CHAPTER I

INTRODUCTION

1.1 Scorpions: evolution, diversity and geographical distribution of medically significant scorpions of the world

1.1.1 The titans of Paleozoic era: the Silurian ancestral scorpions

The scorpion is one of the earliest animals to fully acclimate to the terrestrial environment. Due to the scarcity of their early fossils, it has been challenging to provide definitive answers to critical concerns, such as when and how they evolved to live on land. Scorpions first appeared as aquatic organisms during the Silurian (approximately 450 million years ago – MYA) and experienced few morphological changes since that period [1; 2; 3]. During the late Devonian (416-359 MYA) or early Carboniferous, the first unquestionably terrestrial (air-breathing) scorpion likely was discovered on land [4; 5]. These early scorpions, nearly exclusively aquatic or amphibious, eventually diverged into many super-families and families. The internal phylogeny of scorpions has long been a source of debate, similar to how scorpions are classified among the arachnid orders [6; 7; 8; 9; 10; 11; 12]. Numerous researchers have conventionally emphasized various physical characteristics of scorpions, leading to different phylogenetic hypotheses, none of which have received widespread acceptance [6; 9]. The family Buthidae and the non-buthids are physically distinct categories into which scorpions are traditionally separated [13; 7]. A group that illustrates morphological stability may limit the use of morphological features, which have historically been used to infer higher-level connections between scorpions (and to settle ensuing disagreements) [9; 14]. A scorpion phylogeny based on molecular data has not yet been proposed, despite the extensive use of molecular sequence data for phylogenetic reconstruction.

1.1.2 'Parioscorpio venator gen. et sp. Nov': the earliest scorpion through evolutionary routes

Over 2000 identified extant species of scorpions have survived to the present day [15]. Among them, the species 'Parioscorpio venator gen. et sp. Nov' was the earliest species, as evidenced by its thin exoskeleton, which had a variety of distinctive characteristics, including evolved (apomorphic) traits like primitive compound eyes, pedipalps (with claws), and a slender metasoma ending in a stinger. The small exoskeleton that distinguishes Parioscorpio venator gen. et sp. nov. displays a distinctive range of characteristics. According to previous research, some of these characteristics, including compound eyes, are regarded as primitive (plesiomorphic) for arachnids [16; 17; 18; 19;

20; 21; 3; 10]. Other characteristics, such as pedipalps with claws and a thin metasoma with a stinger, are derived from (apomorphic). It is believed that P. venator is the only species with a mesosoma that has seven tergites and sternites (Fig. 1.1, 1.2). The number of sternites in Paleozoic scorpions has been declining through time.

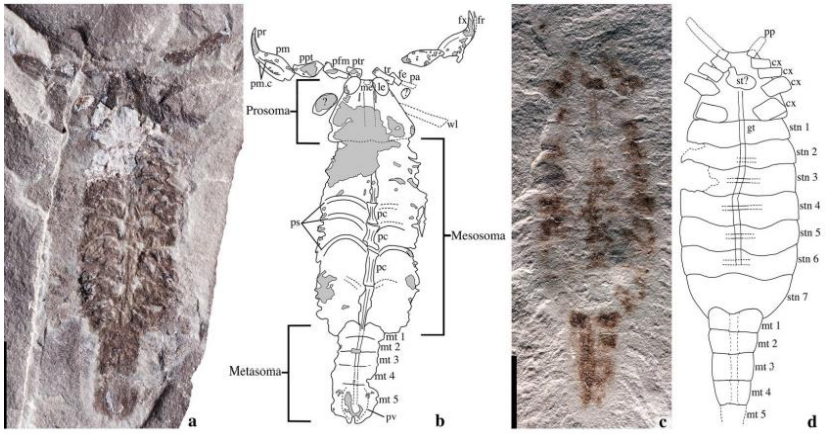

Fig. 1.1. Parioscorpio venator gen. et sp. nov., Wisconsin, USA, Brandon Bridge Formation, Silurian. (a) A low-angle photograph of a holotype, UWGM 2162, exposing internal anatomy; (b) Holotype, an interpretive drawing; (c) a low-angle photograph of a paratype, UWGM 2163; and (d) Paratype, an interpretive drawing. Abbreviations: cx, coxa; fe, femur; fx, fixed finger; fr, free finger; gt, gut; le, lateral eye; me, median eyes; mt, metasomal segment; pa, patella; pfm, pedipalp femur; pm, pedipalpmanus; pc, pericardium; pm.c, pedipalps manus carina; ppt, pedipalp patella; pr, pedipalp ramus; ps, pulmo-pericardial sinus; st, sternum; ptr, pedipalp trochanter; pv, poison vesicle; stn, sternite; tr, trochanter; wl, walking leg. The scale bar equals 5mm [22].

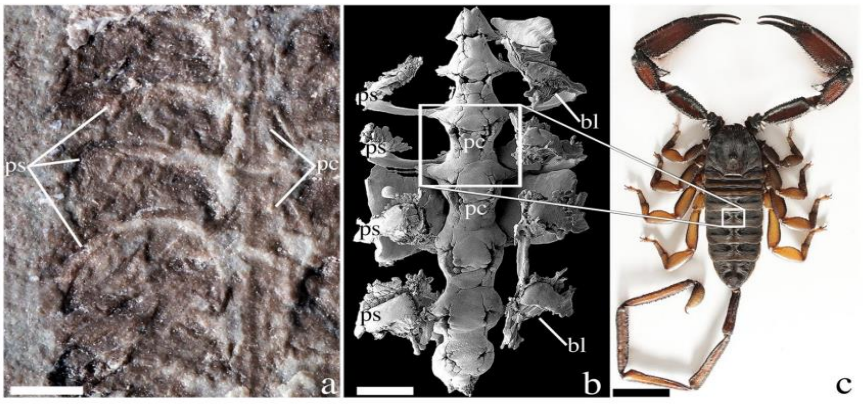

Fig. 1.2. Medial structures linked with the pulmonary-cardiovascular system in **(a)** Silurian and **(b,c)** Holocene scorpions. **(a)** Parioscorpiovenator gen. et sp. nov., holotype, depiction of the medial area displaying the pulmo-cardiovascular structures; **(b)** SEM of Centruroidesexilicauda, pulmo-pericardial sinuses and the pericardium's corroded cast; **(c)** Hadogenes troglodytes, male, dorsal surface, demonstrating medial components that reflect the location of the internal pericardium externally (Abbreviations: bl, book lungs; pc, pericardium; ps, pulmo-pericardial sinus. Scale bars equal 1mm for (a,b); scale bar equals 1 cm for (c) [22].

1.1.3 The origin and diversity of scorpion toxin peptide scaffolds: evolution stings

The family tree of the scorpion is being elucidated using the forms of the toxins present in its venom. The evolutionary history of the scorpion has been further revealed by peptides discovered in its venom. The results might provide a fresh perspective on many intricate relationships in nature. Although there are more than 2400 species of scorpions, scientists have had trouble figuring out how they are all linked to one another [23]. Most scorpion species have relatively similar anatomies, making it challenging to pinpoint the exact period of evolutionary divides.

However, the shape of specific venom peptides has been discovered to assist identify between distinct branches of the scorpion family tree, according to a recent study from the University of Wisconsin-Madison in the USA. To better understand how scorpion venom toxins originated, the study used a combination of phylogenomics and molecular modelling to identify relationships between different scorpion species [24]. Scorpions serve as the model arachnid group for investigations into arthropod terrestrialization, morphological stagnation, and body plan diversification [19; 20; 25; 26].

For many years now, there has been a general consensus that scorpions can be classified among the most ancient and conservative arthropods in origin and body morphology. Scientists and lay people alike find scorpions to be particularly fascinating due to the variety of their venom, which is a complex mixture of bioactive substances (such as proteins and peptides) secreted in specialized organs and used to interfere with the physiological and biochemical functions of the target organisms [27; 28; 29]. The recruitment of paralogs of ancestral housekeeping genes, followed by speciation and neofunctionalization, is hypothesised to be the cause of the toxins found in animal venom. The patchy nature of current taxonomic sampling makes studying the variety of

scorpion venom even more challenging. The availability of transcriptomes, the first scorpion genomes, proteomics, and the development of current-generation sequencing technologies has significantly accelerated the identification of venom diversity. According to scientific consensus, differences in prey preference and/or predatory technique are the primary causes of the dynamic molecular evolution of venom-encoding genes [30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40]. The underlying molecular variety of venom may be concealed, nevertheless, by the episodic nature of selection on the genes that encode them and the severe sequence divergence that occurs over protracted periods of evolutionary time. Venom-encoding genes are widely distributed in some of the oldest venomous lineages, such as cnidarians, centipedes, scorpions, spiders, coleoids, etc.

The venoms that scorpions have developed throughout their more than 400 million-year evolutionary history [41] have harmful effects on various biological targets. The toxin diversity has been amplified because of its lengthy geological history, sluggish migratory rates, and diverse population structures [42; 43; 44]. While some snake venoms have a high concentration of enzymatic toxins, scorpion venoms primarily comprise peptide toxins. The CS/ scaffold (cysteine-stabilized/) is one of several toxin types found in scorpion venoms and is extremely complicated. Scorpion CS/ toxins consist of Na^+ ion channel (NaV) modulators (NaScTx or NaV-CS/Toxin); subtypes: -toxins (site-3 binding) and -toxins (site-4 binding), atypical NaV-CS/ toxins (birtoxin and similar toxins, including the alleged "lipolytic toxins"), K^+ ion channel (Kv) targeting toxins (KTx).

