



**A REVIEW ON SCORPION VENOM: AN UNREVEALED MEDICINE FOR HUMAN
AILMENTS: GREAT SCOPE FOR PHARMACEUTICAL RESEARCH**

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ABSTRACT

Scorpion venom components have multifaceted orientation against bacterial, viral, fungal infections and other neuronal disorders. In ancient era, venoms are considered as toxic substance. But, in this era, it is used as a valuable medicine to cure certain types of diseases and disorders such as antibacterial, anti-rheumatic etc. venomous animals found worldwide except cold geographical regions. Animal venoms are complex mixtures of highly specialized toxic short peptides enzymatic in nature which exert severe pathophysiological effects. We are killing scorpions, because sting was poison but this poison also used as a medicine. An optimum concentration of scorpion venom should not produce side effects while it crosses their limit it will be poisonous. By this the study concludes that, even if the Scorpions are dangerous their venom are useful to us and instead of killing them, they can be nourished and bred for economic purposes. And by nature we have the raw material (scorpion) abundantly in our environment; instead of killing them we should utilize them properly.

KEYWORDS: Scorpion venom, Antiviral, Anti-rheumatic, Antifungal, Poison.

INTRODUCTION

Scorpions are a very ancient group that originated as terrestrial animals approximately 300 million years ago and have persisted ever since. They are widespread around the globe, present in all continents apart from Antarctica, and are adapted to a variety of environments, including high altitudes, deserts, rainforests, and cave. Some scorpion species are endemic and dependent of their original habitats' natural conditions, living in small populations with restrict mobility.^[1] In the olden days venoms are considered as poisonous substance. But in this modern era, it is used as a valuable medicine to cure certain types of diseases and disorders and used in some cosmetic preparation. Most of us want to avoid scorpions and for good reasons. But the venom in a scorpion's sting is much more than just a toxic substance. In fact, much like snakes venom, the venoms found in scorpions have a several application that could be used to save life rather than end them. For example proteins from scorpion venoms can be used in immune suppressants and anti-malarial drugs and an amino acid in scorpion venom can help clinicians more easily detect lethal bright tumours. Now researchers have discovered a type of scorpion venom which contains two compounds that can kill bacteria resistance to Antibiotics. This scorpion

called *Diplocentrus melicis* native to Eastern Mexico and lives underground most of the year, appearing only I Mexico's rainy season. Researchers isolated the compounds in the Scorpion venom and synthesised them in the Lab. They then treated the synthetic version in mice. Unfortunately, Scorpion is the most expensive liquid on the Earth. It costs around \$38,585,507.46 per gallon (3.7 litres). It's even more expensive than Thailand's King cobras venom, which costs around \$153,000 a gallon (3.7 litres). Unfortunately, the scorpion produces just 2 mg of venom at a time. Therefore, it is necessary to make synthetic version of these venom, otherwise there won't be enough to lower the cost, and no one will be able to afford the drugs. Beyond using them to fight off anti-bacterial resistant illnesses, Researchers are looking into using scorpion venom as potential pain killers as well as using a peptide from scorpion venom to suppress immune responses, allowing it to be used in the treatment of auto immune disease. Even cancer is beginning to feel the Scorpions sting. A drug called VIDATOX is obtained from blue scorpions. It is known as Cuba's miracle drug and the drug shows promising anti-cancer activity and it has been tested on more than 10000 cancer patients. So far, the drug has yielded positive results against various

cancers. Scorpion venom may not always be able to help to kill cancer. Researchers have developed a so called tumour paint using Cholorotoxin, a protein found in Death Stalker Scorpion Venom. The molecule attaches itself only to cancerous brain cells and lights them up through a florescent tag attached to the toxin. This enables doctors to pinpoint the exact location and extent of cancerous growth in the body. Scorpion venom can also block bone loss, making it a useful substance for treating condition like rheumatoid arthritis and osteoarthritis. In 2011, a 71 year old Cuban man claimed that he lets scorpions sting him at least once a month and as a result, he fends of body aches and pains. Current research on scorpion venom is progressing very slowly due to lack of large quantity of the venom to be tested. Despite the slow rate of research, it could eventually revolutionize the way we find and treat disease, as well as become an important tool in the fight against the increase in the dangerous anti-bacterial resistance super bugs. As synthesis techniques is improve, the speed of these important research topic may increase, Bringing much needed treatments closer to the hands of patients.

SCORPION FAMILY^[2]

Actually these animals are represented by 16 families and approximately 1500 different species and subspecies which conserved their morphology almost unaltered. The scorpion species that present medically importance belonging to the family Buthidae are represented by the genera *Androctonus*, *Buthus*, *Mesobuthus*, *Buthotus*, *Parabuthus*, and *Leirus* located in North Africa, Asia, the Middle East, and India. *Centruroidesspp* are located in Southwest of United States, Mexico, and Central America, while *Tityus spp* are found in Central and South America and Caribbean. In these different regions of the world the scorpionism is considered a public health problem, with frequent statements that scorpion stings are dangerous.

