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Scorpion's Biodiversity and Proteinaceous Components of Venom

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Abstract

Scorpions are a primitive and vast group of venomous arachnids. About 2200 species have been recognized so far. Besides, only a small section of species is considered disastrous to humans. The pathophysiological complications related to a single sting of scorpion are noteworthy to recognize scorpion's envenomation as a universal health problem. The medical relevance of the scorpion's venom attracts modern era research. By molecular cloning and classical biochemistry, several proteins and peptides (related to toxins) are characterized. The revelation of many other novel components and their potential activities in different fields of biological and medicinal sciences revitalized the interests in the field of scorpion's venomics. The current study contributes and attempts to escort some general information about the composition of scorpion's venom mainly related to the proteins/peptides. Also, the diverse pernicious effects of scorpion's sting due to the numerous neuro-toxins, hemolytic toxins, nephron-toxins and cardio-toxins as well as the contribution of such toxins/peptides as a potential source of anti-microbial and anti-cancer therapeutics are also covered in the present review.

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Introduction

Scorpions are considered to be one of the oldest arachnids existing on earth for 430 million years (Jeyaprakash and Hoy, 2009; Ortiz *et al.*, 2015). Paleontologists consider *xiphosuran* (Shultz, 2007) or *eurypterids* (Dunlop and Braddy, 2001) are the common ancestors of scorpions. They are the most venomous representative of class Arachnida (Zhang *et al.*, 2015; Wang *et al.*, 2017). As these animals are well adapted to extreme conditions, they are found in all the continents except Antarctica. Scorpions are also called living fossils because of their characteristic features of Paleozoic scorpions i.e. book lungs, venom apparatus and pectin (Polis, 1990; Di *et al.*, 2018). However, this assumption lacks major support from the researchers. They have observed major ecological, behavioral, physiological and biochemical changes in these animals over millions of years (Chowell *et al.*, 2006). Scorpions are also referred to as the equilibrium species (Polis, 1980) because of their long life, low fertility rate and excellent exploitation of resources. They are the ‘sit and wait’ type of predators which only tend to sit on the ground. As soon as, scorpions fulfill the energy assimilation requirements, they get back to the borrows to minimize the risk of being preyed (Zhang *et al.*, 2015).

Taxonomical classification of scorpion

The taxonomical position of scorpions shows their belonging to Kingdom *Animalia*, Phylum Arthropoda, Subphylum Chelicerata, Class Arachnida, Subclass Dromopoda and Order Scorpiones (Lourenço, 2001). The study of the familial classification of scorpion had begun at end of the 19th century; which is considered as the beginning of the “golden age’ of scorpion studies as the very first monograph about a scorpion is published by Kraepelin (Kraepelin, 1899). This period is also in correspondence to the emersion of interest in scorpion’s venom (Calmette, 1907). Approximately 2200 known scorpion species have been identified so far and is expected to reach up to 5000 or more in coming decades (Lourenço, 2018). The familial classification of the scorpion is somehow reported gradually by the researchers since 19th century. The supra familial classification of scorpion proposed by Stockwell (Stockwell, 1989) is the most convenient one, which is followed by Lourenço (Lourenço, 1998, 2000). However, the classification proposed by Lourenço in 2015 serves as the combined opinion of all the other proposed classifications (Lourenço, 2015), as is presented in Fig. 1.

Morphology of Scorpion's body

Scorpions are the predatory Arachnids. Their size ranges between 9 mm (*Typhlochactas mitchelli*) to 20 cm (*Hadogenes troglodytes*) (Ruppert *et al.*, 2004). They have segmented bodies covered with thick cuticle made up of tanned proteins and chitin. They have eight walking legs, two Pedipalps, two preoral appendages, chelicerae, no antenna. The body of the scorpion is divided into two parts i.e. cephalothorax (prosoma) and abdomen (opisthosoma) which is further divided into a large mesosoma and a long, narrow and segmented metasoma (tail) with a stringer at the end. The dorsal side of the prosoma is covered by a rectangular carapace, with one and five pairs of medial and lateral eyes respectively. Prosoma also bears twelve appendages i.e. two pincers called chelicerae with teeth, two pedipalps ended with chelae and four pairs of legs. The bases of the legs are attached to the ventral side of the prosoma, while the triangular/pentagonal sternum is only attached with the last pair of legs (Fig. 2 & 3) (Stockmann, 2015; Di *et al.*, 2018).

The mesosoma part of the body carries seven tergites or dorsal plates further aided with carinae, genital operculums, followed by a medial pectiniferous plate carrying pectines (i.e. characteristics appendages of scorpions). Pectines bear a variable number of teeth (or laminae), followed by five sternites, the first four of which are further connected to 8 lungs by spiracles (respiratory orifices). All the tergites or sternites are connected by a flexible articular membrane while the pleural membrane laterally connects both tergites and sternites (Stockmann, 2015; Di *et al.*, 2018).