1.1.4 Geographical distribution of venomous scorpions

Scorpions are fascinating animals. As stated by nationalist general healthy information, around 1.5 million scorpions intoxicates, performed in 2000-3000 demises, are registered yearly universally [45; 46]. There are currently 2,584 species of scorpions in the world, divided into 23 families (according to Chippaux and Goyffon) [46] and updated by Reckziegel and Pinto; Laustsen and his team; and Lourenço [47; 48; 49]. Scorpion toxins may not alone be a medicinal menace to human health. Still, they could demonstrate a worthy origin of bio-vigorous particles that may assist as drives for the evolution of novel curatives versus existing and arising illnesses.

The geography allocation of the generality of those medicinally important species links to the domestic spread of scorpions. All continents, with the exception of Antarctica, are

habitat to scorpions, however in northern South Africa, Saharan Africa, the African Sahel, southern India, the Middle East, Brazil, Mexico, and the Amazon basin region, envenoming is more severe and common [50; 51; 52; 53]. However, there are a few cases of symptoms brought on by the venom of the majority of these species [53].

Scorpionism is a serious public health problem in many parts of the planet, as envenomation are often painful and lethal to human and causes severe health complications [54; 55; 56; 57]. The incidence and severity of scorpionism vary significantly by geographical location. Thus, it is important to identify the local population's specific concerns and the significant risk factors. To determine the prognosis and implement effective treatments, an assessment of the severity of the envenomation, particularly in children, is necessary.

The largest family of scorpions, Buthidae, is found throughout the planet with the exception of Antarctica and New Zealand [58]. The 1,225 species that make up this family (as of January 22, 2021) [59], include roughly 50 species that are regarded as harmful to humans [60]. The Buthidae (C. L. Koch) family of scorpion species account for over 95% of scorpion envenomations (Buthidae family was established by Carl Ludwig Koch in 1837), which comprises the genera *Mesobuthus, Buthus, Tityus, Leiurus, Centruroides, Parabuthus, Hottentota and Androctonus* [48]. Scorpions from the Chactidae family have the potential to cause mild and local effects in humans [61; 62]. The Indian red scorpion (*Mesobuthus tamulus*) has khaki-colored cuticles on its body and measures 2-3.5 inches (5-9 cm) in length [63], has red clawed pedipalps, legs, and a tail (Fig. 1.3). These nocturnal predators are prevalent throughout the Indian subcontinent. In India, the western Maharashtra, Saurashtra, Kerala, Andhra Pradesh, Tamil Nadu, and Karnataka are frequently affected by morbidity and mortality brought on by scorpion stings (Fig. 1.4). They are rarely found outside Eastern Nepal [64], Eastern Pakistan [63], or Sri Lanka [65].

Fig. 1.3. Indian red scorpion (*Mesobuthus tamulus*) [66]

Fig. 1.4. The geographical distribution of the *Mesobuthus tamulus* throughout the Indian sub-continent [Brown fill: Indian states; Blue fill: neighbouring countries of India] [66]

1.1.5 Scorpions: taxonomic classification, anatomy, morphology and reproduction

In 1837, the German arachnologist Carl Ludwig Koch established the order of Scorpiones. He classified them into four families: "Scorpionides" (scorpions with six eyes), "Buthides" (scorpions with eight eyes), "Centrurides" (scorpions with ten eyes), and "Androctonides" (scorpions with twelve eyes). Since then, approximately 2,500

species of scorpions from 22 families have been described, and the 21st century has seen numerous taxonomic additions and reorganizations [23].

The taxonomic framework of scorpion

Kingdom: Animalia

Phylum: Arthropoda

Subphylum: Chelicerata

Order: Scorpiones

Family: **a.**Buthidae, **b.**Hemiscorpionidae, **c.**Scorpionidae

Genus:a. *Tityus, Androctonus, Leiurus, Parabuthus, Centruroides.*

b.*Hemiscorpius*

c.*Scorpio*

1.1.6 Anatomy and Morphology

Scorpions range in size from the *Typhlochactas mitchelli* of the Typhlochactidae, which measures 8.5 mm (0.33 in), to the 23 cm (9.1 in) *Heterometrus swammerdami* of the Scorpionidae [67]. The cephalothorax, also known as the prosoma, and the abdomen, often the opisthosoma, are the two tagmata that constitute a scorpion's body (Fig. 1.5). The opisthosoma is divided into two parts: the sizeable anterior mesosoma, also known as the pre-abdomen, and the small, tail-like posterior metasoma, often known as the post-abdomen [68]. In most animals, there are no evident external distinctions between the sexes. In rare cases, male metasomae are more extended than females [69]. The scorpion body is divided into three major parts, (i) Cephalothorax, (ii) Mesosoma, and (iii) Metasoma [70; 71] (Fig. 1.5).

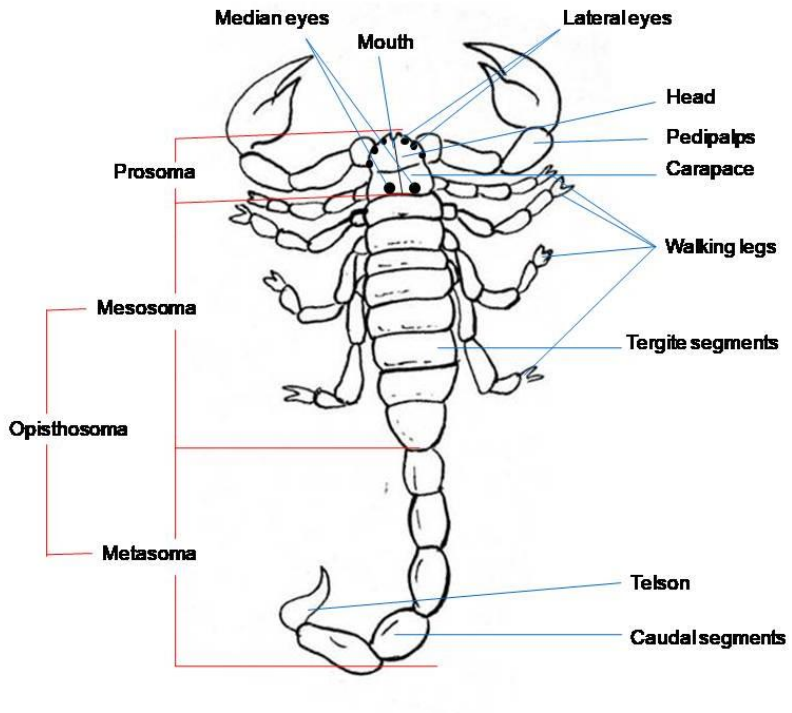

Fig. 1.5. Scorpion anatomy

1.1.6.1 Prosoma or cephalothorax

The cephalothorax consists of the carapace, eyes, chelicerae (parts of the mouth), pedipalps (which have chelae, generally known as claws or pincers), and four pairs of walking legs. The top of the cephalothorax of scorpions has two eyes, while the front corners of the cephalothorax often have two to five pairs of eyes. Its primary eyes are among the most sensitive to light in the animal kingdom, especially in low light, allowing nocturnal species to use starlight to navigate at night, despite their inability to generate precise images. The front and underside of the carapace are home to the chelicerae. They resemble pincers and contain three segments and pointed "teeth" [72]. The scorpion's brain is located immediately above the oesophagus in the back of the cephalothorax.

The nervous system is primarily concentrated in the cephalothorax, as it is in other arachnids (Fig. 1.6). Still, it also contains a lengthy ventral nerve cord and segmented ganglia, which may be a primitive characteristic. The segmented, clawed pedipalp is an appendage utilized for defence, immobilization of prey, and sensory functions. The pedipalp comprises the coxa, trochanter, femur, patella, tibia (which includes the fixed claw and the manus), and tarsus. These parts are listed from closest to the body outward (moveable claw) (Fig. 1.6). The pedipalp segments and other portions of the scorpion's

body have darker or granular elevated linear ridges known as "keels" or "carinae," which are essential taxonomic characteristics [73]. Although females can use them to catch developing young and they can also be used for digging, unlike those of certain other arachnids, the legs have not been changed for other uses. Proprioceptors, bristles, and sensory setae exist throughout the legs. Depending on the species, the legs may contain spines and spurs [73; 74].

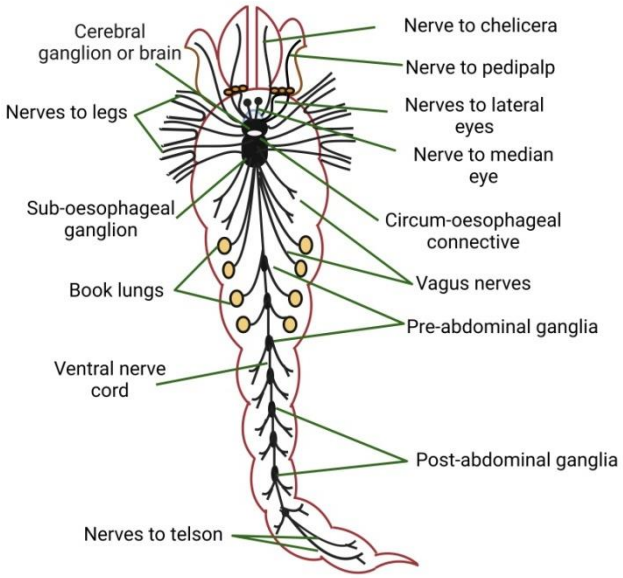

Fig. 1.6. Nervous system of scorpion (created with BioRender.com; agreement number: XG25HMISCM)

1.1.6.2 Preabdomen or mesosoma

The broad portion of the opisthosoma is known as the mesosoma or preabdomen. Eight segments comprise the mesosoma during the early stages of embryonic development; however, the first section disappears before birth in scorpions, leaving only segments 2–8 [68]. A sclerotized plate known as the tergite covers each of the opisthosoma's anterior seven somites (segments) on the dorsal side. Somites 3 to 7 are defended ventrally by sternites, which are matched plates. Two genital opercula cover the gonopore on the ventral side of somite 1. The basal plate consisting of sternite 2 contains the pectines, which serve as sensory organs [75]. The following four somites, 3 to 6, have two spiracles. These act as the book lungs, the scorpion's respiratory system apertures.