VENOMS

Venoms are complex mixtures of bioactive compounds called toxins that have evolved on more than 30 different occasions in the animal kingdom.^[3] Toxins are often highly specific in their activity and can induce a wide range of pharmacological effects.^[4] They can act by binding to ion-channels for example, by destroying cellular components or by disrupting metabolic pathways, which may lead to paralysis, hematological disruptions, tissue necrosis and pain. Venoms have been studied for a long time in order to better understand their physiological effects from a standpoint of development of treatment of envenomation. However, the high specificity and potency of certain toxins renders them useful as experimental tools or as candidates for the development of novel therapeutics.^[5] The field of transcriptomics has changed our understanding of the diversity and composition of animal venoms in the last decades. Venom transcriptome research focuses primarily on studying venom composition through mRNA-transcripts and their relative expression levels.

The main advantage of using transcriptomics over proteomics is the fact that the transcriptome data allows the study of patterns of gene activation through read counts, and gene evolution through the coding sequences.

Scorpions are, apart from snakes, the most widely studied group of venomous animals when it comes to their venom.^[6] This is because scorpion stings are considered a public health problem in tropical countries, with global estimates surpassing 1.2 million cases of envenoming resulting in more than 3,250 fatalities a year.^[7] Scorpion venoms are also studied as candidates of pharmaceutically active molecules with potential drug applications. Scorpion venoms are complex mixtures of proteins, peptides and small molecular compounds, with small peptides and proteins targeting ion channels being most prevalent. Because of their high specificity for these ion channel proteins, scorpion toxins are being studied for their potential use as therapeutics. As these ion channel proteins are major drug targets, scorpion venoms could be an interesting source for novel candidates in the venoms to-drugs pipeline.^[8] Scorpion venoms have been studied via proteomic approaches within the last two decades, but with the emergence of next generation sequencing (NGS) technologies, transcriptome studies have increased in popularity. The fact that the costs of next generation sequencing have decreased tremendously in recent years has revolutionized 'omics'-studies.^[8] The current method for obtaining a scorpion venom gland transcriptome is based on sacrificing the animal to extract the venom gland from the telson (the "stinger" at the end of the tail-like metasoma, containing the venom glands) or to homogenize the entire telson. Although this method of venom gland sequencing allows an in-depth analysis of the expressed genes in the venom gland, it has its limitations. One of the major limitations is the fact that this only allows analysis at a single time point, making it impossible to study the intra individual variation caused by ontogenetic stage, season or diet. Homogenization of the telson also includes tissues not involved in venom production, such as the muscles surrounding the glands, and the cuticle, making the sequencing less target-specific. Furthermore, it faces the ethical drawback and resource depletion of having to sacrifice the animal.^[9]

MECHANISM OF ACTION OF VENOM

Now that you understand how muscles work, let's take a closer look what venom does inside your cells. Scorpion venom contains a very small protein chain called chlorotoxin, only 36 amino acids long. This tiny protein has a very powerful effect though. It is perfectly shaped to block chloride channels and stop chloride ions from entering muscle cells. Without these ions sending signals telling your cells to relax, the muscles in your body all flex at once and paralysis sets in.

A computer model of scorpion venom. The colours show the different amino acids that make up the protein

molecule. The shape of a protein is very important. This is what makes it possible for a protein to interact with other proteins and parts of the cell. It's like having two pieces of a puzzle that fit together, or like having the right key for a certain lock. If a protein is not folded correctly, it doesn't have the right shape and doesn't fit with parts of the cells. Scorpion chlorotoxin, for example can be folded in at least 256 different ways. Yet only one of these works correctly to block chloride channels in your muscle cells. Scientist get samples of venom by gently squeezing a snake's jaws. This is called 'snake milking'. In nature, animals use venom for self-defence or to catch prey. In the lab, scientists are finding out that venomous proteins can be used in medicine. Researchers have had success, for example, in using scorpion venom to treat brain tumour in humans. Instead of causing harm to healthy nerve and muscle cells, venom such as chlorotoxin can be used to block signals from cancer cells. Blocking these signals prevents them from growing. Scientists have also discovered ways in which the effect of paralysis can be helpful for humans. When a patient goes into surgery, for example, it's important for their body to stay very still while the doctor performs the operation. Even a tiny movement could cause a very big mistake! So, in addition to drugs that cause sleep, patients are often given drugs that cause temporary paralysis while the doctor performs the surgery. The more we learn about proteins and their shapes, the more we understand about what might go wrong in our bodies and why. Knowing this helps researchers design better medicines and treatments.

