic potential [8, 17] of scorpion venom [2, 9, 14] and relevant literature is reviewed from 1993 to 2022.

Chemical Nature of Scorpion Venom

The symptoms associated with envenomation are owed to the presence of a large number of bioactive components such as amino acids, nucleotides, lipids and peptides (most important component) in scorpion venom [19]. The toxin peptides of scorpion venom can be categorized into two main classes (i) disulfide-bonded peptides and (ii) non-disulfide-bonded peptides. Disulfide-bonded peptides consist of 3 to 4 disulfide bridges and are generally classified according to their mode of interaction with different ion channels (Ca^{2+} , Na^{+} , Cl^{-} , and

K⁺) of cells. In mammalian organisms, these membrane-bound ion channels play an important role in regulation of the normal cell behavior. Many biological functions such as hemolytic, bradykinin potentiating, anti-inflammatory, anticancer, and anti-microbial activities are regulated by non-disulfide-bonded peptides.

The scorpion toxins have the ability to identify and bind to the ion channels. Toxins vary in the length of their amino acid chains depending upon the nature of metal channels to which they have the ability to recognize. The toxins generally contain 29 to 41 amino acids which are specific for the interaction with K⁺ and Cl⁻ channels. Toxins having the recognition ability of Na⁺ channels are 60 to 76 amino acids longer (4 disulfide bridges), while the toxins interacting with Ca²⁺ channels are rare and have variable lengths of their amino acid residues. However, these toxins are very much similar to each other in terms of their main 3-dimensional folding pattern and primary sequence. The central core of all toxins is generally formed by the α -helix segment and many anti-parallel beta-sheet

stretches. β -toxins have the ability to bind to sodium channels permitting an abrupt shift towards a more negative potential of the membrane. CSS IV and Ts1 (another name Ts γ) obtained from *Centruroides suffusus* (scorpion venom) and *Tityus serrulatus* (Brazilian scorpion), respectively, are β -toxins which can be bound to the sodium channels. The presence of 36 amino acids and 4 disulfide bonds has been verified in the chlorotoxin peptide of *Leiurus quinquestriatus* venom. NMR Spectroscopy has shown the presence of 3 anti-parallel β -sheets, which are cross-linked through 3-disulfide bonds within α -helix and the fourth one is connected to the beta-strand with a small N-terminal. The binding of metalloprotease-2 with chloride channels is blocked by chlorotoxin. Endocytosis of MMP-2 is caused by chlorotoxin; it results in the depletion of Cl⁻ channels in the cell surface. This chlorotoxin only binds to the cancerous cells and not to the normal ones [21].