Depending on the species, the spiracle openings might be oval, circular, elliptical, or slit-shaped [68]. Hence, there are four sets of book lungs. Each set has 140 to 150 air-filled

pulmonary chambers connected on the ventral side to atrial chambers that open into spiracle-like structures. The lamellae are kept separated by bristles. During contraction, dorso-ventral muscles compress the pulmonary chamber, expelling the air, and they then relax to allow the chamber to re-fill. A muscle extends the atrial chamber and opens the spiracle [68]. The seventh and final somite lacks notable exterior features or appendages [76].

The scorpion's open circulatory system is controlled by the heart, also known as the "dorsal vessel," in the mesosoma (Fig. 1.7). A deep artery network that runs throughout the body is continuous with the heart. Deoxygenated blood (hemolymph), which is returned to the heart by the sinuses, is reoxygenated by cardiac pores. The reproductive system is likewise housed within the mesosoma. The female gonads comprise two to four transverse anastomoses that join three or four parallel tubes. Both oocyte production and embryonic development take place in these tubes. They attach to two oviducts, which link to one atrium and the genital orifice [77]. Two gonads are formed of cylindrical tubes arranged in a ladder-like fashion and contain cysts that generate spermatozoa. One on either side of the mesosoma, the two tubes converge in spermiducts. They join to paraxial organs, symmetrical glandular structures that terminate at the genital opening. They produce structures made of chitin that combine to create the spermatophore [78; 77].

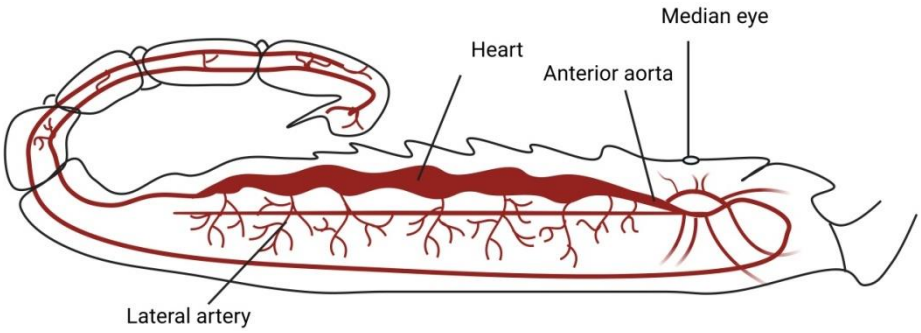

Fig. 1.7. Circulatory system of scorpion mainly controlled by heart (created with BioRender.com; agreement number: QJ25HMJ3NH).

1.1.6.3 Tail or metasoma

The telson, which isn't precisely a segment and five segments, compensate the "tail" or metasoma. The five segments which are body rings, have no discernible sterna or terga and get bigger farther away. These segments feature bristles, setae, and keels that can be used to classify them according to taxa. Four anal papillae and the anal arch surround the anus at the final segment's distal and ventral end [68]. Several creatures have light receptors in their tails (Fig. 1.5) [72]. The vesicle, which has a symmetrical pair of venom glands, is a part of the telson. Its curved, sensory-haired hypodermic aculeus stinger is visible on the outside. Each venom gland contains a separate duct that carries its secretion from the bulb of the gland to the area just next to the tip, where each paired duct has a different venom pore [79].

In comparison, an internal muscle system connected to the glands pumps venom through the stinger into the chosen victim, and an extrinsic muscle system in the tail drives and penetrates the aculeus [77]. Zinc-containing metalloproteins in the stinger harden the tip [80]. An angle of about 30 degrees concerning the tip is ideal for stinging [81].

1.1.6.4 Habitat and food of scorpions

Majority of scorpion species are nocturnal and spend the day hiding in burrows, rock crevices, and tree bark [77]. Several species create a home beneath stones that are a few millimetres long. Some may utilize the tunnels dug by small mammals, reptiles, spiders, and other creatures. Some animals create their own, varying in complexity and depth tunnels. About 2 m (6 ft 7 in) deep burrows are dug by *Hadrurus* species. Legs, claws, and portions of the mouth are used for digging. Individuals may congregate in the same shelter in several species, especially those belonging to the Buthidae family; bark scorpions can aggregate as many as 30 individuals. Families of females and young may occasionally congregate in certain species [69]. Scorpions can resist extreme heat if adequately hydrated; *Leiurus quinquestriatus, Scorpio maurus, and Hadrurus arizonensis* may survive at 45-50 °C (113-122 °F). Scorpions prefer environments with temperatures ranging from 11-40 °C (52-104 °F).

Desert species have to adapt to the drastic shifts in temperature from day to night or from season to season. *Pectinibuthus birulai*, a psammohile scorpion can tolerate temperatures between 30 and 50 °C (22 and 122 °F). Scorpions prefer cooler temperatures when they

live outside of deserts. Desert scorpions have several water-saving adaptations. Without water, they eliminate insoluble substances from the body, such as xanthine, guanine, and uric acid. The primary component, guanine, enhances nitrogen excretion. Using lipids and waxes produced by epidermal glands, a scorpion's cuticle traps moisture and offers UV protection. A scorpion can withstand high osmotic pressure in its blood even when dehydrated [82]. While some desert scorpions can take in water from the damp soil, most receive moisture from their food. Animals that prefer cooler climates and denser flora will drink from puddles and plants [69]. The stinger of a scorpion is used for both offence and defence. Others deliver slower, circular attacks that make it easier to reposition the stinger so it can sting again. Some animal species use their tails to strike hard and rapidly. During a defensive strike, the *Leiurus quinquestriatus* can whip its tail at up to 128 cm/s (50 in/s) [73].

Other arthropods, including ants, solifugids, spiders, and centipedes, may attack scorpions. Lizards, frogs, snakes, birds, and mammals are some of the main predators [69]. Meerkats are reasonably skilled at catching and eating scorpions since they can bite off their stingers and are immune to venom. The grasshopper mouse and the desert long-eared bat are other predators that have evolved to hunt scorpions and are resistant to their venom [83; 84]. Scorpions host various parasites, including bacteria, nematodes, mites, and scuttle flies. Due to their immune systems, scorpions resist many bacterial infections [77]. A scorpion takes a defensive stance when attacked by an object by raising its claws and tail. By rubbing the stinger, or the claws, some species stridulate to frighten away predators [69]. Depending on the size of the appendages, certain species choose to defend themselves by employing either the claws or the stinger [85].

Scorpions feed on insects, especially wasps, grasshoppers, crickets, termites, and beetles (Fig.1.8). Some of the other prey are spiders, solifugids, woodlice, and even tiny vertebrates like lizards, snakes, and mammals. Earthworms and mollusks may be prey for species with big claws (Fig. 1.8). *Isometroides vescus* is a species that only eat burrowing spiders; however, the rest of the species are opportunistic and eat a variety of prey. The species' size influences the size of the prey. As sit-and-wait predators, several scorpion species wait for food at or close to the entrance to their tunnel. Others deliberately look for them. Scorpions use the mechanoreceptive and chemoreceptive hairs on their body to locate their prey and then use their claws to trap it. Especially in the case of large-clawed species, small animals are destroyed with claws. Prey that is larger and

more aggressive receives a sting [77]. Like other arachnids, scorpions also digest their food externally.

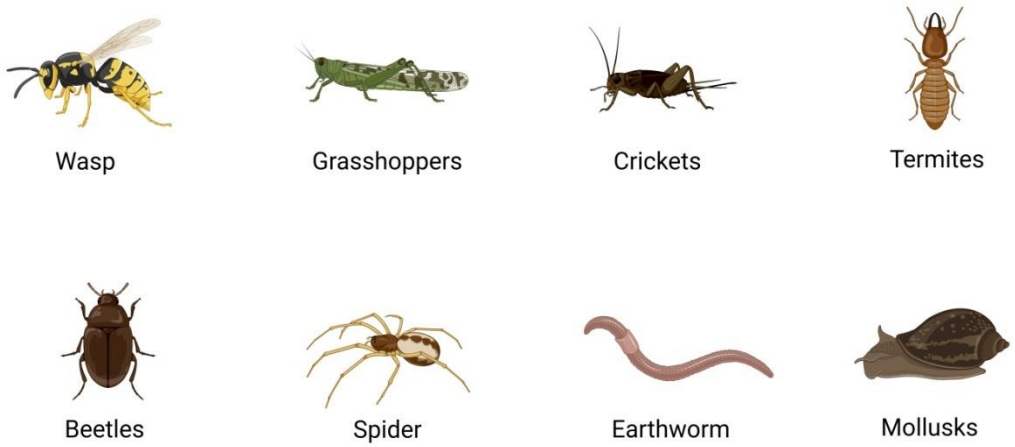

Fig. 1.8. Foods of scorpion (created with BioRender.com; agreement number: JF25HMJNPF)

Little amounts of food are pulled off the prey item and placed into a pre-oral compartment beneath the chelicerae and carapace using the highly sharp chelicerae. Food is digested with the digestive juices from the gut, followed by the liquid digestion of the food being sucked into the gut. Setae catch, and expel any solid, indigestible material (such as exoskeleton fragments) from the pre-oral cavity.The pharynx pushes the food sucked into the midgut, where it is further broken down. The anus and the hindgut are where the waste exits. Scorpions have a high appetite and can eat much at once [68].