The metasoma comprises five narrow, motile segments which get terminated into venom vesicle (or telson), which further ends into aculeus (or sting) i.e.

characteristic needle-like structure. The aculeus comprises a thick external cuticle and two canals are surrounded by loose supporting tissues, which help in the evacuation of venom. It also bears a pair of subterminal laterodorsal orifices, which are responsible for the eviction of venom as a spray in some species (Taylor *et al.*, 2012; Stockmann, 2015; Di *et al.*, 2018).

Morphology of venom apparatus

A pair of venom glands (surrounded by muscles) enclosed in vesicle present in the last segment of the post abdomen i.e. telson, positioned behind the anus. The vesicle of the venom gland is often covered with numerous thin hairs. Highly powerful extrinsic and intrinsic muscle systems control the venom secretion from the venom apparatus. The extrinsic muscle system ensures the penetration of aculeus into the prey while the intrinsic muscle system which is made up of a collection of striated muscles causes contraction and ejection of venom into the prey (Chippaux, 2012; Stockmann, 2015).

Fluorescence phenomenon of scorpion's body

The overall body of the scorpion is covered with a single layer of epidermis that secretes several layers of the cuticle as similar to other arthropods. However, the scorpion's exocuticles contain a characteristic hyaline layer and are comparatively thick which is further strengthen by metals at some places (Schofield, 2001).

The cuticle of the scorpion expresses a characteristic fluorescence (yellow/blue) when subjected to UV-radiation of 360 nm to 390 nm, which seems to be due to two chemical substances i.e. b-carboline and 7-hydroxy-4-methylcoumarin (Stachel *et al.*, 1999; Frost *et al.*, 2001). Another fluorescent molecule i.e. Resilin is also found in some cuticle layers. However, not all the species show the characteristic of fluorescence as it is reported by Lourenço that the genus *Chaerilus* lacks this property (Lourenço, 2012). The exact reason of the fluorescence phenomenon in scorpions is under debate. Some researchers believe that it is involved in the activity of locomotion or finding of sexual partners, while some consider that it doesn't have any particular function and is the simple phenomenon of secondary metabolites with no remarkable role (Stockmann, 2015). However, Gaffin and his workers reported that the fluorescent light emitted from the scorpion's body is having the function of an additional eye, thus it must be helpful for the scorpion to find shelter at night (Gaffin *et al.*, 2012). Additionally, the importance of the characteristic fluorescence in terms of the finding of new species of scorpions is nonnegotiable. It helps the ecologists in finding precious data about these nocturnal insects.

Sensory receptors in scorpion's body

Principally scorpions feed on arthropods, the human stings only occur for self-defense. Scorpions have a diversity of various sensory organs. They have very little use of vision for the detection of prey. The sensory organs have been classified into two types i.e. mechanoreceptors and chemoreceptors. Mechanoreceptors are found abundantly on pedipalps which are sensitive to the air currents thus provide an idea about the distance and direction of the prey (either on the ground or in the air). Some mechanoreceptor hairs are also found all over the scorpion's body, particularly on appendages. They are sensitive to the vibration of the ground. In addition, the cuticle also bears lyrifissures (or slit sense organs) which are membrane-covered slits majorly present on appendages and in collaboration with hairs under the tarsi indicates the presence of prey hiding under the soil. They have the ability to detect the vibration of the prey with the sensitivity of a nanometer (Brownell, 1977; Brownell and Leo van Hemmen, 2001).

Sensilla on the pectines are some of the major chemoreceptors find in scorpions and are highly sensitive to the salts and acid concentrations, as well as for the pheromones (for reproduction) (Foelix, 1985). Hairs on prebuccal cavity, chelicerae, over the fingers of chelae and on the tail of *Orthochirus* also possess the functions of chemoreceptors (Brownell, 1977; Brownell and Leo van Hemmen, 2001).

Biological behaviors of scorpions

circadian rhythms

Scorpions show seasonal vise variations in their behaviors. They have resting periods once (mostly in winter) or twice (in winter and hottest summer) in a year. They show maximum activity in hot weather, in which they increase up their reproduction rate and move farthest from borrows (Stahnke, 1957). Besides, scorpions tend to leave their borrows after heavy rainfall as the rain results in an increased number of insects on the surface (Hadley, 1974).

Scorpions have a different course of activities during a day. Most are inactive states at night or dusk, while in the day they rest in their shelters. However, their behavior differs depends on light and temperature variations. Several genera that include *Leiurus*, *Androctonus* and *Hottentotta* are nocturnal (Hadley, 1974). Others are most active between 9 pm-3 am, like in the case of *Smeringurus mesaensis* (Polis and Farley, 1979; Warburg and Polis, 1990). However, there are also few reported genera that show their exceptionally maximum activities during day time (at the start of the summer or following rain) that include *Parabuthus, maurus palmatus* and *Leiurus* (Polis, 1990; Stockmann, 2015).