Purification And Isolation of The Desired Component of Scorpion Venom

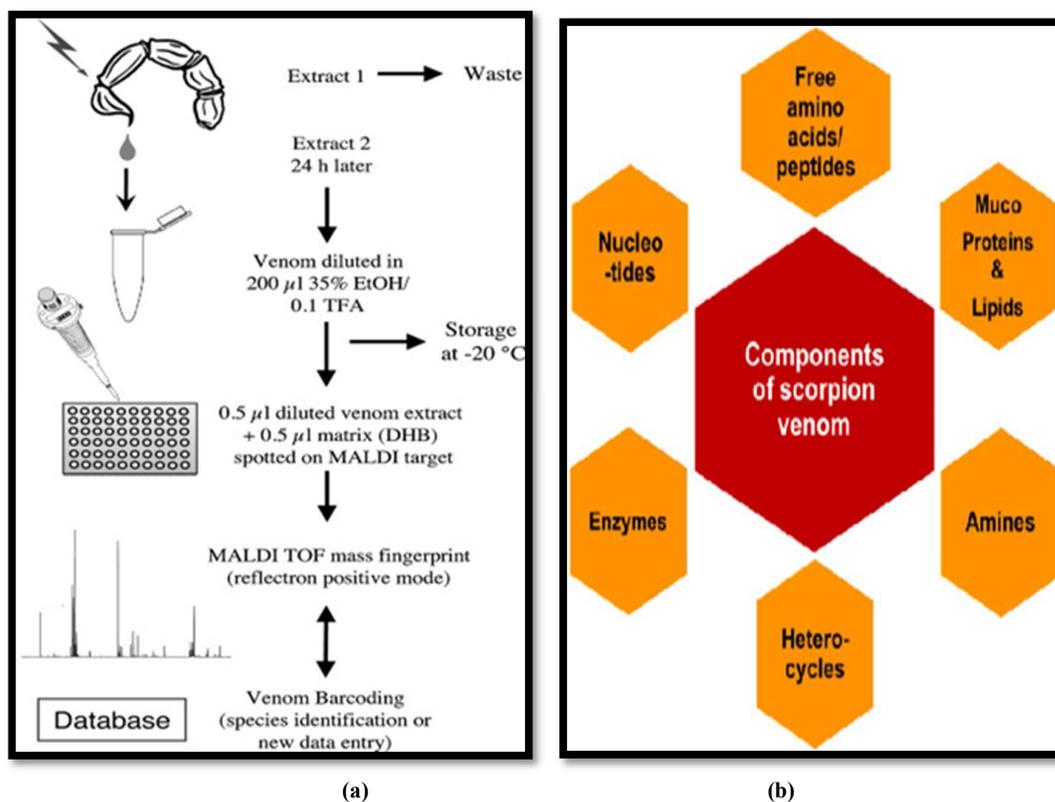


Figure 2: (a) Purification & isolation of chlorotoxin from the scorpion venom, (b) components of scorpion venom

When scorpion venom is injected into the human body, it may cause a lot of medical issues and even death. New bio-therapeutics have been developed from scorpion venom due to the presence of a large number of bioactive molecules.

The presence of several proteins, peptides, amines, and nucleotides enables the scorpion venom to act as an interesting therapeutic agent against many current and emerging diseases [13]. Isolation of the individual components of scorpion venom is necessary for the determination of their biological importance. Scorpion venom contains a diverse range of bioactive compounds (about 100,000 in number) but only 1% of these have been purified, isolated and

characterized. The separation and purification of the venom polypeptides can be performed by applying a 4-step method; it consists of pre-treating the scorpion venom solution, reasonably selecting the protein concentration before separation and purification of scorpion venom solution, use of a buffer liquid and an eluting flow rate. The introduction of recombinant DNA technology (such as transcriptome analysis), has aided in the identification of novel components; however, some components cannot be directly isolated from the venom. Neurotoxins make the major proportion of scorpion venom and are responsible for the various pathological manifestations of

envenoming [13]. Scorpion venom generally contains four kinds of neurotoxins depending upon the peptides which modulate calcium-, chloride-, potassium-or sodium-gated channels.

Peptides are generally recognized as potential therapeutics due to their high selectivity and relatively safe mode of action. Peptides purified as single compounds can be used as useful drugs at appropriate concentrations. These tiny peptides are the most studied scorpion venom components especially due to the broad ranges of their pharmacological applications and diversity. Depending upon their structural features, peptides have been grouped into 3 main superfamilies.

Non-Disulfide Bridged Peptides (NDBPS) [13]

Scorpion venom also contains amines, nucleotides, free amino acids, mixtures of inorganic salts, lipids and enzymes [21]. However, a number of technological hurdles are needed to be overcome before the commercialization of venom-derived bio therapeutics [13].

A comparison of two approaches (manual and electrical stimulation of adult scorpions) for collecting scorpion venoms on a wide scale has been published. It was found that high-quality antivenom with specific antibodies can be produced by using the gentler electrical stimulation method.

Electrical stimulation is used to acquire scorpion venom more quickly and in higher quantities; this procedure also produces venom free from hemolymph contaminants e. g., hemocyanin. However, scorpions suffer from maximal trauma and consequently hemocyanin secretion during manual obtainment. With the improvement of technology over the past century, the separation of venoms and full characterization of the individual peptides and proteins has become very easier. A typical approach for isolating and evaluating peptides and other bioactive substances from venomous. The venom of the deathstalker scorpion (*Leiurus quinquestriatus hebraeus*) can be screened for chlorotoxin and charybdotoxin. Chlorotoxin is one of the venom's most prominent peptides, with 36 residues and four disulfide bonds; it possesses the property of blocking chloride channels and is effective against cancer. Charybdotoxin is a Ca^{2+} -activated K^+ -channel inhibitor that is also active against KV1.3. The margatoxin produced by Central American bark scorpions (*Centruroides margaritatus*) is more than 20 times more effective than charybdotoxin against KV1.3 (Ki 50 pM) and has no effect on Ca^{2+} -activated K^+ channels. The margatoxin was found to be effective against delayed-type hypersensitivity (DTH) in a mini-pig model.