1.1.6.5 Reproduction in scorpions

Most scorpions reproduce sexually, with male and female individuals; however, parthenogenesis, in which unfertilized eggs develop into living embryos, has been reported in some genera, including Hottentotta and Tityus, and the species *Centruroides gracilis, Liocheles australasiae,* and *Ananteris coineaui* [86]. Males on the move gather up pheromones from receptive females using their pectines to comb the substrate. Juddering is the back-and-forth body movement that males use when they first start courting [86].

In some species of scorpions, the gestation period can last up to a year [68]. Both apoikogenic and katoikogenic embryonic development are available to them.

Inside follicles, embryos grow in yolk-rich eggs in the apoikogenic system, mainly found in the Buthidae. In the katoikogenic system, which has been observed in the Hemiscorpiidae, Scorpionidae, and Diplocentridae, the embryos grow in a diverticulum with a teat-like structure through which they can feed [87]. Scorpions appear universally viviparous, giving birth to live young, unlike most arachnids, which are oviparous and hatch from eggs [88]. The female raises her front end before giving birth, positioning her pedipalps and front legs underneath her to collect the baby ("birth basket"). The young leave the genital opercula one by one, expel any embryonic membrane that may have been present, and subsequently placed on their mother's back, where they remain for at least one moult. The pro-juvenile stage is before the first moult; during this stage, the young have suckers on their tarsi to cling to their mother even if they are unable to consume food or sting. This time frame can last 5 to 25 days, depending on the species. The brood's first synchronous moulting signifies the juvenile stage, which takes 6 to 8 hours [89].

Instars or juvenile stages typically resemble scaled-down counterparts of adults and have fully formed pincers, hairs, and stingers. In order to stay safe, they ride on their mother's back as usual because they are still fragile and lack colour. Over the following few days, they became more arduous and more coloured. They might briefly separate from their mother before returning if they spot any threat. The young can hunt prey independently once the exoskeleton has fully hardened, and they may soon leave their mother [77]. Before reaching maturity, which could take anywhere between 6 and 83 months, a scorpion may moult six times on average. Several creatures have a 25-year lifespan [68].

1.2 Scorpions venom: origin, evolution, composition, and functions

1.2.1 The origin and diversity of scorpion toxin peptide scaffolds: evolution stings

The family tree of the scorpion is being elucidated using the forms of the toxins present in its venom. The evolutionary history of the scorpion has been further revealed by peptides discovered in its venom. Most scorpion species have relatively similar anatomies, making pinpointing the exact period of evolutionary divides challenging. However, the shape of specific venom peptides has been discovered to assist in identifying distinct branches of the scorpion family tree (Fig. 1.9) [24].

The origin of venom toxins has been hypothesized to be the consequence of paralogs' recruitment of ancient housekeeping genes, then it comes diversification and neo-functionalization (functional divergence of venom toxins), a process driven by positive selection (Fig. 1.9) [90; 91; 28; 92; 93; 94]. Although novel peptides frequently retain the same molecular architecture as their ancestor proteins, substantial functional residue alterations, typically in surface-exposed locations, give rise to newly derived biological activities which may be necessary for the survival of scorpions [27; 91]. However, two peptides can use the same scaffold despite having statistically insignificant sequence similarities [95], leading to evolutionary convergence in fold structures and challenging homology inference. According to scientific consensus, differences in prey preference and/or predatory technique are the primary causes of the dynamic molecular evolution that venom-encoding genes go through [30; 31; 32; 33; 34; 96; 35; 36; 37; 38; 39; 40].

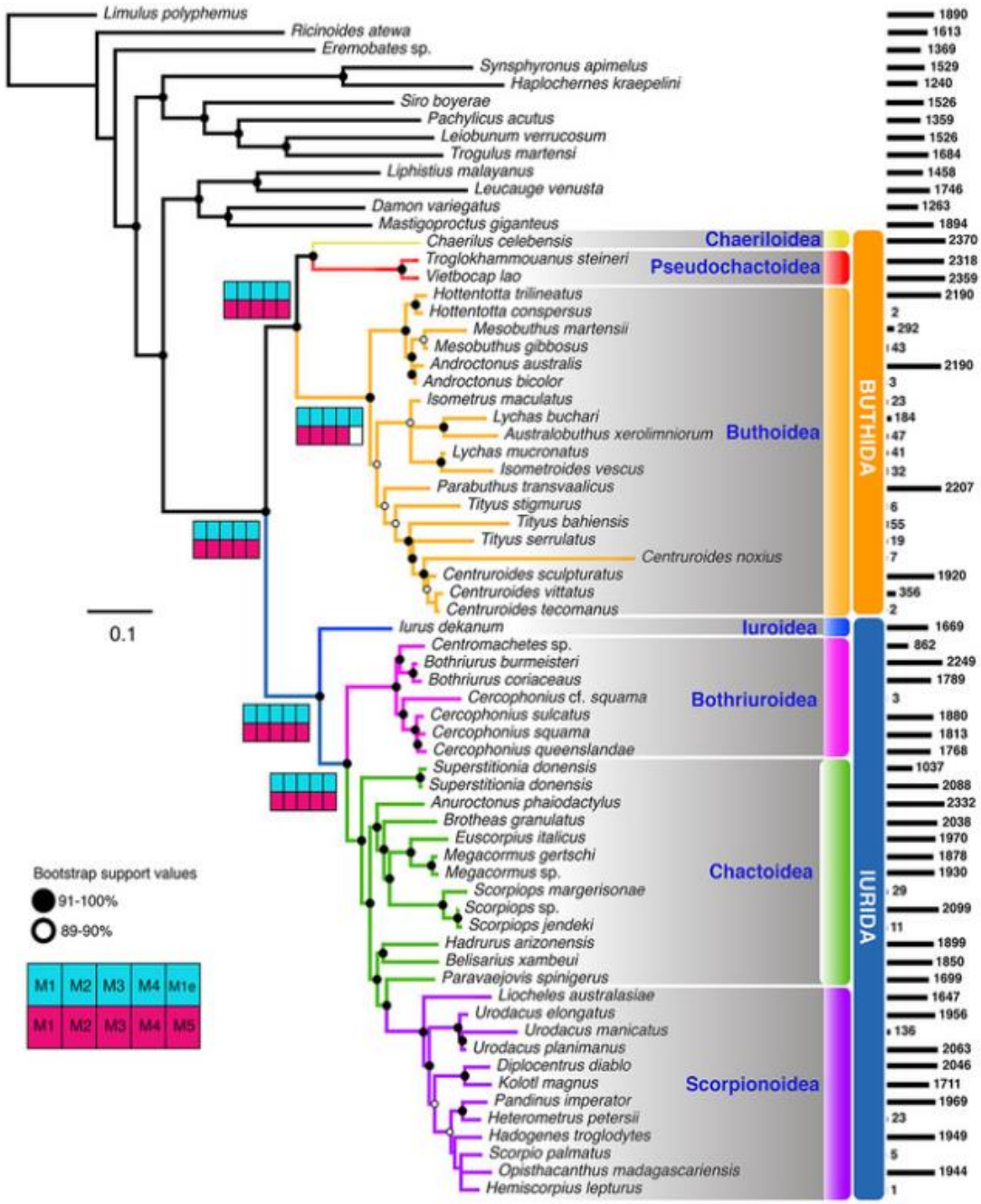

Fig. 1.9. Scorpion life tree. Number of orthologs is indicated by bars to the right of terminals. In Navajo plots, shaded squares denote node recovery from the associated analysis with M = Matrix followed by its number (except M1e = Matrix 1 analyzed with ExaML), and colored as follows: blue squares = IQTree; pink square = ASTRAL [24].

1.2.2 Structure-Function analysis of scorpion toxins

Scorpion venoms contain numerous polypeptides cross-linked via 3-4 disulfide bridges that exert various physiological and pharmacological activities by targeting ion channel (s) function [97; 98; 99]. Regardless of the diverse primary structures, the majority of scorpion toxins have an identical Csαβ (cysteine-stabilized α/β motif) fold [100]. Further, Na^+ channel toxins have been divided into mammalian and insect toxins, with the former sub-divided into α- and β- toxins [101; 102] and the latter sub-classified into depressant, excitatory, and α- insect toxins. Several scorpion toxins that exclusively target Na^+ and K^+ channels have been studied extensively concerning their structure, mode of action, and pharmacological properties [103; 104; 99]. Little attention has been paid to identifying and purifying toxins from *Mesobuthus tamulus* (*M. tamulus*) venom to develop different drug prototypes. However, the sequences of a few purified toxins have been determined. For example, ButaIT, is a novel short lepidopteran-selective toxin with 37 amino acids cross-linked by disulfide bridges and eight cysteine residues; it shares sequence homology with other fast toxins Peptide I, neurotoxin P2, Lqh-8/6, chlorotoxin, insectotoxin I5A, insect toxin 15, and insectotoxin I1. Three-dimensional structural modelling of this toxin revealed that similar to other scorpion toxins, ButaIT contains an α-helix and a β-sheet. Moreover, this toxin showed high target specificity towards *Heliothis virescens*, a notorious budworm on the cotton crop [105].