HOW DO MUSCLE WORK

The muscles in your body are controlled by the movement of special molecules called ions. Depending on the type of ion and whether it is moving in or out of muscle cells, the cells either relax or contract. One such ion is chloride, which helps muscle cells know when to relax. When all the cells in a muscle are contracted, that muscle is flexed. This makes it possible for you to move your arms, legs and other parts of your body. Ions enter muscle cells through openings in the cell membrane called channels. These channels are made of proteins and have a specific shape that let only certain molecules or atoms pass. Chloride channels, for example, are specifically designed to only let chloride ions in and out of the cell.

THE SIGNS OF THE SCORPION ENVENOMATION ARE DETERMINED BY THE FOLLOWING^[10]

- (a) Scorpion species,
- (b) Venom composition, and
- (c) The victim's physiological reaction to the venom.

THE SIGNS AND SYMPTOMS^[11]

The victims usually have the major signs, with the most common being

- Mydriasis
- Nystagmus

- Hyper salivation
- Dysphagia
- Restlessness.

Composition of Scorpion Venom

1. Scorpion α -Toxins: The α -toxins bind to receptor site 3 of the voltage-gated Na⁺ channels of vertebrates in a membrane-dependent manner.^[12] Several studies have showed the effect and the biochemistry of these toxins. The major effects of α -toxins induce a prolongation of the action potential of nerves and muscles by fast inactivation of sodium channels receptor affinity dependent upon membrane potential.^[13]
2. Scorpion β -Toxins: The β -toxins are isolated from American scorpions, bind to receptor site 4 on vertebrate Na⁺ channels and producing a shift to a more negative membrane potential.^[14] Several studies described the mode of action of these toxins that are related with the increment of sodium. The β -scorpion toxin C_{ss} IV obtained from *Centruroides suffusus* scorpion venom is believed to specific bind in sodium channel.^[15]
3. Sodium Channels Toxins (NaTx): Voltage-gated sodium channels are critical for generation and propagation of action potentials initiation and propagation in excitable cells. These channels are targeted for neurotoxins present a large variety of chemically distinct compounds that bind to several receptor sites on the pore-forming α -subunit. With respect to scorpion toxins have been observed that they show a preference for distinct sodium channels subtypes of mammals or insects.^[16]
4. Potassium Channels Toxins (KTx): Potassium channels are part of a large variety of biological processes and also are involved in an increasing number of human pathologies. The diversity of potassium channel blockers and their therapeutic value to overcome in the potential treatment of a number of specific human diseases especially autoimmune disorders, inflammatory neuropathies and cancer.^[17]
5. Calcium Channel Toxins: Ca²⁺ ions play important roles in regulating a variety of cellular functions such as second messenger-coupling-receptor to active many cellular processes that including cellular excitability, neurotransmitter release, intracellular metabolism, and gene expression.

METHODS

Venom obtained manually

Androctonus mauretanicus (Amm) and *Buthus occitanus tunetanus* (Bot) scorpion venoms were manually milked as described by Louis. This method employs manual stimulations of the abdomen to release venom. The venoms of many scorpion specimens were pooled, lyophilized and stocked at -20°C until use.^[18]

Venom obtained electrically

Amm and Bot venoms were collected by the electrical stimulation method described by Ozkan and Filazi. A series of regular currents were applied to shock the scorpion until the venom was ejected. For that purpose, we immersed the body of the scorpion in a saline solution for better electrical conduction and gave a shock with electrode. We used a simple 12-volt battery. The venom droplet was recovered in a Petri dish after which the extract was kept frozen until use. Venom was recovered using distilled water and centrifuged (10,000 g). The supernatant was lyophilized (freeze dried), and then kept at -20°C until use.^[19]

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 anti-venom 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.^[20]

Purification and isolation of the desired component of scorpion venom:

When scorpion venom is injected into the human body, it may cause a lot medical issues and even death. New bio therapeutics has 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.^[21]

Isolation of the individual components of scorpion venom is necessary for the determination of their biological importance.^[22] 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.^[23] The separation and purification of the venom polypeptides can be performed by applying a 4-steped 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.^[24] 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.^[25] Neurotoxins make the major proportion of scorpion venom and are responsible for the various pathological manifestations of envenoming.^[26] Scorpion venom generally contains four kinds of

neurotoxins depending upon the peptides which modulate calcium-, chloride-, potassium-or sodium-gated channels.^[27]

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 super families:

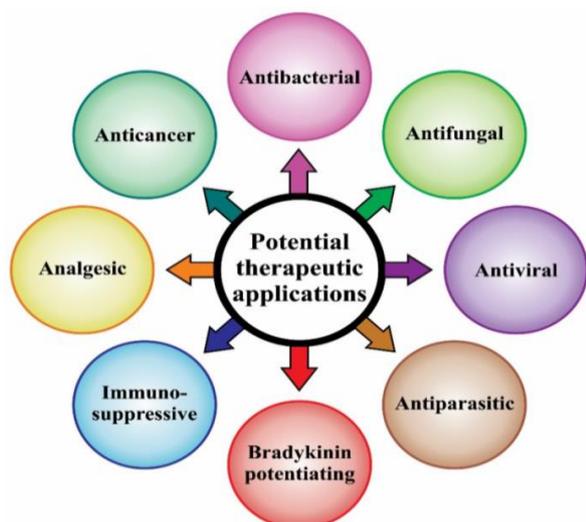
1. Calcins
2. Peptides containing cysteine-stabilized (CS) α/β motifs
3. Non-disulphide bridged peptides (NDBPs).

