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COMPONENTS AND DIAGNOSIS OF SCORPIO NVENOM AND MEDICAL IMPORTANT

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ABSTRACT

Thisreview presents both the detrimental and beneficial properties of scorpion venom toxinsand discusses the newest advances within the development of novel therapies against scorpion envenoming and the therapeutic perspectives for scorpion toxins in drug discovery.

KEYWORD: Theoretical research, Scorpion, venom, sting, diagnosis, morphology, species and medical importance.

INTRODUCTION

Scorpions, belonging to the order Scorpiones, are fascinating arachnids characterized byeight legs, a pair of grasping pincers, and a distinctive segmented tail ending with a venomous stinger or "telson"(Mullen et al., 2019).

With over 1500 recognized species, scorpions are widely distributed in hot, dry areasaround the world rpions are the most primitive arachnids that exist on the earth for 430 millions of years. They are the most venomous arthropods that belong to class Arachnida of phylum Arthropoda. These animals are found in all continents except Antarctica. They are adapted to survive in several habitats such as tropical forests, temperate forests, grasslands, savanna, and caves. All species are nocturnal, hiding during the day understones, tree barks, in loose tiles of hut, inside empty shoes, crevices of windows and doors. Scorpions belonging to Buthidae family are more toxic and medically important Theycause health problems in subtropical and tropical regions. Scorpion venom is the key to their success which ensures their survival by defending themselves from preys, predators, and competitors. Exploitation of natural resources by expansion of human population increased the interaction with arthropods, which increases the incidents of scorpion stinging. Globally, there are 2231 various scorpion species, consist of 208 genera representing in 20 families, from which 1500 scorpion spe- cies are venomous and approximately 50 species are extremely harmful to humans(Saadia Tobassum et al., 2018).

AIM OF THE STUDY

1/Collecting modern information about scorpions inIraq.
2/Explaining the medical importance of scorpions.
3/Components of scorpion venom.
4/Modern diagnostic methods

Scorpion in Iraq

Iraq harbours a lot of scorpion species (Rastegar et al., 2016)

- **Androctonus crassicauda**
- **Buthacus leptochelys**
- **Compsobuthus jakesi**
- **Compsobuthus mathiesseni**
- **Compsobuthus werneri**
- **Hottentotta jaykari**
- **Hottentotta mesopotamicus**
- **Hottentot scaber**
- **Hottentotta schach**
- **Hottentotta saulcyi**
- **Leiurus quinquestriatus**

- **Mesobuthus caucasicus**
- **Mesobuthus eupeus**
- **Odontobuthus doriae**
- **Orthochirus iraqus**
- **Orthochirus**
- **scrobiculosus**
- **hemiscorpius**
- **hemiscorpius**

Androctonus Crassicauda.

Buthacus Leptochelys.

Scorpion in the world

- Scorpion in kuwait(Amr, 2021)
- Acrassicauda
- Compsobuthus Arabicus
- *Apistobuthus pterygocercus*
- *Leiurus quinquestriatus*
- *Scorpio maurus*

Scorpion in Iran (Jalali et al., 2014)

- Androctonus crassicauda
- Mesobuthus eupeus
- Hemiscorpius acanthocercus

Scorpion in Japan (Kawai, K., 2021)

- Liocheles australasiae
- Isometrus maculatus

Scorpion in Jordan (Amr, 2017)

- Leiurus jordanensis
- Leiurus quinquestriatus
- Buthotus judaicus

Scorpion in USA (Gouge et al., 2018)

- Pandinus imperator
- Heterometrus swammerdami
- Androctonus australis

Scorpion in Egypt (Abd El et al., 2019)
- S. marus palmatus
- Leiurus quinquestriatus

Scorpion in turkey (İnanç et al., 2014)
- Androctonus crassicauda
- Mesobuthus sp
- Protoiurus kraepelini

Scorpion in Japan (Kawai, K., 2021)
- Androctonus crassicauda
- Mesobuthus sp.
- Protoiurus kraepelini