Although the structure-function relationship of these toxins from *M. tamulus* venom has not been elucidated, the functional site of Bukatoxin from *Buthus martensii karch* venom activates the Na^+ channel in nitrergic inhibitory fibers, resulting in the neuronal release of nitric oxide (NO) [106; 107; 108]. Bukatoxin shares 78% and 72% structural similarity with neurotoxin X from *Mesobuthus eupeus* venom [109] and neurotoxin IV from *Leiurus quinquestriatus quinquestriatus* venom [110], respectively. Similarly, Makatoxin I from venom of *Buthus martensii karch* contains 64 amino acids with eight half cystein residues, has a short J loop (cys- 16 to cys-22) and a long B loop (cys-36 to cys-46) [111] and exhibits 78% and 81% structural similarity with Bot I [112] and Bot II [113] toxins (both from *Buthus occictanus tunetanus* venom), respectively. Further, Makatoxin I shows 55-77% similarity with Lqq IV and Lqq III from *Leiurus quinquestriatus quinquestriatus* venom [114; 110]. The nitrergic action of Makatoxin I causes a release of NO that mediates a relaxant response in rat-precontracted anococcygeus muscle (ACM) [111].

1.3 Scorpionism: epidemiology, pathophysiology and clinical manifestations

1.3.1 Origin of scorpionism

Originating around 450 million years ago, a million cases of scorpion envenomation are accounted on all continents (except Antarctica), though the epidemiology of scorpionism is poorly known; thus remains a serious health problem worldwide [115; 116; 46]. Public action on scorpionism should be a constant object, with the main goals of improving knowledge and encouraging population behaviour change. The large number of stings that occur throughout the year has significant ramifications for creating prevention strategies aimed at reducing the prevalence of scorpionism [117]. Therefore, comprehending this injury's epidemiology is crucial [118].

The potential for scorpion envenomation depends on several variables in both the scorpion and the victim. From the former, it was possible to identify the species, size, toxin kinds, condition of the telson venom ducts, number of stings, and amount of venom injected [119]. The physiological site of the sting, together with the victim's age, weight, and state of health, should all be considered. It's important to note that children and older adults are especially susceptible to this type of catastrophe [120; 121; 122; 123]. The seasonal pattern in the temporal incidence of scorpion stings is highly associated with climatological factors. There is considerable geographical variation, either in incidence or severity of scorpion envenomation [116; 46]. Their severity are reported higher in the northern Sahara; the southern and eastern regions of Africa; the Middle East; south India; Mexico; Brazil; and the Amazonian basin area [46]. In tropical and subtropical regions, scorpion envenomation is a life-threatening medical emergency resulting in significant health issues such as cardiac malfunction, respiratory failure, hyperglycemia, hypertension and other local and systemic manifestations [124; 65].

1.3.2 Importance of understanding the epidemiology of scorpionism

Scorpion stings and their implications are a significant cause of emergency, particularly among children, in many nations [119; 125; 126]. It is poorly understood how scorpionism spreads around the world. Except for Antarctica, all continents have been home to scorpions since 430 million years ago, making them one of the most venomous and primitive arachnids [127; 128]. These nocturnal species have been adapted to live in various habitats, including temperate and tropical forests, grasslands, and caves [129]. Scorpionism is a severe public health issue in many parts of the world, as envenomation are often painful and lethal to human and causes severe health complications [54; 55; 56;

57]. The incidence and severity of scorpionism vary significantly by geographical location. Thus it is crucial to identify the local population's specific concerns and the major risk factors. To determine the prognosis and implement effective treatments, an assessment of the severity of the envenomation, particularly in children, is necessary. The best way to treat scorpion stings is still a subject of debate. According to some experts [130; 131], anti-scorpion antivenom (ASA), the only specific treatment, is debatable. In contrast, symptomatic or adjuvant treatments, whose significance is now universally acknowledged by experts, frequently depend on specific useful drugs, indications, and dosages [132]. Based on recent literature, it has been sought to specify the incidence and the severity of scorpion stings globally and to precise the principles of the management and treatment.

In India, Western Maharashtra, Saurashtra, Kerala, Andhra Pradesh, Tamil Nadu, and Karnataka are particularly vulnerable to morbidity and mortality from scorpion stings. (Fig. 1.4). The epidemiological study involving children and adults admitted with an authentic *M. tamulus* (MT) stings demonstrated most adverse effects to envenomation such as dyspnoea, chest pain, vomiting, sweating, nausea, priapism, piloerection, hypertension, tachycardia, pulmonary oedema, cardiac and gastrointestinal complications (Table 1.1).

Table 1.1. Comparative list of the pharmacological effects induced by toxins from Indian red scorpion venoms of different geographical regions.

Sl. No.	Pharmacological effects	Responsible toxins	Geographical region				Reference
			Southern India	Western India	Northern India	Sri Lanka	
1	Vomiting, nausea	Na^+ channel toxin (α neurotoxin)	YES [133]	YES [134]	YES [135]	Not known	[136]
2	Sweating	Na^+ channel toxin (α neurotoxin)	YES [133]	YES [134]	YES [135]	YES [65]	[136]
3	Salivation	Na^+ channel toxin (α neurotoxin)	Not known	YES [134]	Not known	YES [65]	[136]
4	Bradycardia, hyperkalamia, vasoconstricti	Na^+ channel toxin (α neurotoxin)	Not known	Not known	Not known	Not known	[136; 137]

	on						
5	Tachycardia	Na^+ channel toxin (α neurotoxin)	YES [134; 133]	YES [138]	Not known	YES [65]	[136]
6	Pulmonary oedema	Na^+ channel toxin (α neurotoxin)	YES [134; 133]	YES [138]	Not known	Not known	[136]
7	Chest pain	Na^+ channel toxin (β neurotoxin)	YES [133]	Not known	YES [135]	Not known	[139]
8	Breathlessnes s, cough	Na^+ channel toxin (β neurotoxin)	Not known	Not known	YES [135]	Not known	[139]
9	Cardiac arrythmias	K^+ channel toxin	Not known	YES [134]	Not known	Not known	[140]
10	Hypotension	Bradykinin potentiating peptide	YES	Not known	Not known	YES [65]	[141]
11	Hypertension	Ca^{2+} channel toxin	YES [133]	YES [138]	Not known	YES [65]	[142] [143]
12	Priapism	Bukatoxin and Makatoxin	YES [133]	YES [134]	Not known	Not known	[106]
13	Piloerection	Not characterized	YES [133]	Not known	Not known	YES [65]	-
14	Myocarditis	Na^+ channel toxin (α neurotoxin)	YES [134; 144; 133]	Not known	Not known	Not known	[136]

1.3.3 Scorpion envenomation: Prevention and treatment against MT stings

Scorpion stings are a frequent cause of emergencies in many regions of the world [46]. The controversy over the proper care of scorpion stings has returned [46]. This controversy, i.e., passive immunotherapy against symptomatic treatments, predominantly originated in Africa and Asia because medical critical care services were expanded into provincial hospitals in many scorpion-affected nations. As a result, symptomatic therapy has become more accessible and is now considered a suitable option for other urgent treatments.

Scorpion stings frequently happen at night, at the victim's house, in the middle of small towns or their suburbs, and in rural regions. Due to the patient's initial preference for traditional medicine, the location of the health centre, or the fact that they were referred from another health centre that lacked the appropriate medical resources, they may arrive

at the health centre up to 1-2 hours after the sting [46; 145]. First aid is typically provided by medical personnel who have had little formal training. Treatment for symptoms and adjuvant pain is frequent and strong. Thus using analgesics is still valideven if they are not the most criticalmedications in envenoming. An essential component of treating scorpion stings is relieving the severe pain. A local anaesthetic is the most efficient analgesic to treat stings on the fingers and toes by digital block (Table 1.2) [146]. Early diagnosis of cardiopulmonary complications at the referral centre, such as myocarditis, left ventricular failure, and cardiogenic shock based on clinical manifestation, electrocardiographic abnormality, biomarkers, and echocardiography, can aid in patient risk assessment and facilitate decision-making in the management of scorpion envenomation cases [147].

As the MT stings can be lethal, significant effort must be directed towards understanding the associated pathophysiological symptoms and adequately treating the envenomated victim. Despite advances in understanding the pathophysiology and therapy of scorpion bites, mortality remains high in many rural areas, mainly due to inefficient access to medical facilities [148]. Patients should be observed for 24 hours following a scorpion sting, irrespective of the species involved. For the cases of severe envenomation, therapeutic efforts should be directed towards treating the over-stimulated autonomic nervous system and correcting hypovolemia. Depending upon the severity of the sting, antivenom availability, and access to proper medical facilities, a single or a combination of treatment methods may be administered [149].

Intravenous administration of equine anti-scorpion antivenom (ASA) is the preferred treatment for scorpion stings. However, the efficacy and quality of commercial anti-scorpion antivenoms (ASAs) are significant concerns for successful antivenom therapy against scorpion stings. Stimulation of the α1-adrenergic receptor by *M. tamulus* venom (MTV) plays an important role in its pharmacology, resulting in clinical symptoms such as hypertension, tachycardia, myocardial dysfunction, pulmonary edema, and cool extremities in patients [124]. Therefore, α1-adrenoreceptor agonists (AAAs), such as Prazosin, are also used alone or in combination with commercial ASA for treating scorpion stings [149]. However, treatment with AAAs (Prazosin) also has limitations; for example, it causes hyperglycemia in patients at a higher dose [150; 151]. MTV also causes hyperglycemia in stung patients [152].

Consequently, AAA and MTV in unison would cause a sudden abrupt increase in blood glucose resulting in hyperglycaemic shock to the patients. For a diabetic patient, it would be a severe life-threatening consequence. Thus, antibodies raised explicitly against low molecular mass toxins using toxicovenomics, antivenomics, and affinity purification can supplement commercially available scorpion antivenoms and would be an ideal approach for better in-patient management of *M. tamulus* sting. Repurposed drugs or a therapeutic drug formulation can also be explored as possible antidotes to treat scorpion stings.