WHY SCORPION VENOM IS SO EXPENSIVE

The death stalker is one of the most dangerous scorpions on the planet, and what makes it so dangerous also happens to be the most expensive liquid in the earth. You couldn't just go buy a gallon of the stuff; because you can only get it in tinny, minimum amount \$130 will get you a droplet that's smaller than a grain of sugar. The reason why is pretty simple. The stuff is hard to get. Scorpions are almost always milked hand, one by one and one scorpion produces, at the most, just 2 milligrams of venom at a time. If you owned one scorpion and milked it every two days, it would take you 10,371 years to fill up that gallon. There are actually tons of useful components that are helping pioneer break through medicines. Chlorotoxins, for example, are the perfect size to bind with certain cancer cells in the brain and spine, which is helpful for identify the specific size and location of the tumours. And research has used scorpion to eliminate malaria in mosquitos. Kaliotoxin has been given to rats to fight in bone disease. Scientist hope it could works in humans too. These are just a few of the medical benefits that researchers have found in scorpion venom. And the more they research it, the more uses they find. Which means demand for this miracle venom continuous to grow? So scientists are now trying to figure out ways to get more of it faster.

Scorpion Venom in Medicine

Disulphide-bridged peptides (DBPs/DBs) and non disulphide-bridged peptides (NDBPs/NDBs) are the important constituents of scorpion venom that display various pharmacological activities. Several advancements to characterize the structure, properties and pharmacological activities of disulphide-bridged neurotoxic peptides have been carried out successfully till date. NDBPs were out of the limelight till the last decade and henceforth with their remarkable activities have mustered enough attention from researchers. These peptides are flexible, usually cationic, potent antimicrobials, α -helical and amphipathic.



As Antimicrobial:

Mucroporin, scorpine, hadrurin etc. are some antimicrobial peptides (AMP) obtained from scorpions that have broad-spectrum activity against viral pathogens namely rotavirus, measles virus, adenovirus etc. Mucroporin derivative mucroporin-M1 (from the venom of scorpion *Lychas mucronatus*) has proven to possess antimicrobial activity against bacteria and measles virus and Hadrurin (from scorpion *Hadrurus aztecus*) inhibits the growth of gram positive and gram negative bacteria. Antibiotics (amoxicillin, cefuroxime, and erythromycin) in combination with Parabutoparin (from scorpion *Parabuthus Schechter*) and Opistoparin1 (derived from African yellow leg scorpion *Opisthophthalmus carinatus*) display synergistic antibacterial activity. Parabutoparin is an antibiotic peptide obtained from scorpions with significant immunoregulatory effects. BmKn2, another NDBP identified in *Buthus martensii* Karsch established itself of being a satisfactory antimicrobial candidate against both gram negative and positive bacteria. Stigmurin and TsAP-2, two NDBPs from scorpion *Tityus stigmurus* exhibited bactericidal and bacteriostatic activity in a study conducted by Daniele-Silva et al and both were potent in controlling sepsis in lung and caecum of animals.

As Neurotoxins:

Scorpion neurotoxins can bind effectively for a long time because they have a three-dimensional backbone that is highly stable by the presence of three or four DBs. Compounds present in scorpion venom mostly target the nervous system. *Buthus martensii* Karsch (BMK, Family: Buthidae) scorpion or Chinese scorpion has been widely used as “ethnomedicine” in China in the treatment of neurological diseases that includes cerebral palsy, epilepsy and apoplexy. Antinociceptive effect had been observed with Bmk AS (obtained from *Buthus martensii* Karsch) in sensory nerves. Other scorpion derived toxins that exhibit antinociceptive activity include α -anatoxin, Amm VIII and β -toxin LqqIT2. Envenomation associated death of individuals is due to

cardiovascular toxicity causing catecholamine release which initiates pulmonary oedema finally cardiac arrest. The venom of scorpion *Leiurus quinquestriatus* develops synergistic effect along with alkaloid neurotoxins like veratridine, batra - chotoxin and aconitine in the regulation of action potential. Reversible heterotrophic cooperation between the site of action of the neurotoxins and venom toxin reorients the properties of Na⁺ ionosphere by non-covalent interactions. Presently, researchers at the University of Colima (UCOL) have investigated on animal model that scorpion venom toxins have an effect on the release of dopamine when attached to receptors on dopaminergic neurons. This release of dopamine can be a cure for Parkinson’s disease (a condition when dopamine release is inhibited and muscle movement is prevented).