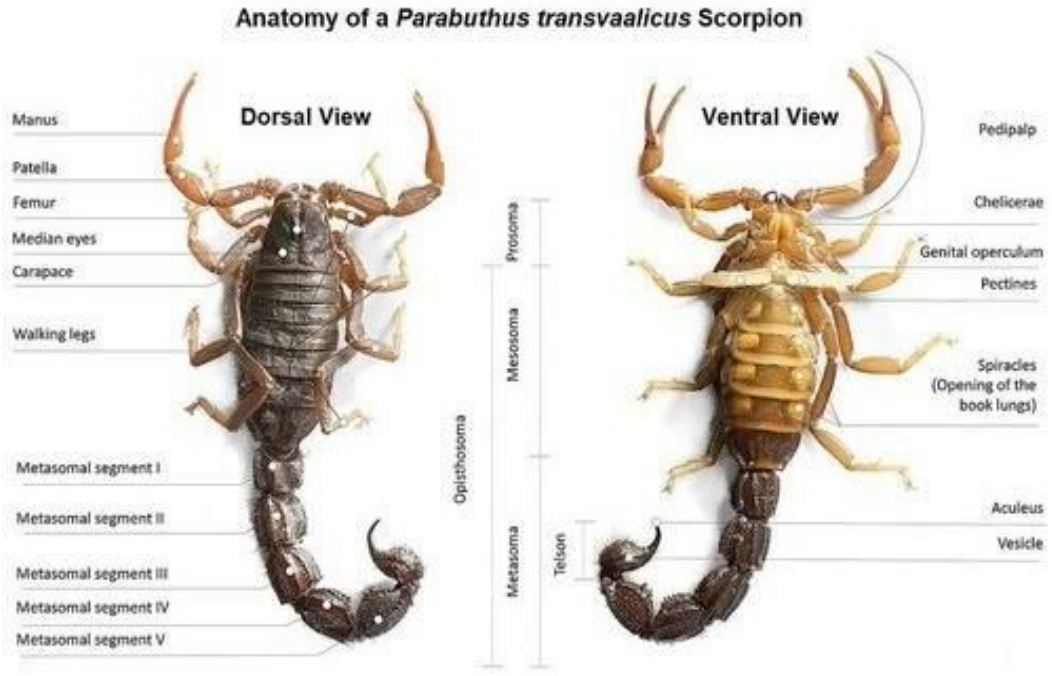
Ecology And Habitats

Scorpions are largely nocturnal and hide during the day in the confines of their burrows, in natural cracks, or under rocks and bark. Individuals become active after darkness has fallen and cease activity sometime before dawn. Because scorpions fluoresce under ultraviolet light, biologists can study their natural behaviour and ecology by using portable camping lights equipped with ultraviolet (black-light) bulbs. On a moonless night, scorpions can be seen at distances of 10 metres (33 feet). Scorpion habitats range from the intertidal zone to snow-covered mountains. Several species live in caves, with one species (Alacran tartarus) found at depths of more than 800 metres (2,600 feet). Some species have specific habitat requirements. For example, sand-dwelling (psammophilic) species exhibit a morphology that both adapts and restricts them to living in this substrate. Movable bristles (setae) form combs on the legs that increase the surface area and allow them to walk on sand without sinking or losing traction. Lithophilic ("stone-loving") species such as the South African rock scorpion (Hadogenes troglodytes) are found only on rocks. They possess stout spinelike setae that operate in conjunction with highly curved claws to provide the legs with a strong grip on rock surfaces. They can move rapidly along surfaces at any angle, even upside down. Other species show adaptability in habitat use. (Sridhara et al., 2016).