Table 1.2. Different treatment regimes utilized for scorpion sting

Types of treatment	Treatment methods	Mode of action of drug/auxiliary treatment	References
Treatment of local symptoms	• Ice packs • lignocaine (without adrenaline) using ring block • Dipyrone, a pyrazolone derivative • local anaesthesia is applied with lidocaine • oral diazepam and non-steroidal anti-inflammatory drugs (NSAIDs)	• Ice pack can reduce blood flow and nerve activity which reduces pain The main mechanism of action of NSAID is the inhibition of cyclooxygenase (COX)	[153; 132; 154]
Treatment of shock	• Elevation of the foot end of bed to maintain cerebral circulation in cases of peripheral circulatory failure • Metoclopramide, oral and parenteral fluids • Intravenous glucose, normal saline • 100mg of hydrocortisone after every 4 hours	Metaclopramide can prevent nausea and vomiting due to its action at D_2 receptor in central nervous system	[155; 132; 156]
Treatment by prazosin	Prazosin is administered either orally or sometimes given through a nasogastric tube if the patient is vomiting	Prazosin can control the arterial blood pressure and other pharmacological effects by blocking the alpha1 receptors in muscle cell and cause vasodilatation of the blood vessel.	[157; 148]
Treatment by insulin	Administration of insulin with or without alpha blocker and sodium bicarbonate	Insulin can neutralize the effect of catecholamines favouring glucose uptake, enormous boost in glycogen content in the liver, skeletal and cardiac muscles, and promote lipogenesis in animals with scorpion sting (Yugandhar et al., 1999). Moreover, administration of insulin along with an alpha	[158]

		blocker and sodium bicarbonate can diminish the rate of arrhythmias and also reverse the metabolic and electrocardiographic changes after scorpion envenomation (Radha et al., 1988).	
Specific treatment by antivenom	Administration of PSVPL , Haffkine scorpion antivenom,	The immunoglobulin present in antivenom will bind to venom toxins blocking its functional site and thus prevent to show its activity	[159]
Auxiliary treatment	Morphine, Dopamine and dobutamine, Intravenous metoprolol or esmolol and bradyarrhythmiasare, nifedipine, nitroprusside, hydralazine, Captopril, glucoseinsulin-potassium drip, lytic cocktail (pethidine-chlorpromazinepromethazine)	Morphine is used to prevent pain by binding with opioid receptor in central nervous system. Dopamine is used to treat hypotention, bradycardia via its interaction with receptors in pre- and post-synaptic cleft of neurons.	[160; 161; 162; 163; 164; 165; 166; 148; 167]

Bibliography:

[1] Dunlop, J. A., Scholtz, G. and Selden, P. A. Water-to-land transitions. *Arthropod Biology Evolution: Molecules, Development, Morphology*: 417-439, 2013.

[2] Dunlop, J. A. and Webster, M. Fossil evidence, terrestrialization and arachnid phylogeny. *Journal of Arachnology*: 86-93, 1999.

[3] Selden, P. A., Dunlop, J. A. and Edgecombe, G. Fossil taxa and relationships of chelicerates. *Arthropod Fossils Phylogeny*: 303-331, 1998.

[4] Aj, J., 2001. Paleontology, in: Brownell P, P.G., editors (Ed.), Scorpion biology and research. New York: Oxford University Press, pp. 370-392.

[5] Lourenço, W. R. and Gall, J. C. Fossil scorpions from the Buntsandstein (early Triassic) of France. *Comptes Rendus Palevol,* 3(5): 369-378, 2004.

[6] Fet, V. and Soleglad, M. E. Contributions to scorpion systematics. I. On recent changes in high-level taxonomy. *Euscorpius,* 2005(31): 1-13, 2005.

[7] Lamoral, B., 1980. A reappraisal of suprageneric classification of recent scorpions and of their zoogeography.

[8] Lourenco, W. R., 1985. Essai d'interprétation de la distribution du genre Opisthacanthus (Arachnida, Scorpiones, Ischnuridae) dans les régions néotropicale et afrotropicale. Museum National d'Histoire Naturelle, Labo. de Zool.(Arthropodes).

[9] Prendini, L. and Wheeler, W. C. Scorpion higher phylogeny and classification, taxonomic anarchy, and standards for peer review in online publishing. *Cladistics,* 21(5): 446-494, 2005.

[10] Sissom, W. D. Systematics, biogeography and paleontology. *The Biology of Scorpions,* 65: 64-160, 1990.

[11] Soleglad, M. E. and Fet, V. High-level systematics and phylogeny of the extant scorpions (Scorpiones: Orthosterni). *Euscorpius,* 2003(11): 1-56, 2003.

[12] Stockwell, S. A., 1989. Revision of the phylogeny and higher classification of scorpions (Chelicerata). University of California, Berkeley.

[13] Coddington Ja, G. G., Harvey Ms, Prendini L, Walter De. Arachnida. In Assembling the tree of life (eds J Cracraft, MJ Donoghue). *New York, NY: Oxford University Press*: 296 – 318, 2004.

[14] Prendini, L. L., H Peter. Phylogeny of the South African species of restioid leafhoppers, tribe Cephalelini (Homoptera: Cicadellidae, Ulopinae). *Insect Systematics Evolution,* 29(1): 11-18, 1998.

[15] Prendini, L. Species or supraspecific taxa as terminals in cladistic analysis? Groundplans versus exemplars revisited. *Systematic Biology,* 50(2): 290-300, 2001.

[16] Dunlop, J. A. Geological history and phylogeny of Chelicerata. *Arthropod Structure Development,* 39(2-3): 124-142, 2010.

[17] Dunlop, J. A., Erik Tetlie, O. and Prendini, L. Reinterpretation of the Silurian scorpion *Proscorpius osborni* (Whitfield): integrating data from Palaeozoic and Recent scorpions. *Palaeontology,* 51(2): 303-320, 2008.

[18] Hjelle, J. T. Anatomy and morphology. *The Biology of Scorpions*: 9-63, 1990.

[19] Jeram, A. J., 1997. Phylogeny, classification and evolution of Silurian and Devonian scorpions, Proceedings of the 17th European colloquium of arachnology, Edinburgh, pp. 17-31.

[20] Kjellesvig-Waering, E. N., 1986. A restudy of the fossil Scorpionida of the world. Paleontological research institution.

[21] Petrunkevitch, A., 1953. Paleozoic and Mesozoic Arachnida of Europe. Geological Society of America.

[22] Wendruff, A. J., Babcock, L. E., Wirkner, C. S., Kluessendorf, J. and Mikulic, D. G. A Silurian ancestral scorpion with fossilised internal anatomy illustrating a pathway to arachnid terrestrialisation. *Scientific Reports,* 10(1): 14, 2020.

[23] Howard, R. J., Edgecombe, G. D., Legg, D. A., Pisani, D. and Lozano-Fernandez, J. Exploring the evolution and terrestrialization of scorpions (Arachnida: Scorpiones) with rocks and clocks. *Organisms Diversity Evolution*, 19: 71-86, 2019.

[24] Santibáñez-López, C. E., Kriebel, R., Ballesteros, J. A., Rush, N., Witter, Z., Williams, J., Janies, D. A. and Sharma, P. P. Integration of phylogenomics and molecular modeling reveals lineage-specific diversification of toxins in scorpions. *PeerJ,* 6: e5902, 2018.

[25] Sharma, P. P., Kaluziak, S. T., Pérez-Porro, A. R., González, V. L., Hormiga, G., Wheeler, W. C. and Giribet, G. Phylogenomic interrogation of Arachnida reveals systemic conflicts in phylogenetic signal. *Molecular Biology Evolution,* 31(11): 2963-2984, 2014.

[26] Waddington, J., Rudkin, D. M. and Dunlop, J. A. A new mid-Silurian aquatic scorpion—one step closer to land? *Biology Letters,* 11(1): 20140815, 2015.

[27] Casewell, N. R., Wüster, W., Vonk, F. J., Harrison, R. A. and Fry, B. G. Complex cocktails: the evolutionary novelty of venoms. *Trends in Ecology Evolution,* 28(4): 219-229, 2013.

[28] Haney, R. A., Clarke, T. H., Gadgil, R., Fitzpatrick, R., Hayashi, C. Y., Ayoub, N. A. and Garb, J. E. Effects of gene duplication, positive selection, and shifts in gene expression on the evolution of the venom gland transcriptome in widow spiders. *Genome Biology Evolution,* 8(1): 228-242, 2016.

[29] King, G. F. and Hardy, M. C. Spider-venom peptides: structure, pharmacology, and potential for control of insect pests. *Annual Review of Entomology,* 58: 475-496, 2013.

[30] Barlow, A., Pook, C. E., Harrison, R. A. and Wüster, W. Coevolution of diet and prey-specific venom activity supports the role of selection in snake venom evolution. *Proceedings of the Royal Society B: Biological Sciences,* 276(1666): 2443-2449, 2009.

[31] Brust, A., Sunagar, K., Undheim, E. A., Vetter, I., Yang, D. C., Casewell, N. R., Jackson, T. N., Koludarov, I., Alewood, P. F. and Hodgson, W. C. Differential evolution and neofunctionalization of snake venom metalloprotease domains. *Molecular Cellular Proteomics,* 12(3): 651-663, 2013.

[32] Casewell, N. R., Wagstaff, S. C., Harrison, R. A., Renjifo, C. and Wüster, W. Domain loss facilitates accelerated evolution and neofunctionalization of duplicate snake venom metalloproteinase toxin genes. *Molecular Biology Evolution,* 28(9): 2637-2649, 2011.

[33] Daltry, J. C., Wüster, W. and Thorpe, R. S. Diet and snake venom evolution. *Nature,* 379(6565): 537-540, 1996.