As Antimalarial:

Antimalarial activity is exhibited by peptides that have cytolytic and K⁺ channel blocking activity at the N- and C-terminus respectively. Scorpine, a DBP, was the first described antimalarial peptide isolated from the venom of Emperor Scorpion, *Pandinus imperator* (family: Scorpionidae) (Ortiz et al. 2014). This peptide at 15 and 5 mm concentrations respectively displayed 98% death in sexual staged *Plasmodium berghei* and 100% depletion of *Plasmodium falciparum* parasites. AMPs meucin-13 and meucin-18 reveal cytolytic activity on bacteria, fungi and yeasts while meucin-24 and meucin-25 (obtained from genetic sequences in venom gland) have intense activity in the inhibition of malarial parasites without impairing normal functioning of mammalian cells. Meucin-18, pandinin 2, ctriporin are some NDBPs that have an inhibitory role in the growth of fungus *Candida albicans* (responsible for candidiasis infection in humans); yeast *Saccharomyces cerevisiae* can be inhibited by parabutoparin, opistoparin 1 and meucin-18.

Bradykinin Potentiating Activity:

Bradykinin potentiating scorpion venom peptides are devoid of disulphide bridges and enriched with proline residues at the C-terminus. Studies report that proline enrichment at the C-terminal end contributes in its increased bradykinin potentiating activity. A unique characteristic of these peptides is that their functioning involves a synergistic action or bradykinin proteolysis prevention. The thirst to excavate bradykinin potentiating arthropod venom peptides that activate argininosuccinate synthetase is ongoing as they can act as potential targets to reduce arterial blood pressure (Camargo et al. 2012). Venom extracted from scorpions *T. serrulatus* and *B. occitanus* contain bradykinin-potentiating peptides (peptide T and K12 respectively). Peptide T was the first discovered NDBP that was capable of initiating in-vivo bradykinin activity. These peptides are notable for being strong hypotensive agents. Further studies on *T. serrulatus* reveal that its bradykinin potentiating activity regulates blood pressure as bradykinin receptor synthesis and ACE activity is averted. The first member of T.

serrulatus hypotension family, TsHpt1, achieved success as an initiator of hypotensive effect of bradykinin in normal rats. TsHpt1 ([17–25]), a synthetic analog designed using the C-terminal peptide of the native member and both compounds showed bradykinin independent hypotensive activity. Bmkbpp, a bradykinin potentiating peptide was identified by cDNA cloning from scorpion. (2017) conducted a study to illustrate the bradykinin potentiating activity of three Iranian scorpions namely *Hottentotta saulcyi*, *Odontobuthus doriae* and *Mesobuthus eupeus* and demonstrated their effect using organ bath instrument on Guinea pig ileum and rat uterus tissues.

As Antineoplastic Agent:

Natural therapy, be it plant or animal derived, is occupying a vast section gradually as antineoplastic or cytotoxic agent due to the increasing uncontrollable adverse effects and ineffectiveness (possibly in metastasis and recurrence conditions) of chemotherapy and radiotherapy. The last three decades have seen attempts at detecting promising anticancer activity of animal venoms and toxins, some of which are presently under clinical trial. Scorpion venom can be an amazing therapeutic agent against cancer as it inflicts upon cancer cells by arresting cell cycle at the S-phase thereby acting as a proliferative curb. SVTs are an inducer of apoptosis, aggravates neoplastic cells by amplifying production of nitric oxide, shows caspase-3 activity and depolarizes mitochondrial membrane. Presently, positive results from in-vivo, in-vitro examination and Phase I and II clinical trials have proven SVTs as anticancer therapeutic agent. Cuba and Dominican Republic islands dwelling Blue (or Red) Scorpion (*Rhopalurus junceus*) is steadily gaining fame as an antineoplastic and is the thrust area for inquisitive researchers as numerous experiments are being executed on this arthropod to evaluate its pharmacological aspects. A protein constituent of this scorpion can abolish cancer cell proliferation. Natives of the Caribbean island have been using this venom as an antitumor agent since 1997. Novel discovery elucidates venom of this scorpion acts as a pain reliever and replenisher of energy in cancer patients (Lorenzo *et al.* 2012). A recent research work proposed by Diaz Garcia *et al.* (2017) on treatment recalcitrant Triple Negative Breast Cancer (TNBC) cell line (MDA-MB-231) demonstrated high cytotoxic activity of this arthropod venom breaking grounds for new therapeutic approaches. Traditionally used, venom of BMK scorpion is a possessor of multiple pharmacological activities including cancer and brain tumor (found effective against brain tumor cell line U251-MG). Antitumor-analgesic peptide (AGAP) obtained by the application of recombinant DNA technology from this scorpion venom and expressed in *Escherichia coli* have confirmed to have both analgesic and antitumor activity in mice. This peptide in a much lower dose compared to other antineoplastic agents has revealed of increasing antitumor activity with very few adverse effects. It can inhibit glioma cell proliferation by regulating their ion

channels (Gomes *et al.* 2010). A peptide isolated from this scorpion has proven to be an anti-thrombotic and another polypeptide having dose-dependent inhibitory activity arrested cell cycle of prostate cancer cell line DU-145 at G1 phase.