Scorpions live in the desert

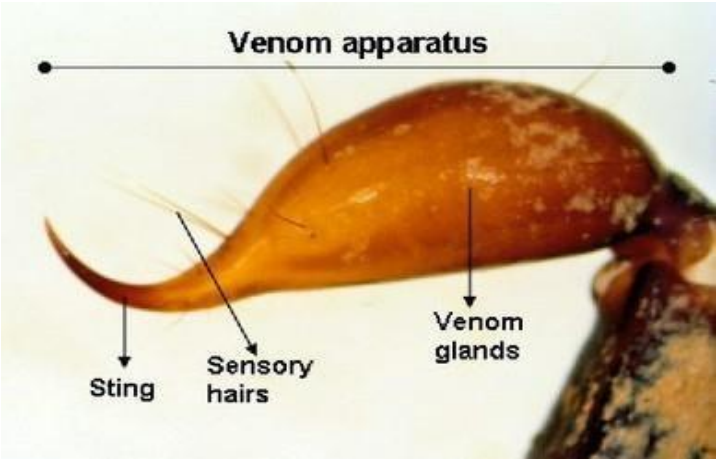
Scorpions live in mountains and caves

MORPHOLOGY



Scorpions range in size from the 8.5 mm (0.33 in) Typhlochactas mitchelli of Typhlochactidae, to the 23 cm (9.1 in) Heterometrus swammerdami of Scorpionidae. The body of a scorpion is divided into two parts or tagmata: the cephalothorax or prosoma, and the abdomen or opisthosoma. The opisthosoma is subdivided into a broad anterior portion, the mesosoma or pre-abdomen, and a narrow tail-like posterior, the metasoma or post- abdomen. External differences between the sexes are not obvious in most species. In some, the metasoma is more elongated in males than females. The cephalothorax comprises the carapace, eyes, chelicerae (mouth parts), pedipalps (which have chelae, commonly called claws or pincers) and four pairs of walking legs. Scorpions have two eyes on the top of the cephalothorax, the central eyes are amongst the most light sensitive in the animal kingdom, especially in dim light, which makes it possible for nocturnal species to use starlight to navigate at night. The chelicerae are at the front and underneath the carapace. The pedipalp is a segmented, clawed appendage used for prey immobilization, defense and sensory purposes(Gherghel, I., 2016).

The telson includes the vesicle, which contains a symmetrical pair of venom glands. Externally it bears the curved stinger, the hypodermic aculeus, equipped with sensory hairs. Each of the venom glands has its own duct to convey its secretion along the aculeus from the bulb of the gland to immediately near of the tip, where each of the paired ducts has its own venom pore. An extrinsic muscle system in the tail moves it forward and propels and penetrates with the aculeus, while an intrinsic muscle system attached to the glands pumps venom through the stinger into the intended victim. The stinger contains metalloproteins with zinc, hardening the tip. Theoptimal stinging angle is around 30 degrees relative to the tip(Chakravarthy et al., 2016).



Shape and parts of the scorpion's venom gland

Prevalence of scorpion

Scorpion exhibit a remarkable global distribution, inhabiting all major landcontinental masses with the exception of Antarctica. Their adaptability allows them to thrive in diverse climates and terrains, contributing to their presence in regions such as North Africa, Southern Europe, the Middle East, Southern Central Asia, North and South America, and beyond(Lourenço et al., 2003).

Prevalence of scorpion stings

Scorpionism (scorpion stings) is very harmful to humans and cause severe health problem in tropical regions. Worldwide there are 1.2 million cases of stings which results in approxi mately 3250 deaths per year. There is a high preva lence of mortality related to scorpionism in developing countries compared to the developed countries due to the low socio-economic status and inadequate health facilities. However, age, venom dosage, nutritional state, geographical area, and season of the scorpion, as well as weight and ageof the victim, indi vidual sensitivity, and site of sting are important parameters which affect the severity of envenomation.

Scorpion sting on the hand.

Scorpion sting on the feet.

Characteristics and Side Effects

Accidents caused by scorpion stings are a relatively common event in subtropical and tropical countries and can cause lethal envenomation in humans, especially in children. The signs of the scorpion envenomation aredetermined by the following:

(a) scorpion species, (b) venom composition, and (c) the victim's physiological reaction to the venom. The symptoms of the sting start immediately with a few minutes after the sting and usually progress to a maximum severity within 5 hours. At this period the massive release of neurotransmitters results in sweating, nausea, and vomiting. The victims usually have the major signs, with the most common being mydriasis, nystagmus, hypersalivation, dysphagia, and restlessness. They may exhibit signs and symptoms involving the central nervous system, stimulation of the autonomic nervous system, and occasionally, respiratory and heart failure, and even death. After stings by dangerous scorpions from different parts of the world the signs and symptoms are similar. The victims of scorpion envenoming that presented multi-system-organ failure characterized by changes in hormonal environment with a massive release of counter- regulatory hormones, such as catecholamine, glucagon, cortisol, angiotensin-II, and with decreased levels of insulin and an increase blood glucose level. The grading of these scorpions envenomation depends on local signs and whether or not neurological signs predominant(Mebs D. etal., 2002).