The physiological functions follow the above-mentioned circadian rhythm, as briefly reviewed by Stockmann: the activity of the muscles and hepato-pancreatic enzymes vary throughout the day as observed in the case of *Heterometrus*, in which glucose concentration was high at 8 pm while glycogen concentration was at its lowest. Similarly, the respiratory rate was also at its maximum during 8 pm-4 am (Kalarani *et al.*, 1992; Stockmann, 2015). Furthermore, the activity of the nerve chain also displays the circadian rhythm (Goyffon, 1978), as in the case of *Euscorpius tergestinus*: where ocular pigment flows according to the light intensity. The seasonal circadian rhythms in scorpion's physiology and behavior are mainly controlled by nerve centers and by neurosecretory nerve endings which end in the retina of the medial eyes. The lateral eyes also synchronize these rhythms mainly in dark hours, the phenomenon is known as zeitgeber synchronization (Fleissner, 1974; Fleiśsner and Fleissner, 1985). In context to the above all references it is thus concluded that the photoperiod (particularly scotophase) has remarkable effects on circadian rhythms of scorpion's behavior.

Survival in extreme temperatures

Scorpions are one of the most resistant terrestrial animals towards the extreme temperature. They can resist the temperature up to 50℃ because of their well-hydrated body. It is the highest temperature at which coagulation of protein occurs, enzyme activities reach maximal and waxes get the fuse. To survive in such drastic conditions, the scorpion must have gone through some biochemical adaptations in tissues, teguments and hemolymph. As in certain arthropods, molecular conformations of hydrocarbon chains in cuticle occur and in some cases, genetic factors like the synthesis of heat shock proteins may also be involved to resist the extremely high-temperature environment (Hadley, 1974). Just like the high-temperature resistance some scorpions also show resistance against extremely low temperature by altering the concentrations of various biochemical compounds such as glycerol and Trehalose. Some antifreeze compounds such as nucleation proteins also synthesize in the *Centruroides vittatus* that prevents crystal formation. Moreover, high concentrations of sodium, cysteine and hemocyanin also affect the anti-freezing characteristic of scorpion in cold weather (Whitmore *et al.*, 1985). Another interesting behavioral phenomenon has also been reported by a researcher, the phenomenon is known as "stilting behavior" in which the scorpion lifts its body off the overheated ground as much as possible to provide some insulation against heat (Alexander and Ewer, 1958).

Survival in drought conditions

Scorpions are the toughest animal that can survive without food and water for a long period. They often fulfill their water needs by feeding on the prey, some drink water from puddles; some use their chelae for drinking water from the mist. Some scorpions don't drink at all from the hot regions. They also prevent water loss from evaporation by accommodating themselves according to their habitat (Gefen, 2011). Furthermore, they can also endure dehydrating concentration by producing metabolic water that comes from the mobilization of water from stored glycogen (Kalra and Gefen, 2012). In contrast to other arthropods, scorpions excrete nitrogen as guanine and xanthine (*Paruroctonus mesaensis*) (Yokota and Shoemaker, 1981) which are more favorable in terms of survival than that of uric acid. Apart from the above adaptations scorpion often tolerate the water loss by simply increasing the osmolality of hemolymph until the complete replenishment of water from the body (Hadley, 1974).

It has been experimentally reported by Pimenta that *Tityus serrulatus* can survive without food for 400 days (Pimenta *et al.*, 2019), which is astonishing evidence for the successful survival of these animals on land. The resistance to the lack of food is correlated with their slow metabolic rate.

Scorpion envenomation

Apart from being an engrossing animal for the researchers, the scorpions have been well notorious because of their aggressive nature and also have been falsely assumed as 'man killers' by humans. However, the researchers who invested their efforts in the understanding of scorpion's venom reject this misleading concept. As there is only a limited number of species (approximately 50) that are responsible for the life-threatening incidents (Lourenço, 2015, 2016). They are only limited to certain regions of Asia, North and South America, the Middle East and North Africa. Two questions are being addressed in a review (Lourenço, 2018) about the noxious species of scorpions: that why only a limited number of scorpions have the potency to kill humans and why they are only limited to certain regions of the world? The answers have been partially explained by Lourenço that evaluation of mammal specific toxins (particularly targeting Na+ channel) have occurred during the tertiary period of eradication of Palearctic region in which rapid emergence of small burrowing animals like rodent have occurred in arid landscapes where impressive populations of scorpions reside. Thus, the imbalance of the ecosystem resulted, which could tentatively explain the questions being inquired.

Family Buthidae considered being the deadliest among all the reported families, followed by two other families of Hemiscorpiidae and Scorpionidae. The species of the Buthidae family that are reported to cause serious life-threatening conditions for humans include *Hottentotta* and *Mesobuthus* (Asia), *Leiurus* (Middle East), *Buthus* and *Androctonus* (North Africa), *Tityus* (South America), *Centruroides* (North America) and *Parabuthus* (South Africa) (Yugandhar *et al.*, 1999; Murthy, 2000; Brownell and Polis, 2001). Scorpion envenomation causes lethal health issues in different regions of Mexico, Brazil, Northern Sahara, South India and Middle East due to its high incidences (Chippaux and Goyffon, 2008; Bucaretchi *et al.*, 2014; Ward *et al.*, 2018). The exact number of the incident by scorpion's sting around the world is not well known due to several reasons: (i) hard to access the medical facility in endemic areas, (ii) non regularized reporting system, (iii) parsimonious record of non-severe cases, (iv) common practice of self-medication/traditional medications. However, few studies published in the past few years reported 1.2 million stings per year with 3250 recorded deaths (Chippaux and Goyffon, 2008; Costa *et al.*, 2016; Ward *et al.*, 2018). Thus, the average envenomation rate all around the world is approximately 20/100,000 inhabitants (Abroug *et al.*, 2020).