The Action of Toxins on Various Ion Channels

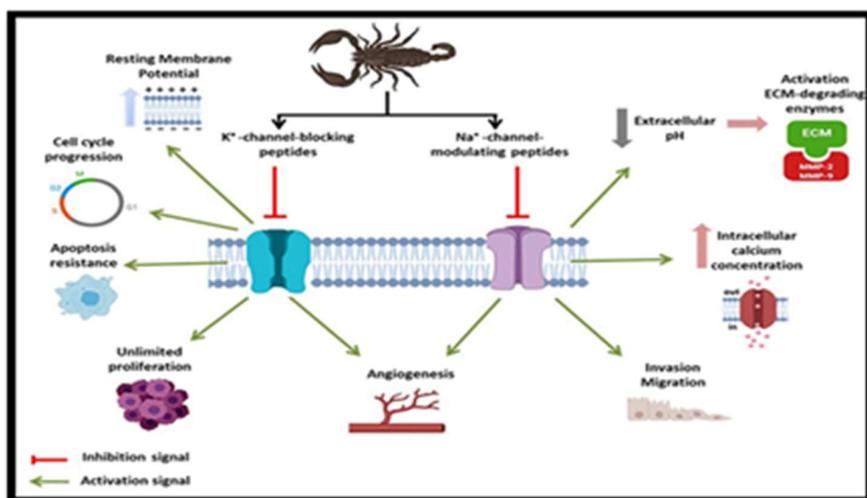


Figure 3: Mechanism of k⁺channel activity (a) closed state (b) open state (c) n-type inactivation (d) c-type inactivation

It has been reported that many toxins can change the normal functioning of K⁺ channels. It is proposed that computational studies may play a crucial role in developing ion channel drugs from venom peptides. Many short-chain peptides are blockers of potassium ion channels and cause immune suppression. While long-chain peptides are blockers of sodium ion channels and can treat pain.

Martentoxin, a pure 37-amino acid toxin was extracted from Chinese scorpion venom. It can block large-conductance Ca²⁺-activated K⁺ (BK) channels in chromaffin cells in the adrenal medulla. Martentoxin at a dose of 100 nM has the ability to strongly block the BK channels of chromaffin cells in the adrenal medulla. The BK currents blocked by martentoxin can be recovered much faster as compared to those

caused by charybdotoxin. By reversible blockage of the K⁺ channels, the toxins of Brazilian scorpions (such as *T. stigmurus*, *T. bahiensis*, and *T. serrulatus*) can limit T cell proliferation and IL-2 production. In scorpion venom, a lot of enzyme inhibitors were also reported, which help to understand the biological functions of scorpion toxins. Specific toxins present in Chinese scorpion species play an important role as protease inhibitors, antimicrobial peptides, K⁺ channel blockers, and Na⁺ channel modulators. The propagation and generation of action potentials are dependent on sodium channels.

There were investigations on the peptides that can recognize Ca²⁺-, K⁺-or Na⁺-channels of excitable cells. The most important are the peptides specific for Na⁺-channels due to their medical relevance;

they are more than 300 in number. They can detect mammalian Na^+ -channels and alter the opening/closing kinetic mechanisms of ion channels and thus cause anomalous depolarization of excitable cells. Peptides that target K^+ -channels act as pore blockers. Although they are not life-threatening, yet they block potassium permeability, cause many electrophysiological issues (as well as discomfort) and are involved in many intoxication symptoms. More than 140 K^+ -channels have been reported till now. The scorpion venom also consists of calcins (peptide toxins), including opicalcin 1 and 2, hadrucalcin, hemicalcin, maurocalcine and imperatorin, which can recognize Ca^{2+} -channels. Some of these calcins have gained popularity in designing novel drugs because they show direct interaction with ryanodine receptors. The harmful effects of these 3 peptides can be neutralized by using specific anti-venoms e.g., immunoglobulins prepared from horses.