Table 1

.Neurotoxic and Cytotoxic local effects

Neurotoxic	Cytotoxic
Local evidence of a sting may be minimal or absent in approximately 50% of cases of .neurotoxic scorpion stings	A macula or papule appears initially at the sting site, occurring within the first hour of the sting. If the lesion progresses to a purple plague that will necrosis and .ulcerate
Pain sensation at the sting site, followed by itch, erythema, local tissue swelling, and ascending hyperesthesia, that persists for several weeks, and is the last symptom to .resolve before the victim recovers	The diameter of the lesion is dependent .on the quantity of venom injected
	The progression of lesion to a purple .plaque that will necrosis and ulcerate
The site is hypersensitive to touch and .temperature	Lymphangitis results from the transfer of .the venom through the lymphatic vessels

Table 2

.Central nervous system signs

Signs	Characteristics
Sympathetic	Hyperthermia, tachypnea, tachycardia, hypertension, arrythimia, hyperkinetic pulmonary, oedema, hyperglucaemia, diaphoresis, .piloerection, hyperexcitability, and convulsions
Parasympathetic	Bronchoconstriction, bradycardia, hypotension, salivation, lacrimation, urination, diarrhea, priapism, dysphagia, and gastric .emesis
Somatic	.Inactivation of sodium channels, increased tendon reflexes
Cranial	.Ptosis, dysphagia, pharyngeal reflex loss or muscle spasm
Peripheral nervous system	.Paralysis and convulsions

Table 3

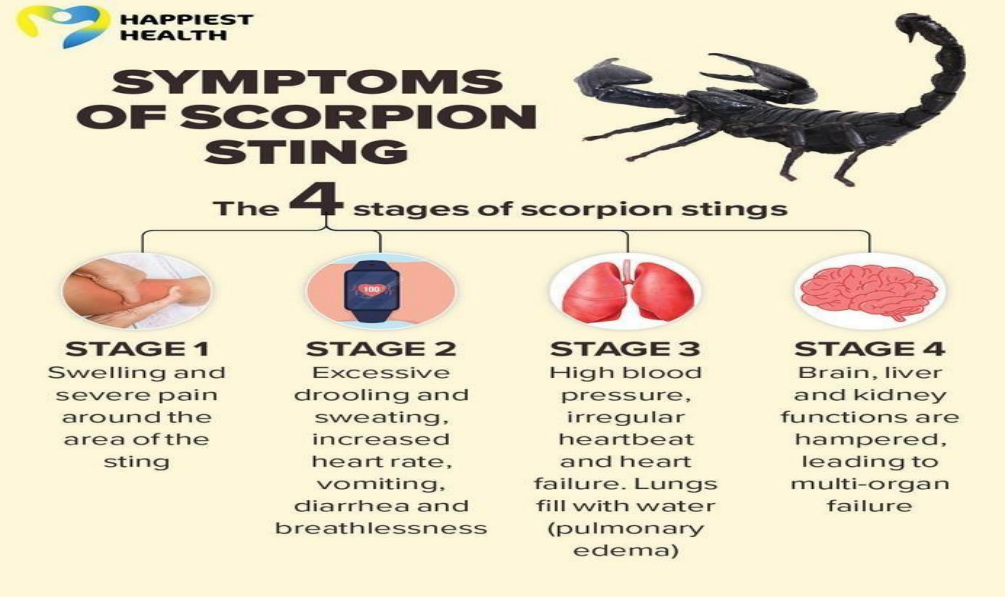
.Grade of envenomation

Grade	Characteristics
I	*Mild envenoming*
	.Patients presenting only local symptoms, local pain, and a burning sensation
II	*Moderate envenoming*
	.Patients with local and general symptoms
III	*Severe envenoming*
	Patients presenting with local and general symptoms, together with cardiocirculatory shock, respiratory failure, acute pulmonary edema, hyperthermia, .and neurologic symptoms such as priapism, convulsions, and coma