Despite the abundance of hundreds of scorpion species, unfortunately, there is less published/unpublished data about the epidemiology of scorpion sting in Pakistan. So far only one such study has been reported in Sargodha Pakistan (Ahsan *et al.*, 2015), in which the authors illustrated that about 52% females and 48% males between the age group of 16 to 45 have been victimized by scorpion's sting. However, no death is reported by concerned health care centers. Similarly, another reported study has also been published from Sindh Institute of

Urology and Transplantation Karachi Pakistan. The authors reported the eighteen patients (11=females, 7=males) with acute kidney injury with a history of scorpion's sting. The patients were brought from Balochistan province during summer and were between the age group of 29.22±18.48 (Naqvi, 2015).

Symptoms associated with scorpion's sting

A great number of clinical signs and symptoms associated with scorpion's sting are reported so far. Nonetheless, a unique classification of clinical manifestations related to scorpion's sting is developed by a group of researchers; who's main aims were (i) to standardize the methods of treatment for the victims, (ii) to improve the quality of the management of treatment and (iii) to improve the effectiveness of the treatment. For this purpose, all the published sign and symptoms were taken into reconsideration and classified into four classes i.e. class I: local manifestations, class II: minor manifestations and class III: sever manifestations while class IV include lethal envenomation that includes the death of the victim. (Khattabi *et al.*, 2011).

The details of proposed signs and symptoms with the respective classes have been shown in Table 1 below.

Table 1. Classification of clinical manifestations related to scorpion's sting.

Class I Local manifestations	Swelling, Pain, Tingling Sensation, Burning Sensation, Itching, Purpura, Erythema, Necrosis, Blistering, Ecchymosis, Paresthesia and Hyperesthesia (Khattabi, Soulaymani-Bencheikh, Achour, & Salmi, 2011).
class II minor manifestations	Abdominal distension, myoclonia, agitation or excitement, mydriasis, Anisocoria, Meiosis, Arthralgia, Local muscular cramps, Ataxia, Lacrimation, Confusion & Convulsion, hypo/hyperthermia, Diarrhea & dry mouth, hypertension, headache, Dystonia, Hematuria, Encephalopathy, Gastrointestinal hemorrhage and Fasciculation, nausea/Vomiting, Wheezing, Urinary retention, Tachycardia, sweating, Stridor, Lethargy, Nystagmus, Odinophagia, Salivation, Rhinorrhea, Pallor, Pancreatitis, Priapism and Prostration (Khattabi, Soulaymani-Bencheikh, Achour, & Salmi, 2011).
class III sever manifestations	Cardiogenic failure; hypotension, Ventricular arrhythmia, Bradycardia, Cardiovascular collapse Respiratory failure; Cyanosis, Dyspnoea, Pulmonary edema Neurological failure; Glasgow Score (≤6), Paralysis (Khattabi, Soulaymani-Bencheikh, Achour, & Salmi, 2011).

Pathophysiology of scorpion's venom in human

Severe manifestations of scorpion sting are mainly due to the toxins. It specifically impairs the functions of ion-channels (specifically sodium channel) by inhibiting their inactivation. It also results in neuronal excitations that leads to the autonomic excitations in which both sympathetic and parasympathetic systems are involved (Quintero-Hernández *et al.*, 2013). Nevertheless, the severity of parasympathetic effects is less than that of the sympathetic effects. The effects of parasympathetic start soon after the envenomation and may involve respiratory impairment, in contrary sympathetic effects results in the release of adrenal gland hormones that cause severe systematic manifestations (Bahloul *et al.*, 2013), the details of which are given below.

Cardiac manifestations

It is one of the serious systematic envenomation that occurs in about 1/3 to ½ of the patients suffering from class III severe manifestation. The effects include the ventricular extrasystoles, imbalanced junctional rhythm, atrial standstill, sinus arrest bundle-branch block (Poon-King, 1963; Bahloul *et al.*, 2013). In addition, hypertension is also very common and occurs as an early response to envenomation due to sympathetic excitation. The hypotension is less common and occurs in cases of severe envenomation. It may be the result of cholinergic stimulation, myocardial depression, or fluid loss.

In most serious cases when the sting is occurred by the extremely toxic scorpion's species such as *mesobuthus, androctonus, tityus* and *buthus* scorpions (Bahloul *et al.*, 2004; Bawaskar and Bawaskar, 2011), cardiac dysfunction result which may also result in cardiogenic shock and pulmonary edema (Poon-King, 1963; Bahloul *et al.*, 2013).

Neurological manifestations

A selective number of scorpion's species (*tityus, parabuthus* & *centruroides*) cause neuro-muscular excitation in human which results in uncontrolled oculomotor movements, wild trashing and flailing of the limbs, impaired vision, muscular spasms (face, tongue, legs & arms) as well as the respiratory arrest (Berg and Tarantino, 1991; Boyer *et al.*, 2009).