In Other Fields of Medicine:

Scorpions, the age-old arthropods possessing venoms were first utilized in the field of medicine in 1909 as anti-venom or rather antibody to scorpion stings. Highly toxic venoms with elevated LD50 value are considered effective when formulated as anti-venoms. Further investigations on this ejected fluid have turned fruitful in its manifold application in medicine. Doctors prefer using the venom as an anesthetic by paralyzing the body when performing long-term surgery. The venom of *Uroplectes lineatus* finds clinical application in the field of dermatology. A possessor of hyaluronidase, scorpion venom inhibits hyaluronan (important because of its metastasis causing capacity) present in breast cancer cell lines. Increase in calcium ion influx or rather an immunomodulatory role of NDBPs is another notable activity of SVTs (Daniele-Silva *et al.* 2016). Examples include peptides parabutopirin and opistopirin that indulges in modifying productivity of superoxide, chemotaxis at concentration 10⁻⁷ to 10⁻⁶ M. Pantinin-3, a cysteine-free peptide from venom of scorpion *Pandinus* can inhibit the growth of pathogen S13, a vancomycin resistant *Enterococcus* (VRE) and causative organism of many human infections; thus gaining notice in the treatment of VRE infections. Toxins with short-chains act as potassium voltage-gated channel blockers thereby reducing T-lymphocyte (T-cell) proliferation and this principle is applied in the treatment of autoimmune disorders like rheumatoid arthritis. These toxins are sources of peptidyl inhibitors of potassium channels of which some possess anti-inflammatory and anti-proliferative role by depolarizing human T cells.

Potential against the proliferation of cancerous cells:

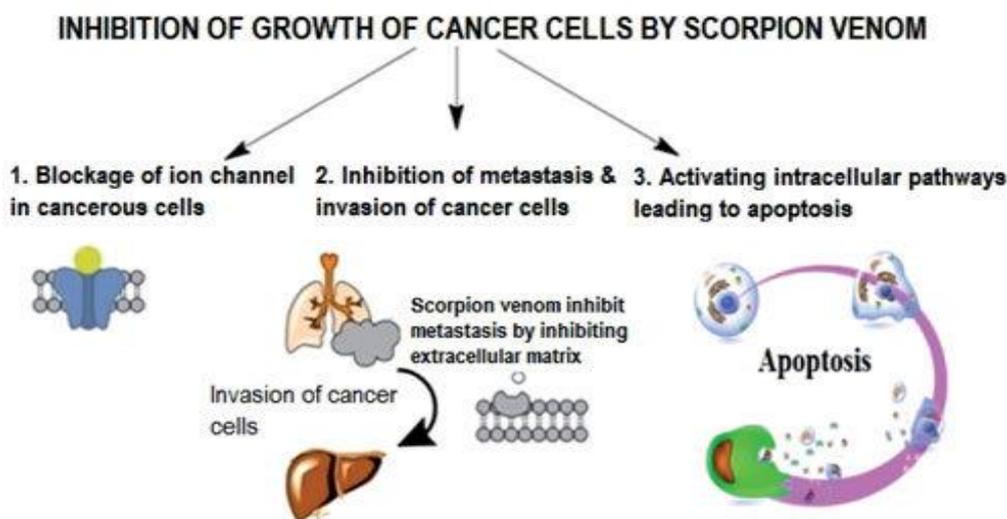
There have been claims that scorpion venom can be used to treat cancer.^[28] Scorpion venom is a complex mixture of peptides and proteins, most of which are neurotoxins. These toxins can bind and modulate multiple ion channels (Ca²⁺, Cl⁻, K⁺ and Na⁺) in excitable and non-excitable tissues.^[29] The characteristic feature of these peptides is to decrease cell proliferation and apoptosis and also to inhibit many signalling processes which result in cancer. Kv expression and apoptosis are strongly linked to potassium ion channels.^[30] The medical significance of venom is owed to the presence of a broad spectrum of ion channel toxins. Some animal venom were successfully applied to treat breast cancer.^[31] 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.^[32]

Various scorpion species in cancer treatment

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.^[33] 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.^[34] The venom of *Tityus discrepans* scorpion contains two peptides, namely neopladine and neopladine, which cause apoptosis in human breast cancer cells and show marked defects.^[35] The venom of *Odontobuthus doriae* has proteolytic enzymes. It possesses lactase 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*.^[36] 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 tumour size.^[37]