The local signs observed in victims can present effects that can separate in aneurotoxic and cytotoxic local (Table 1). Central nervous system signs are sympathetic, parasympathetic, somatic, cranial, and peripheral nervous system and their major characteristics are shown in Table 2. The signs are also classified as nonneurological and neurological. The nonneurological signs which include cardiovascular, respiratory, gastrointestinal, genitourinary, hematological, and metabolic signs. With respect the neurological signs, most of the symptoms are due to either the release of catecholamine from the adrenal glands or the release of acetylcholine from postganglionic parasympathetic neurons. Table 3shows the summarized characteristics of the different grade of envenomation caused by scorpion venom.

Clinical Aspect

The local symptoms most commonly reported included local pain, edema, hyperemia, swelling, burning, numbness and itching, whereas systemic symptoms consisted of dry mouth, thirst, sweating, hypotension, hypertension, cramps, tremor, nausea, vomiting, breathing difficulty, tachycardia, sialorrhea, restlessness, hemolytic-uremic syndrome, cyanosis, cardiac failure and/or acute pulmonary edema, and death.



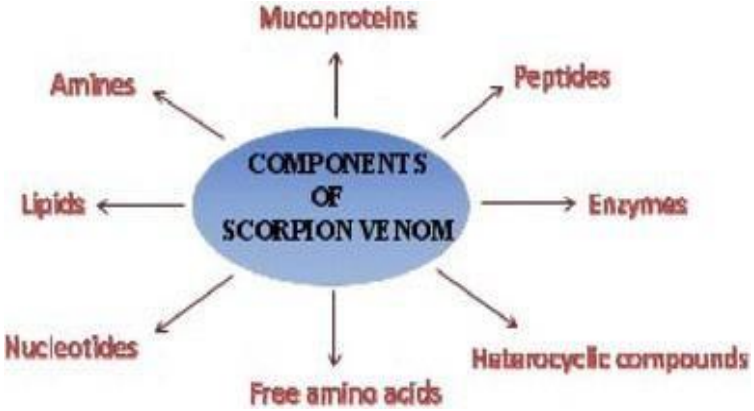
Scorpion Venom Compounds

Scorpion venom is a complex mixture of bioactive compounds that play crucial roles in predation and defense. The venom composition varies among different scorpion species, but common components include(Ortiz et al., 2015).

1. Peptides: Scorpion venom is rich in peptides, which are short chains of amino acids. Thesepeptides can have various effects on the prey or predator, such as neurotoxicity, antimicrobial properties, and modulation of ion channels.
2. Enzymes: Venom often contains enzymes that aid in breaking down tissues and disabling the prey's

defense mechanisms. Proteases, phospholipases, and hyaluronidases are common enzyme types found in scorpion venom.