Gastrointestinal manifestations

It may involve abdominal pain, vomiting & nausea with increased diarrhea, gastric motility and acute pancreatitis have also been reported in few sting cases caused by *Leiurus quinquestriatus and tityus* (Poon-King, 1963; Otero *et al.*, 2004).

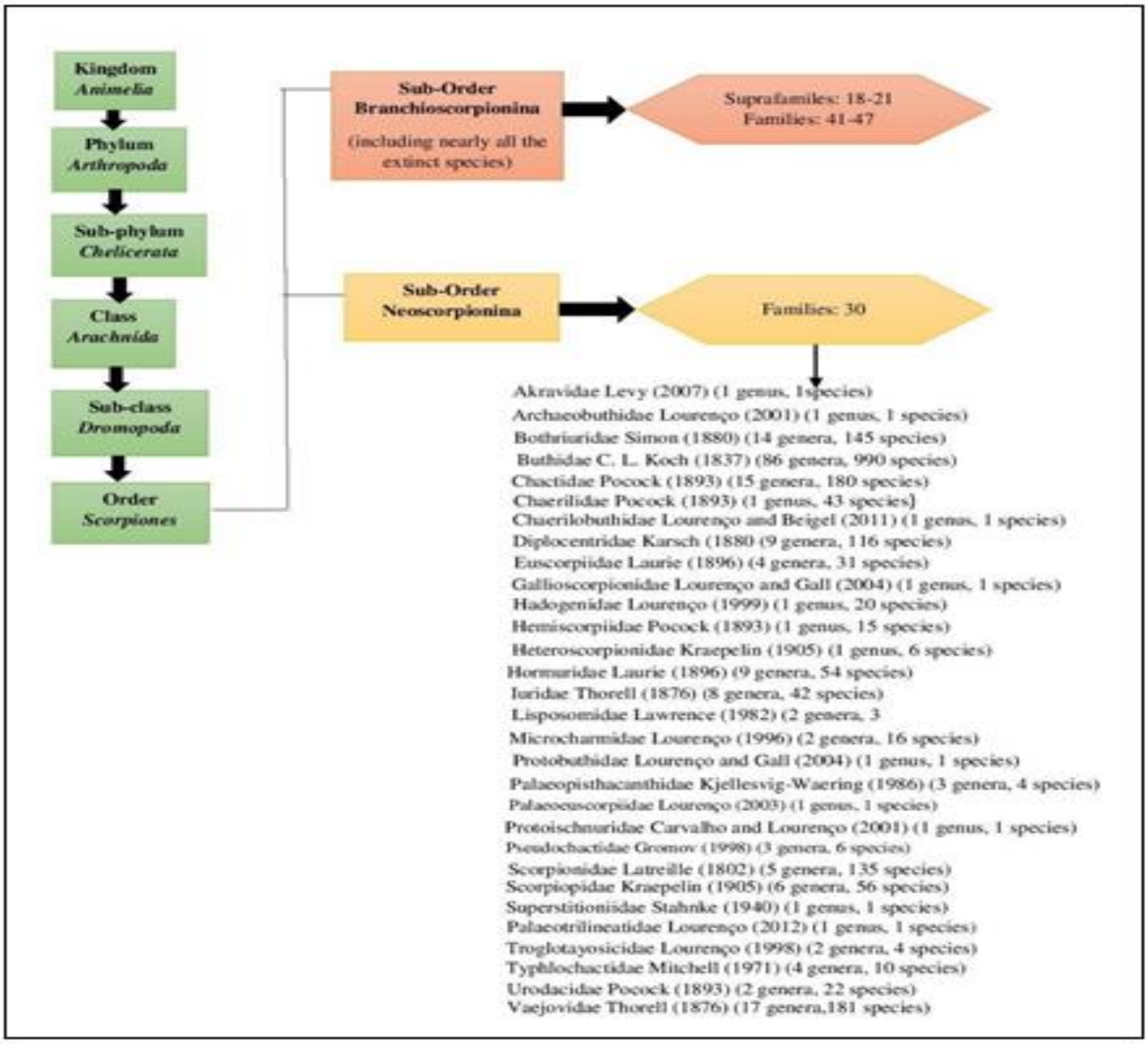

Fig. 1. Summary of familial classification of scorpions.

Cytotoxic manifestations

It is one of the rare systematic envenomation symptoms that is caused by the *Hemiscorpius lepturus* scorpion's sting. The sting only shows some mild symptoms of autonomic effects, together with nausea, vomiting and sometimes erythema and lesions at the start, but, in about 20% of the cases, the localized necrosis occurs after days.

Furthermore, hemoglobinuria, and acute kidney injury that often leads to dialysis have also been reported in some cases (Pipelzadeh *et al.*, 2007).

Composition of scorpion's venom

Scorpion's venom is primarily considered as the cocktail of chemicals which is injected into the prey/predators to disrupt their biological systems. The composition of the venom highly depends upon the ecological niche in which the organism lives and the diet they consume (de la Vega *et al.*, 2010). Moreover, the venom composition also varies from species to species or genus to genus (Cordeiro *et al.*, 2015). Approximately 100,000 chemical components have been estimated to be present in scorpion's venom, only 1% of which have been identified/characterized so far (Al-Asmari *et al.*, 2016; Al-Asmari *et al.*, 2016; Ferreira *et al.*, 2016). The components of scorpion's venom have been divided into proteinaceous and non-proteinaceous components, the details of which are given in Fig. 4.