[34] Duda, T. F. and Lee, T. Ecological release and venom evolution of a predatory marine snail at Easter Island. *PloS One,* 4(5): e5558, 2009.

[35] Fry, B. G., Wüster, W., Kini, R. M., Brusic, V., Khan, A., Venkataraman, D. and Rooney, A. Molecular evolution and phylogeny of elapid snake venom three-finger toxins. *Journal of Molecular Evolution,* 57: 110-129, 2003.

[36] Kordiš, D. and Gubenšek, F. Adaptive evolution of animal toxin multigene families. *Gene,* 261(1): 43-52, 2000.

[37] Low, D. H., Sunagar, K., Undheim, E. A., Ali, S. A., Alagon, A. C., Ruder, T., Jackson, T. N., Gonzalez, S. P., King, G. F. and Jones, A. Dracula's children: Molecular evolution of vampire bat venom. *Journal of Proteomics,* 89: 95-111, 2013.

[38] Puillandre, N., Watkins, M. and Olivera, B. M. Evolution of Conus peptide genes: duplication and positive selection in the A-superfamily. *Journal of Molecular Evolution,* 70): 190-202, 2010.

[39] Sunagar, K., Johnson, W. E., O'brien, S. J., Vasconcelos, V. and Antunes, A. Evolution of CRISPs associated with toxicoferan-reptilian venom and mammalian reproduction. *Molecular Biology Evolution,* 29(7): 1807-1822, 2012.

[40] Weinberger, H., Moran, Y., Gordon, D., Turkov, M., Kahn, R. and Gurevitz, M. Positions under positive selection—Key for selectivity and potency of scorpion α-toxins. *Molecular Biology Evolution,* 27(5): 1025-1034, 2010.

[41] Dunlop, J. A. and Selden, P. A. Calibrating the chelicerate clock: a paleontological reply to Jeyaprakash and Hoy. *Experimental Applied Acarology,* 48: 183-197, 2009.

[42] Bryson Jr, R. W., Riddle, B. R., Graham, M. R., Smith, B. T. and Prendini, L. As old as the hills: montane scorpions in southwestern North America reveal ancient associations between biotic diversification and landscape history. *PLoS One,* 8(1): e52822, 2013.

[43] Yamashita, T. and Rhoads, D. D. Species delimitation and morphological divergence in the scorpion Centruroides vittatus (Say, 1821): insights from phylogeography. *PLoS One,* 8(7): e68282, 2013.

[44] Zeh, D. W., 1990. The Biology of Scorpions. Stanford University Press, Stanford, CA.

[45] Behrend, M. R., Basáñez, M.-G., Hamley, J. I., Porco, T. C., Stolk, W. A., Walker, M., De Vlas, S. J. and Consortium, N. M. Modelling for policy: the five principles of the Neglected Tropical Diseases Modelling Consortium. *PLoS Neglected Tropical Diseases,* 14(4): e0008033, 2020.

[46] Chippaux, J. P. and Goyffon, M. Epidemiology of scorpionism: a global appraisal. *Acta tropica,* 107(2): 71-79, 2008.

[47] Laustsen, A. H., Solà, M., Jappe, E. C., Oscoz, S., Lauridsen, L. P. and Engmark, M. Biotechnological trends in spider and scorpion antivenom development. *Toxins,* 8(8): 226, 2016.

[48] Lourenço, W. R. The evolution and distribution of noxious species of scorpions (Arachnida: Scorpiones). *Journal of Venomous Animals Toxins Including Tropical Diseases,* 24, 2018.

[49] Reckziegel, G. C. and Pinto, V. L. Scorpionism in Brazil in the years 2000 to 2012. *Journal of Venomous Animals Toxins including Tropical Diseases,* 20: 02-08, 2014.

[50] Chippaux, J. P. Emerging options for the management of scorpion stings. *Drug design, development*: 165-173, 2012.

[51] Pezzi, M., Bonacci, T., Leis, M., Mamolini, E., Marchetti, M. G., Krčmar, S., Chicca, M., Del Zingaro, C. N. F., Faucheux, M. J. and Scapoli, C. Myiasis in domestic cats: a global review. *Parasites Vectors,* 12(1): 1-14, 2019.

[52] Santos, M. S., Silva, C. G., Neto, B. S., Júnior, C. R. G., Lopes, V. H., Júnior, A. G. T., Bezerra, D. A., Luna, J. V., Cordeiro, J. B. and Júnior, J. G. Clinical and epidemiological aspects of scorpionism in the world: a systematic review. *Wilderness Environmental Medicine,* 27(4): 504-518, 2016.

[53] Ward, M. J., Ellsworth, S. A. and Nystrom, G. S. A global accounting of medically significant scorpions: Epidemiology, major toxins, and comparative resources in harmless counterparts. *Toxicon,* 151: 137-155, 2018.

[54] Bawaskar Hs, B. P. Scorpion sting: update. *Journal of Association of Physicians of India,* 60): 46-55, 2012.

[55] Chippaux, J.-P. Epidemiology of envenomations by terrestrial venomous animals in Brazil based on case reporting: from obvious facts to contingencies. *Journal of Venomous Animals Toxins Including Tropical Diseases,* 21: 1-17, 2015.

[56] Ebrahimi, V., Hamdami, E., Moemenbellah-Fard, M. D. and Jahromi, S. E. Predictive determinants of scorpion stings in a tropical zone of south Iran: use of mixed seasonal autoregressive moving average model. *Journal of Venomous Animals Toxins Including Tropical Diseases,* 23, 2017.

[57] Khatony, A., Abdi, A., Fatahpour, T. and Towhidi, F. The epidemiology of scorpion stings in tropical areas of Kermanshah province, Iran, during 2008 and 2009. *Journal of Venomous Animals Toxins Including Tropical Diseases,* 21, 2015.

[58] Mullen, G. R. and Sissom, W. D., 2019. Scorpions (scorpiones), Medical and veterinary entomology. Elsevier, pp. 489-504.

[59] Rein, J. O. The scorpion files - Buthidae 2020.

[60] Lourenço, W. R. Scorpion incidents, misidentification cases and possible implications for the final interpretation of results. *Journal of Venomous Animals Toxins including Tropical Diseases,* 22, 2016.

[61] Goyffon, M. and Kovoor, J. Chactoid venoms. *Arthropod Venoms*: 395-418, 1978.

[62] Nishikawa, A., Caricati, C. P., Lima, M., Dos Santos, M., Kipnis, T. L., Eickstedt, V., Knysak, I., Da Silva, M., Higashi, H. G. and Da Silva, W. D. Antigenic cross-

reactivity among the venoms from several species of Brazilian scorpions. *Toxicon,* 32(8): 989-998, 1994.

[63] Kovařík, F. A revision of the genus Hottentotta Birula, 1908, with descriptions of four new species (Scorpiones, Buthidae). *Euscorpius,* 2007(58): 1-107, 2007.

[64] Bhadani, U., Tripathi, M., Sharma, S. and Pandey, R. Scorpion sting envenomation presenting with pulmonary edema in adults: a report of seven cases from Nepal. *Indian Journal of Medical Sciences,* 60(1): 19-23, 2006.

[65] Kularatne, S. A., Dinamithra, N. P., Sivansuthan, S., Weerakoon, K. G., Thillaimpalam, B., Kalyanasundram, V. and Ranawana, K. B. Clinico-epidemiology of stings and envenoming of *Hottentotta tamulus* (Scorpiones: Buthidae), the Indian red scorpion from Jaffna Peninsula in northern Sri Lanka. *Toxicon,* 93: 85-89, 2015.

[66] Das, B., Saviola, A. J. and Mukherjee, A. K. Biochemical and proteomic characterization, and pharmacological insights of indian red scorpion venom toxins. *Frontiers in Pharmacology,* 12: 710680, 2021.

[67] Rubio, M., 2008. Scorpions: Everything about purchase, care, feeding, and housing. Barron's Educational Series.

[68] Polis, G. A., 1990. The biology of scorpions.

[69] Stockmann, R., Ythier, E. and Fet, V. Scorpions of the World, 2010.

[70] Klußmann-Fricke, B.-J., Prendini, L. and Wirkner, C. Evolutionary morphology of the hemolymph vascular system in scorpions: a character analysis. *Arthropod Structure Development,* 41(6): 545-560, 2012.

[71] Lourenço, W. R. The coevolution between telson morphology and venom glands in scorpions (Arachnida). *Journal of Venomous Animals Toxins including Tropical Diseases,* 26), 2020.

[72] Sridhara, S., Chakravarthy, A. K., Kalarani, V. and Reddy, D. C. Diversity and ecology of scorpions: evolutionary success through venom. *Arthropod Diversity Conservation in the Tropics Sub-tropics*: 57-80, 2016.

[73] Coelho, P., Kaliontzopoulou, A., Rasko, M. and Van Der Meijden, A. A 'striking'relationship: scorpion defensive behaviour and its relation to morphology and performance. *Functional Ecology,* 31(7): 1390-1404, 2017.

[74] Farley, R. D. The ultrastructure of book lung development in the bark scorpion *Centruroides gracilis* (Scorpiones: Buthidae). *Frontiers in Zoology,* 8(1): 1-24, 2011.

[75] Knowlton, E. D. and Gaffin, D. D. Functionally redundant peg sensilla on the scorpion pecten. *Journal of Comparative Physiology A,* 197: 895-902, 2011.

[76] Wanninger, A., 2015. Evolutionary Developmental Biology of Invertebrates 3: Ecdysozoa I: Non-Tetraconata. Springer.