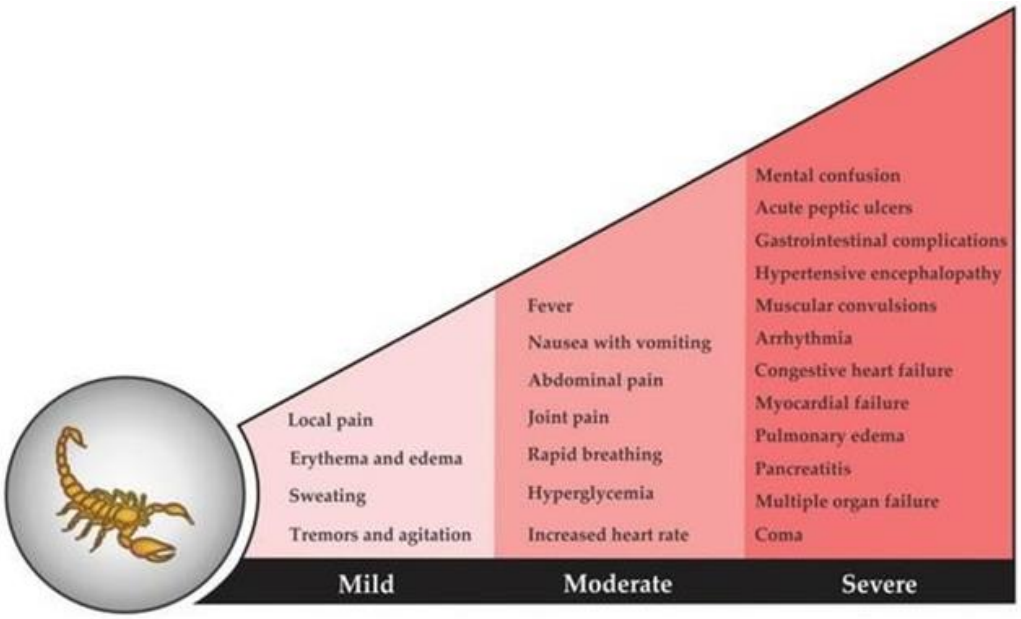
3. Neurotoxins: Many scorpion venoms contain neurotoxins that target the nervous systemof their prey. These toxins interfere with ion channels, leading to paralysis and facilitating the capture of the prey.
4. Cytolytic Peptides: Some scorpion venom compounds have cytolytic properties, causingcell membrane disruption. These peptides contribute to the overall toxicity of the venom.
5. Antimicrobial Peptides: Scorpions produce antimicrobial peptides within their venom, providing protection against bacterial and fungal infections.
6. Biogenic Amines: Venom may contain biogenic amines like histamine and serotonin, contributing to the inflammatory response and local effects of envenomation.
7. Toxin Modulators: Scorpion venoms may contain compounds that modulate the activity of other venom components, enhancing their effectiveness.
8. Understanding scorpion venom compounds is crucial for both scientific research and potential medical applications. Researchers explore these compounds for their therapeutic potential, including the development of novel drugs, pain management, and antimicrobialagents.



Compouds present in scorpion

Detriments of Scorpion Venom: Scorpion Envenoming

Scorpion envenomings can cause severe pathological effects and even death in humans. The intensity of an envenoming usually depends on the victim's sensitivity and body mass, the anatomical location of the sting, the amount of injected venom, and the scorpion species. Commonly, based on the severity of symptoms, scorpion envenomings are classified into three Biomedicines levels: mild, moderate, and severe (Figure 1). Mild envenomings result in local inflammatory reactions, whereas moderate and severe envenomings may provoke lethal systemic responses (Ahmadi et al., 2020).



Clinical manifestations and symptoms of mild, moderate, and severe scorpion envenomings.

Diagnosis of Scorpion Venom Envenomation

Scorpion stings can be distressing, and prompt diagnosis is crucial for appropriate management. When evaluating a patient suspected of scorpion envenomation (Ahmadi et al., 2020):

1. Clinical Assessment

History: include the circumstances surrounding the sting, including the time, location, and any symptoms you've experienced.

Symptoms: The clinical presentation varies but often includes intense pain, localized swelling, and redness at the sting site. Other symptoms may include sweating, nausea, vomiting, and muscle spasms.

Physical Examination: The affected area is examined for signs of envenomation, such as redness, edema, and local tenderness.

2. Severity Assessment

Scorpion stings can range from mild to severe. Severity depends on factors like the species of scorpion, the amount of venom injected, and the individual's sensitivity. Tap Test: A simple "tap test" involves tapping the sting site to assess pain intensity. Increased pain upon tapping suggests a scorpion sting1.

3. Laboratory and Imaging Tests: Blood Tests: In severe cases, blood tests may be performed to evaluate the effects of venom on various organs. These tests assess liverfunction, cardiac enzymes, and other parameters. Imaging: Imaging studies (such as ultrasound or CT scans) may be used to examineinternal organs affected by venom.

4. Differential Diagnosis: Scorpion envenomation must be differentiated fromother conditions and we can do that using different methods and machines.