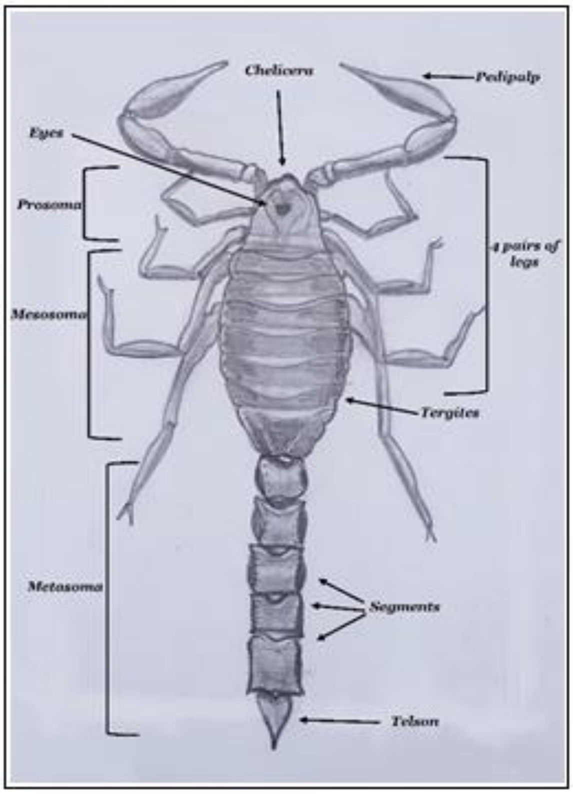

Fig. 2. Dorsal View of Scorpion.

Proteinaceous components of the scorpion's venom have been of great interest to researchers due to their significant roles in pharmacology *(Ortiz et al., 2015).* Enzymes and Host Defense Peptides (DBPs & NDBPs) are the major Proteinaceous components of the venom. The details of these proteinaceous components have been discussed below.

Disulfide Bridge Peptides (DBPs)

Disulfide Bridge Peptides (DBPs) are small ion channel modulators with some (3-4) disulfide bonds in them. The high toxicity of scorpion's venom is due to the presence of these low molecular weight (i.e. 30-75 AA) peptides (Romero-Gutierrez *et al.*, 2017). There are several toxins present in the scorpion's venom, having adverse effects on the human body; including neuro-toxins, cardio-toxins, hemolytic toxins and nephron-toxins, which specifically affect the enzymes and ion channels (Almeida *et al.*, 2012; Saini *et al.*, 2012).

Neurotoxins are the small ion channel modulator peptides that are reported to be responsible for impaired functioning of excitable cells of nerves and muscles (Restano-Cassulini *et al.*, 2017), thus are capable of blocking the ion-channels (Aboutorabi *et al.*, 2016) which resulted in numerous biological and metabolic disturbances (Al-Asmari *et al.*, 2016). Scorpion's venom consists a variety of neurotoxins that specifically target different ion-channels like $Na+$ channel, $K+$ channel, $Ca2+$ channel, $Cl-$ channel, TRP channel toxins (Rao *et al.*, 2015).

Non-Disulfide Bridge Peptides (NDBPs)

Non-Disulfide Bridge Peptides represent one of the major components of scorpion's venom, comprises about 13 to 56 AA with very unique sequences. Many of them have cationic nature and show remarkable flexibility in structure. Due to their cationic nature, they can bind with any biological membrane by interacting with the lipid polar head and express their biological activities (Huang *et al.*, 2010). Unlike Disulfide Bridge Peptides, NDBPs don't show their activities toward a specific molecule which makes them reactive against a broad range of targets. Thus, they have been reported as an excellent reactive tool against a great number of microorganisms (i.e. bacteria, virus, fungi, parasites). They have also been reported to have dynamic roles as immune-modulators and bradykinin potentiating peptides. Hence, NDBPs have been discovered as a promising source of therapeutic drugs (Almaaytah and Albalas, 2014; Ortiz *et al.*, 2015).

Both Disulfide Bridge Peptides and Non-Disulfide Bridge Peptides are referred to as Host Defense Peptides (HDPs) which are present in almost all the living organisms as a part of the innate immune system (Hancock *et al.*, 2016; Boto *et al.*, 2018). Scorpions from Buthidae family showed lower constitutes (20%) of these HDPs as compared to that of the non-Buthidae family (i.e.55%) as discussed briefly by (Cid-Uribe *et al.*, 2020).