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.^[38] 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. The venom of *Leiurus quinquestriatus* (Death stalker scorpion) contains thirty-six amino acid peptides which block the chloride channels. *Heterometrus bengalensis* contains anti-proliferative and apoptogenic properties against chronic myelogenous and bengaline.^[39] 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.^[40]



Potential against HIV/AIDS

One CD4 receptor and two other co-receptors (CXCR4 and CCR5) of HIV-1 can affect T cells.^[41] CCR5 is considered as the major co-receptor for the transmission of HIV-1.^[42] 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.^[43]

Potential against herpes simplex virus

The herpes simplex virus type 1 can infect human epithelial tissues, causing a variety of problems like blinding keratitis, encephalitis, oral mucosal lesions and meningitis.^[44] HSV-1 greatly infects the sensory ganglia. The venom of *heterometrus petersii* (scorpion) contains

cationic peptides, which are effective against Herpes simplex virus type 1 infection. Both Hp1239 and Hp1036 peptides exhibit extracellular viricidal effects, morphological changes and strong inhibitory potential against HSV-1 when they are added to the infectious site. Some activities, such as viricidal activities and membrane penetration (which cause intracellular anti-viral effects) are related to amphipathic α -helix. The peptides of scorpion venom can make viral particles inactive and thus inhibit viral proliferation at the post-infection stage.^[45]

Potential against measles, influenza H5N1, Severe acute respiratory syndrome

RNA viruses cause diseases such as measles, influenza H5N1, and SARS-CoV, which are responsible for mortality and morbidity in children. Available treatments

for measles viral infection possess varying side effects, such as anemia and teratogenicity.^[46] Many approaches such as adenosine, peptide inhibitors, guanosine nucleosides, coumarins, modulators of cholesterol synthesis, brassinosteroids, and anti-sense molecules have also been failed.^[47]

A famous cationic peptide, namely mucroporin is found in the scorpion venom of *Lychas mucronatus*; it shows bacteria inhibition. Gram-positive bacteria are efficiently inhibited after the substitution of their amino acid with Mucroporin-M1.^[48] Hp1090 (a helical peptide in scorpion venom) acts as infection initiation and inhibits replication of HCV.^[49] Mucroporin-M1 shows activities against bacteria and viruses. The dual antimicrobial activity of this peptide enables it to be used as a good antiseptic agent for hand/mouthwashes. Mucroporin-M1 blocks the functions of SARS-CoV, influenza, H5N1, and MeV by direct viricidal action.^[50]

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.^[51] 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.^[52]

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.^[53]

Potential against epilepsy

For the treatment of epilepsy, various antiepileptic drugs (AEDs) are used, which cause severe side effects, including teratogenesis, sedation, chronic toxicity, and cognitive impairment.^[54] The specific peptides present in the venom of Chinese scorpion-*Buthus martensii* Karsch find applications as effective AEDs. The scorpion's entire body, particularly its tail, has been used in Chinese medicine to treat nervous disorders such as epilepsy, paralysis, and apoplexy.^[55] The neurotoxins present in venom have a 3D backbone that helps them to bind efficiently for a long time. The venom of *Leiurus quinquestriatus* with alkaloid neurotoxins causes synergistic effects to regulate the action potential. When scorpion toxins are attached to receptors on dopaminergic neurons, then release of dopamine is

observed, which may be effective for curing of Parkinson's disease.^[56]

Potential against malaria

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.^[57] *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.^[58]

Future Prospects in Drug Discovery

The increment in newer techniques in the field of Research and Development (R&D) have led scientists to brood over to find cure from nature be it from plant or animal. A rough estimate brings forth the fact encompassing constant usage (nearly 40%) of Nature in the formulation of pharmaceuticals. With the evolution of proteomics, genomics and transcriptomics, drug discovery from Nature and her resources has been a splendid approach. Though only a handful of 'biologically important' toxins could be derived from toxin-secreting animals still it calls for a revolution to fetch cure from these animals. Thus, it is mandatory to gain a thorough knowledge of the evolutionary history and the ecology of these animals before putting them into practice for the development of future pharmaceuticals.