The machine commonly used to differentiate between scorpion and other living- being venom is a mass spectrometer. Mass spectrometry can analyze the protein and peptide composition of venom samples, allowing for precise identification ofthe specific toxins present. This technique is highly effective due to its ability to detect unique molecular signatures that distinguish different types of venom.

Additionally, enzyme-linked immunosorbent assays (ELISAs) are frequently employed. These assays use antibodies specific to either scorpion or other living-being venom to detect and differentiate the two based on their antigenic properties.

5. Observation and Monitoring: Patients with mild symptoms may not require extensivetesting. They can be observed for a few hours to ensure symptom stability. Severe cases warrant close monitoring, especially if systemic effects (e.g., cardiovascular instability) are present.

Mass spectrometer machine.

Electrocardiogram (ECG or EKG).

Venom detection kit.

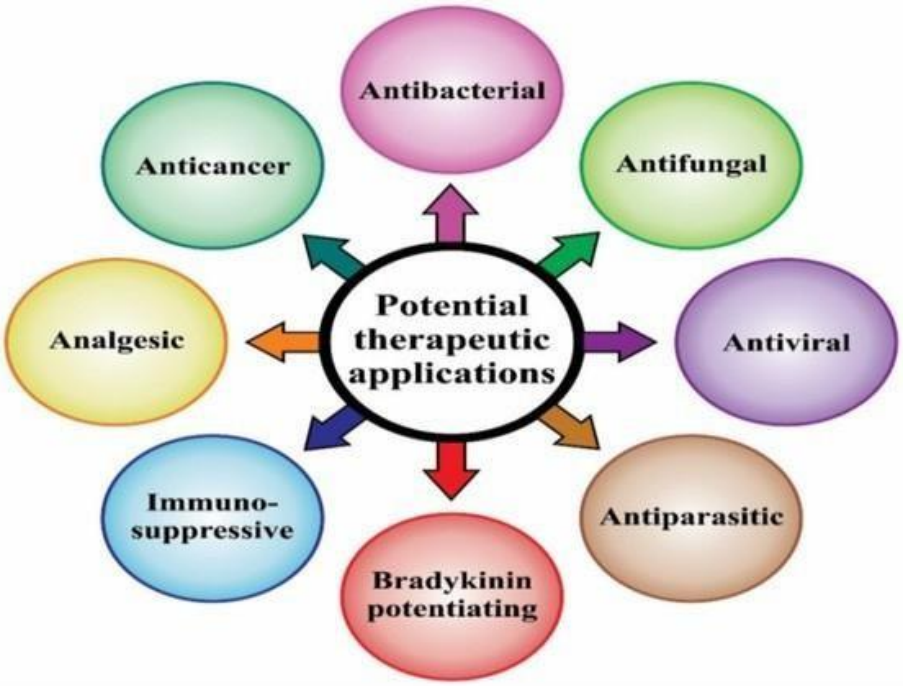
Scorpion Envenoming Treatment

The first treatment strategies that are undertaken after an envenoming event focus on pain relief and possibly intravenous hydration to decrease the negative e ects of strong salivation and sweating. In order to relieve acute pain after a scorpion sting, either cooling by ice or intravenous injection of paracetamol or nonsteroidal anti-inflammatory drugs, such as diclofenac and indomethacin, or topical administration of lidocaine cream at the site of the sting can be used. However, it is not surprising that the analgesic e ect of lidocaine might be superior to the former treatments. Further substances that are considered for application in envenoming cases are prazosin (which counteracts catecholamine-induced hypertension), antihistamines and steroids (which reduce inflammatory responses), sodiumphenobarbital (which prevents convulsion sandlunge dema), andcalcium gluconate (which eases muscle spasms). While partially being used in practice, there does not seem to be a general consensus on the e cacy and possible adverse of these treatment options. Yet, in the case of prazosin, it has been shown that the mortality and the mean residence timein the hospital could be significantly reduced by the administration of two doses of the drug, one immediate and one three hours after the envenoming incident. Additionally, small molecules, such as heparin, ethylenediaminetetraacetic acid EDTA, and aristolochic acid have been shown to neutralize scorpion venom enzymes, such as hyaluronidases, phospholipases A2, and metalloproteases. Thus, these molecules might be considered as a starting point for the development of future treatments. In more severe envenoming cases, antivenoms are employed to neutralize the venom and diminish the morbidity and mortality of scorpion stings(Ahmadi et al. ,2020).