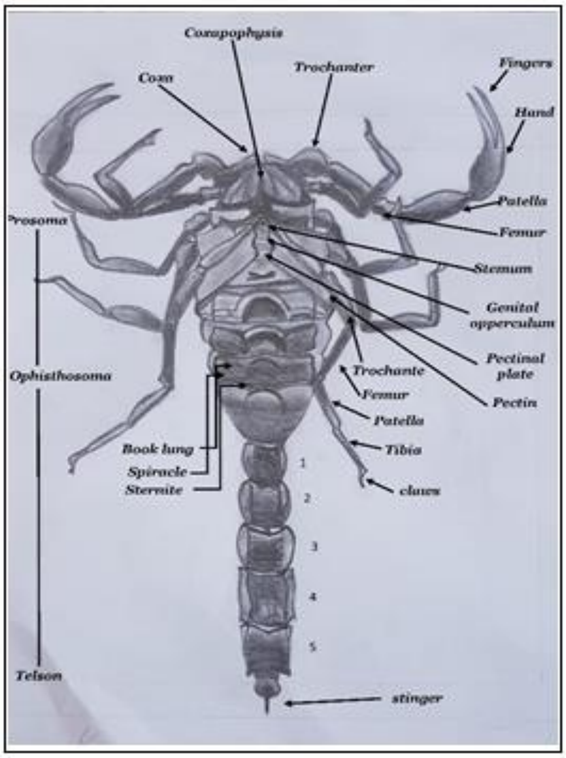

Fig. 3. Ventral View of Scorpion.

Functional Proteins (Enzymes)

Scorpion's venom contains several enzymes that show diverse activities including proteolytic (Almeida *et al.*, 2002; Brazón *et al.*, 2010), hyaluronolytic (Morey *et al.*, 2006; de Oliveira-Mendes *et al.*, 2019) and phospholipidolytic (Louati *et al.*, 2013). According to a review published by Cid-Uribe in 2019, a total of 749 transcripts have been reported to code for enzymes in scorpions, which were elucidated as metalloproteases, serine proteases, cysteine proteases, nucleotidases, phospholipases and hyaluronidases (Cid-Uribe *et al.*, 2020). However, the heterogeneity of these enzymes have been observed to be dissimilar between the families and genera like the proteomic analysis showed that the genera *Heterometrus*, *Hemiscorpius*, *Tityus*, *Serradigitus*, *Centruroides*, *Thorellius* and *Megacormus* are rich in terms of enzymes in their venoms, on the other hand in genus *Androctonus* none of the enzyme have been identified so far (Cid-Uribe *et al.*, 2020). Apart from all the above-mentioned enzymes, scorpion's venom also contains protease inhibitors which prevent the venom's enzyme degradation by the enzymes of other organisms (i.e. prey/predators), thus aids in the effectiveness of the venom (Hakim *et al.*, 2016).

Treatments for scorpion's envenomation

Several treatments have been tested for scorpion sting which includes prazosin (Bawaskar and Bawaskar, 2011), atropine, benzodiazepines, vasodilators, inotropic agents (Bouaziz *et al.*, 2008) and anti-venom (Boyer *et al.*, 2009), etc. Nevertheless, the type and effectiveness of the treatments depend upon the region as well as the severity of the envenomation from person to person. For the localized symptoms limited to the site of the sting, the uses of analgesics (ibuprofen, acetaminophen, etc) have been in common practice. They have anti-inflammatory and antipyretic effects and help in pain relief. In case of severe pain, local anesthetic agents also get into use. By observing the severity of the symptoms the health care center may also provide the following medications.

Prazosin: in the case of hypertension and excess release of catecholamine in blood prazosin has been used as it decreases the peripheral vascular resistance without putting any effect on cardiac activity or contributing to the elevated level of catecholamine (Isbister and Bawaskar, 2014).

Dobutamine (inotrope): Dobutamine is used to treat hypotension resulted from cardiogenic shock. As it helps in the retrieval of cardiogenic shock by decreasing the level of catecholamine and myocardial injury (Isbister and Bawaskar, 2014).

Nitroglycerin: in the case of pulmonary edema Nitroglycerine is used as a vasodilator. Few other vasodilators such as Hydralazine, sodium nitroprusside, captopril, clonidine and nifedipine also decrease vascular pressure and hypertension. These medications have some adverse effects (i.e sympathetic stimulation) which is why are not recommended for normal practice (Isbister and Bawaskar, 2014). Benzodiazepine: these medications are recommended in case of severe systematic envenomation i.e. neuromuscular incoordination, seizures and sympathetic agitations, etc. Benzodiazepine act as an anticonvulsant and is also used for sedation and symptomatic relief to treat neuromuscular excitability as well as the associated hypertension (Isbister and Bawaskar, 2014). Atropine: Atropine act as the blocker of muscarinic receptors in the nervous system, thus slow down the cholinergic effects of venom, which include bradycardia, salivation and excess sweating and hypotension (Isbister and Bawaskar, 2014). The uses of anti-venom in the case of scorpion's envenomation have been remained controversial as the reported studies showed both positive and negative effects.