Potential Against the Proliferation of Cancerous Cells

There have been claims that scorpion venom can be used to treat cancer. Scorpion venom is a complex mixture of peptides and proteins, most of which are neurotoxins. These toxins can bind and modulate multiple ion channels (Ca^{2+} , Cl^- , K^+ and Na^+) in excitable and non-excitable tissues. The characteristic feature of these peptides is to decrease cell proliferation and apoptosis and also to inhibit many signaling processes which result in cancer. Kv expression and apoptosis are strongly linked to potassium ion channels. The medical significance of venom is owed to the presence of a broad spectrum of ion channel toxins. Some animal venoms were successfully applied to treat breast cancer. There are reports for the treatment of thousands of cancer cases through the blue scorpion venom (endemic to Cuba). The cancer cells are attacked by the protein chain which is present in the blue scorpion venom.

Mechanism For Inhibition of Growth of Cancer Cell By

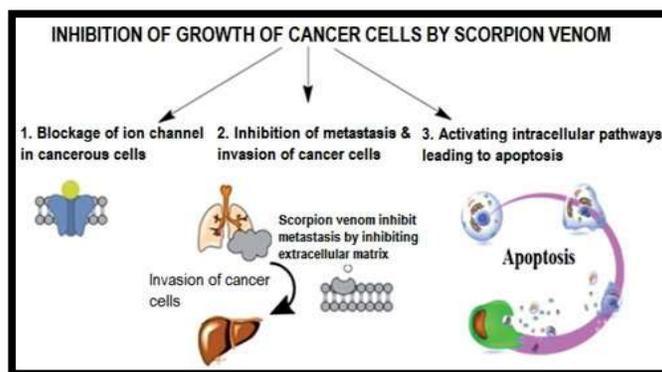


Figure 4: Mechanism for inhibition of growth of cancer cell by

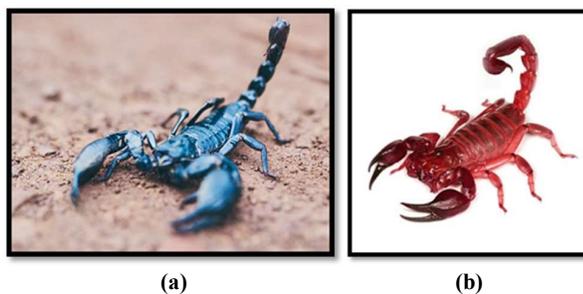
VARIOUS SCORPIO SPECIES IN CANCER TREATMENT


Figure 5: (a) Blue scorpion & (b) Red scorpion

Blue or red scorpion (*Rhopalurus junceus*) is famous due to its antineoplastic activity in the Dominican islands and Cuba. Its venom maintains energy in cancer patients and also acts as a pain reliever. The protein present in it can inhibit the proliferation and growth of cancer cells. The venom of the Blue or Red Scorpion (*Rhopalurus junceus*) also reduces the intensity of pain and restores energy in cancer patients. The venom extract of Blue Scorpion can behave as an anti-inflammatory, analgesic and anti-cancer agent. The venom of *Tityus discrepans* scorpion contains two peptides, namely neoplamine and neoplamine, which cause apoptosis in human breast cancer cells and show marked defects. The venom of *Odontobuthus doriae* has proteolytic enzymes. It possesses lactate dehydrogenase (LDH), which is a cytotoxic and apoptotic agent and can lower cell viability as it activates the caspase-3 and depolarization of mitochondria. Proteolytic and gelatinolytic proteases, which act against adenocarcinoma cell lines of human lungs are extracted from

the scorpion *Mesobuthus gibbosus*. By arresting S-phase and increasing reactive N intermediates, *Odontobuthus doriae* venom promotes apoptosis in human breast cancer cells. Peptides present in the venom of *Centruroides margaritatus* cause a reduction in tumor size.