Benefits of Scorpion Venom: Ongoing Research on Scorpion Toxins with Potential Therapeutic Applications

It is widely reported in the literature that scorpion venom is a rich source of bioactive compounds, and as such, their toxins are of interest to the pharmaceutical and biotech industries. However, despite the fact that substantial research efforts are

ongoing and the prospects for scorpion-derived therapeutic peptides are very promising, chlorotoxin is the only toxin from scorpion venom that has been taken into clinical trials. Moreover, no scorpion toxin-based drug is currently found in the market. In this section, potential applications of scorpion venom compounds, which have been the subject of therapeutic research, are presented (Figure 2), with a focus on results recently reported in the scientific literature. A comprehensive overview of such compounds, including older research reports, can be found elsewhere(Ahmadi et al., 2020).



The potential therapeutic applications of scorpion venom compounds discussed in thisarticle.

1- Antibacterial Effects

It was reported that the folding pattern of charybdotoxin, a KTx isolated from L. quinquestriatus hebraeus venom, was strikingly similar to that of the insect antibacterial component, defensin. This discovery the Biomedicines of 31 stage for studies on scorpion-derived antimicrobial peptides (AMPs), which have led to a large number of discoveries that may be of relevance for therapeutic applications.

2- Antifungal Effects

Antifungal drug resistance among Candida species is increasingly reported, and the emergence of MDR C. glabrata, which can acquire resistance following exposure to antifungal agents, presents significant challenges in many medical centers. Moreover, only three drug classes are licensed for monotherapy against Candida infections including azoles, polyenes, and echinocandins.

3- Antiviral Effects

Few antiviral vaccines and drugs are commercially available against the more than 200 viruses known to infect humans, which is a situation that has been highlighted by the current SARS-CoV-2 pandemic and puts an emphasis on the importance of discovery and development of new antiviral agents. To this end, venomous animals are considered by many researchers as promising sources for such discoveries. While some scorpion toxins show specific antiviral effects against just one type of virus, other toxins are active against several different viruses. Mucroporin-M1, a derivative of mucroporin from the Lychas mucronatus venom.

4- Antiparasitic Effects

Scorpion toxins have been demonstrated to possess inhibitory effects against a number of parasites. Scorpine, purified from Pandinus imperator venom, was the first isolated scorpion toxin that demonstrated antiprotozoan effects against Plasmodium berghei.

5- Bradykinin-Potentiating Effects

The multifunctionality of scorpion toxins is in the limelight once again regarding the bradykinin-potentiating effects of scorpion venoms. It has been demonstrated that the C-terminal fragment of BmKbpp, an AMP from M. martensii venom with antibacterial and antifungal activities.

6- Immunosuppressive Effects

Several scorpion toxins can modulate the immune system. Indeed, the contribution of released inflammatory mediators (e.g., cytokines, eicosanoids, and reactive oxygen species) and activation of the complement system is well explored in the envenoming pathophysiology following Biomedicines scorpion stings. For instance, an increase in the regulatory cytokines, interleukin (IL)-10.

7- Analgesic Effects

are known to modulate voltage-gated ion channels (mainly sodium and potassium channels.

CONCLUSION

The scorpion venom is a highly complex mixture of molecules with high molecular activities. It is a rich source of bioactive peptides that offer promising bio molecules that may lead to the discovery and devel opment of new drugs against a variety of diseases, that is, epilepsy, malaria, cardiovascular diseases, diabetes, and autoimmune diseases. It induces antipro liferative, apoptogenic, cytotoxic, and immunosuppres sive effects which are achieved mainlythrough the inhibition of cancer growth, arrest of cell cycle, induc tion of apoptosis, and suppression of cancer metasta sis. Therefore, scorpion venom can be used against a vast variety of cancers like, human neuroblastoma, gli oma, brain tumor, leukemia, breast cancer,prostate cancer, and lung adenocarcinomas.

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