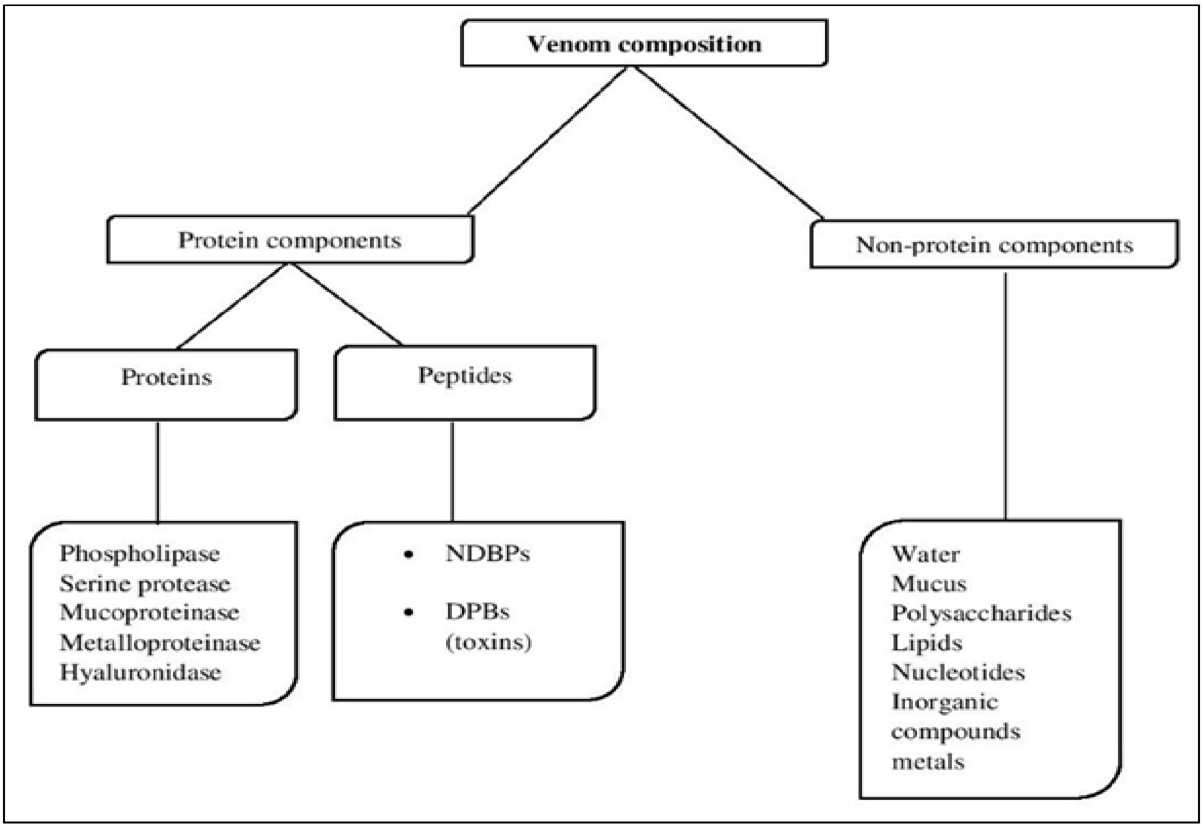

Fig. 4. Chemical components of scorpion's venom.

A study reported from Tunisia showed no effect of anti-venom in routine administration (Abroug *et al.*, 1999). However, the study wasn't contributed to a large number of patients with severe systematic manifestation, in which the use of anti-venom has favorable effects, as have been clinically proved by another study from North America which injected the anti-venom in the victims (with neurotoxic effects) of *centruroides* scorpion's sting and reported the recovery in all the patients within 4 hours as compared to the patient who was administrated with placebo (Boyer *et al.*, 2009). Similarly, another study from India has also reported the rapid recovery in all patients which were get administrated by anti-venom in combination with prazosin, as compared to those patients who were only subjected to prazosin (Bawaskar and Bawaskar, 2011).

The combined effect of anti-venom and prazosin has also been reported by another similar study and concluded with the same results (Pandi *et al.*, 2014). The evidence about the use of anti-venom in the case of scorpion's sting suggests that the administration of the anti-venom has some benefits. However, it is not much cost-effective, so it should only be used in case of severe cases of envenomation (Armstrong *et al*., 2013). Since the mechanism of action of anti-venom is mainly involved in binding with toxins, it doesn't reverse the established pathophysiological damage, thus can't predict any promising effects in case of severe manifestation of scorpion's sting.

Conclusion

Scorpion venomics is an extensive research topic. It covers many aspects of proteomic, transcriptomic and genomic by means of a large number of novel technological advances. It provides better understandings of the venom components and their structure, biodiversity, genetic grounds and biological roles as well as the productive use of these components in the field of taxonomy and pharmacology.

The present review summarized the findings reported on the Proteinaceous components of scorpion's venom. However, many of the newly reported components need further research through high through-put methods. Additionally, the activity, chemical synthesis and the heterogeneous expression of many components of scorpion's venom need to be executed to find out the physiological effects and mechanism of actions. Several components of the scorpion venom are responsible for antimicrobial and anticancer activities. Further researches are required to identify more pharmacologically active substances that could be used in biotechnology and medical-related fields. Although scorpion's envenomation is not a major help problem, by reviewing the pathophysiological effects of certain scorpion's venom in humans, the need for public health education among the locales is mandatory. It can help them to prevent being stung in rural areas of Balochistan, Pakistan.

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