The process of establishing a chemical entity as a clinical candidate is an enormous and time-consuming process. Thousands of potential candidates are screened and only a few with potentialities emerge to face challenges in the pharmaceutical market. Till date, only a few venom peptide derived drugs have been approved by the FDA and furthermore are undergoing clinical trials or at the stage of pre-clinical development. Captopril, ziconotide, atracurium, eptifibatid are some of the established drug products formulated from venom toxins (Harvey 2014). The synergistic property exhibited by K^+ salt and peptide (scorpion pre-venom and venom constituents) indicates the discovery of effective pharmaceuticals in the near future. Drugs and pharmaceuticals tend to have an affinity towards the ion channels of our body in conserving human physiology and usually, therapeutic advancement is being made by targeting these channels. Venom peptides being reservoir of chemical components are the tools to identify or characterize the function and structure of ion channels of our body. The rationale underlying the choice in targeting ion channels lies in their increased accessibility and success in delivering intended pharmacological activity upon being targeted by traditional or novel drug. The failure of a drug

candidate or a new drug application (NDA) often lies in the interaction with unrelated targets or channels. The key to ion channel drug discovery is embedded in the approaches that include in-vivo, in vitro targeting by the candidate drug product and other traditional drugs. Ziconotide, one such example, was developed to treat pain induced by intrathecal administration and by in vivo methods, was hence confirmed to treat pain as a calcium channel blocker. Voltage-gated sodium channels have enormous contribution in blooming of metastasis as many cancers are enriched with these channels. It is said that potassium channel has ardent activity in promoting proliferation of tumors cells and SVTs being bona fide blockers of the K⁺ channels can be highly efficacious as active pharmaceutical agents. This channel seldom acts as therapeutic target in the diagnosis of cardiovascular diseases, autoimmune disorders and inflammation (Bergeron and Bingham 2012). Reports confirm that Ca²⁺ signaling and Ca²⁺ channel expression are often associated with cancer proliferation and metastasis. Innumerable Ca²⁺ channels mark heart diseases and migraine (Niemeyer et al. 2001). Venomous animals are enriched with diverse venom components and are proficient in targeting voltage-gated ion channels; favouring analysis of these channels and their isoforms (Israel et al. 2017). Noxiustoxin, the first K⁺ channel blocker isolated from scorpion *Centruroides noxius* dates back to more than 30 years. SVT components that modify sodium channels were first identified as neurotoxins that abolish specific channel activity (Zhu and Gao 2006). The sodium and potassium channel aiming SVTs are composed roughly of 60–76 amino acids with disulphide bridges and 30–39 amino acids respectively (Petricevich et al. 2013). Long-chain SVTs that exert their effect on vertebrate voltage-gated sodium channel (Gwee et al. 2002; Petricevich et al. 2013) are of two types— α -toxins and β -toxins (Petricevich et al. 2013) (Fig. 3); α -toxins bind to receptor site 3 lingering the inactivation of the channel (Gwee et al. 2002) and β -toxins to receptor 4 that boosts up the activation of the channel (Gwee et al. 2002). The K⁺ channel toxins are accordingly classified into α , β and γ potassium toxins on the basis of their cysteine pairing and sequence identity (Dutertre and Lewis 2010). K⁺ channel SVTs bind reversibly to the exterior portion of the channel hindering the passage of ions through the membrane (Gwee et al. 2002; Petricevich et al. 2013). The sole selective inhibitor of K⁺ channel is iberiotoxin (obtained from the scorpion *B. tamulus*) (Gwee et al. 2002). Peptide components of venom collected from the scorpion *Buthotus hottenta* were the first to exert activity over the ryanodine receptor (receptors that release stored calcium from endoplasmic or sarcoplasmic reticulum) (Quintero-Hernández et al. 2013). Ryanotoxin, another peptide that can induce the receptors to a state, was purified from scorpion *Buthotus judaicus* (Quintero-Hernández et al. 2013). Venom peptides from *Pandinus imperator* have high affinity for the ryanodine receptor (Quintero-Hernández et al. 2013). Researchers persistently ponder over to reshape a drug candidate to act as ligand to other

receptors and a new therapeutic approach is thus achieved (Burke 2015). A venom toxin with therapeutic approach can be modified by making amendments in its outer coating or by orienting its release kinetics such that it acts as a prodrug at the time of administration and upon contact with its substrate exhibits its activity (Zargan et al. 2011). In spite of being a potent bradykinin, potentiator, TsHpt1 (Ts14), on further examination was found to exert anti-inflammatory, proangiogenic and anti-fibrogenic activities thereby proposing to be a drug candidate for chronic diseases.

CONCLUSION

In ancient times, scorpion venom was deemed toxic and poisonous, leading to its exclusion from medical use. However, through extensive research and advances in technology, the venom has undergone a careful extraction process to eliminate its harmful effects. Today, it has emerged as a valuable resource employed by cosmetic industries and pharmaceutical manufacturers for the development of drugs to tackle various human ailments.

Considering the abundance of scorpions present in our surrounding environment, it is indeed worth pondering whether an alternative approach could be pursued. Rather than inadvertently harming these creatures when they cross our path, one could explore the potential of breeding scorpions for their valuable venom.

The diverse applications of scorpion venom range from pain management and immunotherapy to anti-cancer treatments. Researchers have discovered unique biochemical compounds within the venom that exhibit remarkable healing properties once isolated and purified. Exploiting this abundant resource could significantly contribute to advancements in medical science.

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