The cell cycle, cell proliferation, and cell growth can all be influenced by various components of scorpion venom. In Cuba, the use of *Rhopalurus junceus* as traditional medicine has been reported for the treatment of cancer [17]. The venom from Indian black scorpion (*Heterometrus bengalensis*) can induce the inhibition of K562 and U937 cell growth; it also possesses the specific characteristics of apoptosis such as DNA degradation, chromatin condensation, and membrane blebbing [8]. The venom of *Leiurus quinquestriatus* (Deathstalker scorpion) contains thirty-six amino acid peptides which block the chloride channels. *Heterometrus bengalensis* contains antiproliferative and apoptogenic properties against chronic myelogenous and bengaline

[8]. The *Buthus martensia* (Chinese red scorpion) venom contains hyaluronidase (BmHYA1) which is responsible for metastasis and decreases the proliferation of

breast cancer and possesses antineoplastic therapeutics with no toxic side effects.

Potential Against HIV/AIDS

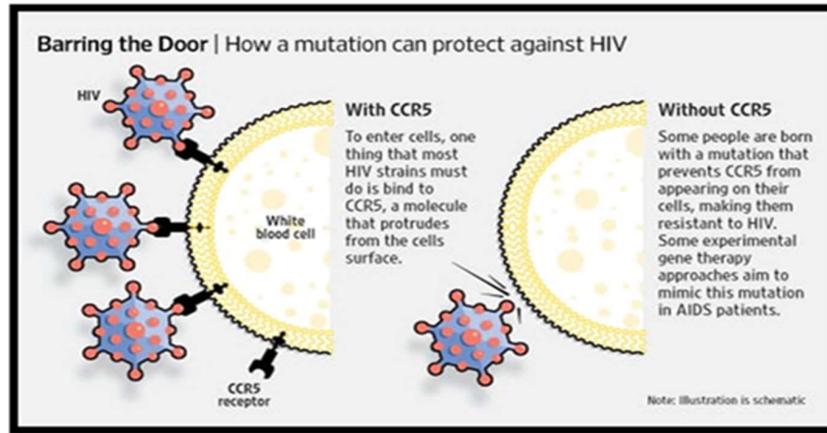


Figure 6: Potential against HIV/AIDS

One CD4 receptor and two other co-receptors (CXCR4 and CCR5) of HIV-1 can affect T cells. CCR5 is considered as the major co-receptor for the transmission of HIV-1. Kn2-7 from *Mesobuthus martensii* scorpion was recognized as an effective anti-HIV-1 peptide; it has the ability to inhibit

HIV-1 subtype CCR5-tropic, pseudotyped virus (PV) and CXCR4 tropic (NL4-3) PV strains. It was reported that the peptide Kn2-7 can protect against HIV-1 by interacting with viral components.

Potential Against Cardiovascular Diseases

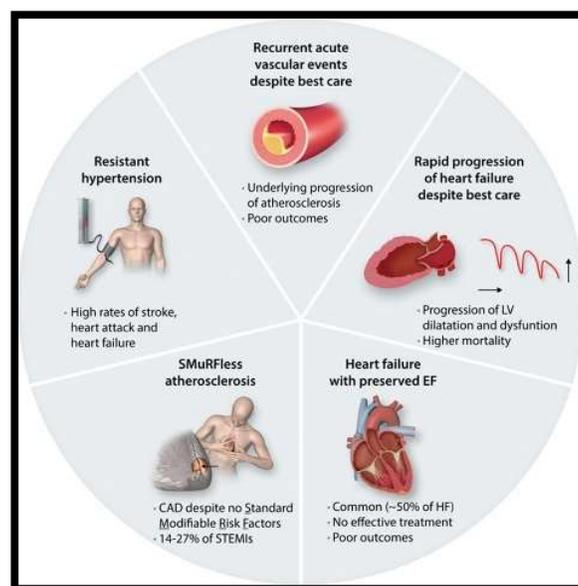


Figure 7: Potential against cardiovascular diseases

Cardiovascular illnesses are the leading cause of death in modern society. Several toxins, including integrins are present in scorpion venom, which have the ability to disrupt blood coagulations. A peptide toxin present in the venom of *Androctonus australis garzonii* can induce the atrial natriuretic peptide secretion while the venom of *Buthus martensii* scorpion contains BmK I toxin, which moderates the contraction of the heart. The venom of *Centruroides margaritatus* contains a peptide margatoxin which inhibits the voltage-dependent potassium channels. It increases

the time taken by a cell in order to execute an action potential in response to stimulation. It also affects nicotinic Ach-receptor in order to release norepinephrine which shows impacts on sympathetic control of cardiovascular function.

Potential Against Diabetes

Studies have revealed the anti-diabetic effects of scorpion toxins which also activate and generate β -islets. Scorpion venom along with Chinese drugs is used to cure diabetes.

Potential Against Malaria



Figure 8: Emperor Scorpion

Peptides (present in scorpion venom) display anti-malarial properties (through their K^+ channels) and cell breakage by restricting activity at the carbon and nitrogen terminals. The first anti-malarial peptide was isolated from the venom of *Pandinus imperator* (family: Scorpionidae). This peptide can induce 98% of deaths in *Plasmodium berghei* at its sexual state; it causes 100% of death of *Plasmodium falciparum* parasites. *Mesobuthus eupeus* contains antimalarial peptides namely meucin-13 and meucin-18 which induce

cytolytic activity in various microbes, while meucin-24 and meucin-25 inhibit the activity of malarial parasites without causing any loss/impairment of normal mammalian cells.

RESULTS AND DISCUSSION

The venoms of many animals (scorpion, frog, toad, snake, etc) and their active components (protein/non-protein toxins, enzymes, peptides, etc) possess anticancer potential [18]. Various bioactive components (such as peptides, nucleotides, amino acids and lipids) of scorpion venom

may cause severe systemic inflammation after they are injected into human beings [19]. Toxin peptides of scorpion venom greatly interact with the normal functioning of excitable/non-excitable cells; they can modify or block the ion-channel functions and thus find applications to control cell excitability. Many venom proteins find potential applications as antibiotics. The deleterious effects of venom on human beings can be neutralized by venom itself. Moreover, venom has also been found effective in the production of many antibodies in experimental animals (sheep and horse) [19]. The toxicity of scorpion venom is governed by some factors i.e. scorpion's age, genus and species, physiology, region, and feeding habits [20]. There is a very critical procedure to collect high-quality venom from scorpion. By abdomen stimulation, less toxic and transparent venom is produced but when the stimulation is done externally through electric shock the scorpion generates very concentrated toxin [18]. Both kinds of venoms (less toxic and concentrated) differ from each other in physical and chemical properties as the latter contains a high concentration of salts which greatly affect the potassium ions of the targeted creature [20]. Scorpion finds a fantastic potential against various diseases and is used to synthesize

vaccines which have ability of neutralizing several toxins. Novel methods and separation techniques have been adopted to characterize venom components; these components are highly valuable for the development of medicinal drugs. Scorpion venom is constituted of small neuro-toxic peptides, amino acids, enzymes, enzyme inhibitors, histamine, lipids and different salts [21]. Approximately 800 natural protein toxic components were listed in data banks of scorpion venoms [22].

CONCLUSION

A large number of neurotoxins are present in scorpion venom. These toxins have the ability to interrupt the normal functioning of multiple ion channels (Ca^{2+} , Cl^- , K^+ , and Na^+) in excitable and non-excitable tissues. The scorpion venom finds an immense significance in the therapy of numerous diseases, including cancer, cardiovascular diseases, diabetes, AIDS, apoplexy, paralysis, epilepsy, malaria, measles, influenza H5N1, severe acute respiratory syndrome, Herpes simplex virus type 1 infection and diabetes etc with minimum or no side effects. It can induce anti-proliferation, apoptosis, cytotoxicity, and immunosuppressive effects that mainly inhibit the growth of disease-causing cells. The cell cycle, cell proliferation, and cell growth can all be influenced by various components of scorpion venom.

Mucroporin-M is a component of venom which can be extracted from scorpion *Lychas mucronatus*; it is a good antiseptic agent for hand washes and mouthwashes due to its dual antimicrobial activity (antiviral and antibacterial). The computational studies may have a crucial role while developing ion channel drugs from venom peptides.

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