[77] Stockmann, R., 2015. Introduction to scorpion biology and ecology, in: Gopalakrishnakone, P., Possani, L., F. Schwartz, E., Rodríguez de la Vega, R. (Ed.), Scorpion Venoms. Springer, Dordrecht, pp. 25-59.

[78] Lautie, N., Soranzo, L., Lajarille, M.-C. and Stockmann, R. Paraxial organ of a scorpion: structural and ultrastructural studies of *Euscorpius tergestinus* paraxial organ (Scorpiones, Euscorpiidae). *Invertebrate Reproduction Development,* 51(2): 77-90, 2008.

[79] Yigit, N. and Benli, M. Fine structural analysis of the stinger in venom apparatus of the scorpion *Euscorpius mingrelicus* (Scorpiones: Euscorpiidae). *Journal of Venomous Animals Toxins including Tropical Diseases,* 16: 76-86, 2010.

[80] Schofield, R. Metals in cuticular structures. *Scorpion Biology Research*: 234-256, 2001.

[81] Van Der Meijden, A. and Kleinteich, T. A biomechanical view on stinger diversity in scorpions. *Journal of Anatomy,* 230(4): 497-509, 2017.

[82] Cowles, J., 2018. Amazing arachnids. Princeton University Press.

[83] Holderied, M., Korine, C. and Moritz, T. Hemprich's long-eared bat (*Otonycteris hemprichii*) as a predator of scorpions: whispering echolocation, passive gleaning and prey selection. *Journal of comparative Physiology A,* 197: 425-433, 2011.

[84] Thompson, B. M. The Grasshopper Mouse and Bark Scorpion: Evolutionary Biology Meets Pain Modulation and Selective Receptor Inactivation. *Journal of Undergraduate Neuroscience Education,* 16(2): R51, 2018.

[85] Van Der Meijden, A., Lobo Coelho, P., Sousa, P. and Herrel, A. Choose your weapon: defensive behavior is associated with morphology and performance in scorpions. *PloS One,* 8(11): e78955, 2013.

[86] Lourenço, W. Parthenogenesis in scorpions: some history-new data. *Journal of Venomous Animals Toxins including Tropical Diseases,* 14: 19-44, 2008.

[87] Warburg, M. Reproductive system of female scorpion: a partial review. *The Anatomical Record: Advances in Integrative Anatomy Evolutionary Biology,* 293(10): 1738-1754, 2010.

[88] Warburg, M. R. Pre-and post-parturial aspects of scorpion reproduction: a review. *European Journal of Entomology,* 109(2): 139, 2012.

[89] Lourenço, W. R. Reproduction in scorpions, with special reference to parthenogenesis. *European Arachnology,* 2002: 71-85, 2000.

[90] Dowell, N. L., Giorgianni, M. W., Kassner, V. A., Selegue, J. E., Sanchez, E. E. and Carroll, S. B. The deep origin and recent loss of venom toxin genes in rattlesnakes. *Current Biology,* 26(18): 2434-2445, 2016.

[91] Fry, B. G., Roelants, K., Champagne, D. E., Scheib, H., Tyndall, J. D., King, G. F., Nevalainen, T. J., Norman, J. A., Lewis, R. J. and Norton, R. S. The toxicogenomic multiverse: convergent recruitment of proteins into animal venoms. *Annual Review of Genomics Human Genetics,* 10: 483-511, 2009.

[92] Juarez, P., Comas, I., Gonzalez-Candelas, F. and Calvete, J. J. Evolution of snake venom disintegrins by positive Darwinian selection. *Molecular Biology Evolution,* 25(11): 2391-2407, 2008.

[93] Rokyta, D. R., Wray, K. P., Lemmon, A. R., Lemmon, E. M. and Caudle, S. B. A high-throughput venom-gland transcriptome for the Eastern Diamondback Rattlesnake (*Crotalus adamanteus*) and evidence for pervasive positive selection across toxin classes. *Toxicon,* 57(5): 657-671, 2011.

[94] Wong, E. S. and Belov, K. Venom evolution through gene duplications. *Gene,* 496(1): 1-7, 2012.

[95] Orengo, C. A., Jones, D. T. and Thornton, J. M. Protein superfamilles and domain superfolds. *Nature,* 372(6507): 631-634, 1994.

[96] Fry, B., Scheib, H. and Weerd, L. Van der, Young B, McNaughtan J, Ramjan SFR, Vidal N, Poelmann RE, Norman JA: Evolution of an arsenal. *Molecular and Cellular Proteomics,* 7: 215-246, 2008.

[97] Gordon, D., Moskowitz, H., Eitan, M., Warner, C., Catterall, W. A. and Zlotkin, E. Localization of receptor sites for insect-selective toxins on sodium channels by site-directed antibodies. *Biochemistry,* 31(33): 7622-7628, 1992.

[98] Rochat, H., Bernard, P. and Couraud, F. Scorpion toxins: chemistry and mode of action. *Advances in Cytopharmacology,* 3: 325-334, 1979.

[99] Zlotkin, E., Eitan, M., Bindokas, V., Adams, M., Moyer, M., Burkhart, W. and Fowler, E. Functional duality and structural uniqueness of the depressant insect-selective neurotoxins. *Biochemistry,* 30(19): 4814-4821, 1991.

[100] Fontecilla-Camps, J. C., Habersetzer-Rochat, C. and Rochat, H. Orthorhombic crystals and three-dimensional structure of the potent toxin II from the scorpion

Androctonus australis Hector. *Proceedings of the National Academy of Sciences,* 85(20): 7443-7447, 1988.

[101] Couraud, F., Jover, E., Dubois, J. and Rochat, H. Two types of scorpion toxin receptor sites, one related to the activation, the other to the inactivation of the action potential sodium channel. *Toxicon,* 20(1): 9-16, 1982.

[102] Jover, E., Couraud, F. and Rochat, H. Two types of scorpion neurotoxins characterized by their binding to two separate receptor sites on rat brain synaptosomes. *Biochemical Biophysical Research Communications,* 95(4): 1607-1614, 1980.

[103] Delepierre, M., Prochnicka-Chalufour, A. and Possani, L. D. A novel potassium channel blocking toxin from the scorpion Pandinus imperator: a 1H NMR analysis using a nano-NMR probe. *Biochemistry,* 36(9): 2649-2658, 1997.

[104] Miller, C., Moczydlowski, E., Latorre, R. and Phillips, M. Charybdotoxin, a protein inhibitor of single Ca $^{2+}$-activated K^{+} channels from mammalian skeletal muscle. *Nature,* 313: 316-318, 1985.

[105] Wudayagiri, R., Inceoglu, B., Herrmann, R., Derbel, M., Choudary, P. V. and Hammock, B. D. Isolation and characterization of a novel lepidopteran-selective toxin from the venom of South Indian red scorpion, *Mesobuthus tamulus*. *BMC Biochemistry,* 2: 1-8, 2001.

[106] Gibson, A. and Mcfadzean, I. Biology of the anococcygeus muscle, 2001.

[107] Reis, M. B., Zoccal, K. F., Gardinassi, L. G. and Faccioli, L. H. Scorpion envenomation and inflammation: Beyond neurotoxic effects. *Toxicon,* 167: 174-179, 2019.

[108] Srinivasan, K., Nirthanan, S., Sasaki, T., Sato, K., Cheng, B., Gwee, M., Kini, R. and Gopalakrishnakone, P. Functional site of bukatoxin, an α-type sodium channel neurotoxin from the Chinese scorpion (*Buthus martensi Karsch*) venom: probable role of the 52PDKVP56 loop. *FEBS Letters,* 494(3): 145-149, 2001.

[109] Grishin, E., Soldatov, N., Soldatova, L. and Ovchinnikov, Y. Studies of the toxins from *Buthus eupeus* scorpion venom. *Toxicon,* 17(60): 0041-0101, 1979.

[110] Kopeyan, C., Martinez, G. and Rochat, H. Primary structure of toxin IV of *Leiurus quinquestriatus quinquestriatus*: Characterization of a new group of scorpion toxins. *FEBS Letters,* 181(2): 211-217, 1985.

[111] Gong, J., Kini, R. M., Gwee, M. C., Gopalakrishnakone, P. and Chung, M. C. Makatoxin I, a novel toxin isolated from the venom of the scorpion *Buthus martensi*

Karsch, exhibits nitrergic actions. *Journal of Biological Chemistry,* 272(13): 8320-8324, 1997.

[112] Vargas, O., Gregoire, J., Martin, M. F., Bechis, G. and Rochat, H. Neurotoxins from the venoms of two scorpions: *Buthus occitanus tunetanus* and *Buthus occitanus mardochei*. *Toxicon,* 20: 79, 1982.

[113] Gregoire, J. and Rochat, H. Covalent structure of toxins I and II from the scorpion *Buthus occitanus tunetanus*. *Toxicon,* 21(1): 153-162, 1983.

[114] Kopeyan, C., Mansuelle, P., Martin-Eauclaire, M. F., Rochat, H. and Miranda, F. Characterization of toxin III of the scorpion *Leiurus quinquestriatus quinquestriatus*: a new type of alpha-toxin highly toxic both to mammals and insects. *Natural Toxins,* 1(5): 308-312, 1993.

[115] Adiguzel, S., Ozkan, O. and Inceoglu, B. Epidemiological and clinical characteristics of scorpionism in children in Sanliurfa, Turkey. *Toxicon,* 49(6): 875-880, 2007.

[116] Bahloul, M., Chabchoub, I., Chaari, A., Chtara, K., Kallel, H., Dammak, H., Ksibi, H., Chelly, H., Rekik, N. and Hamida, C. B. Scorpion envenomation among children: clinical manifestations and outcome (analysis of 685 cases). *The American Journal of Tropical Medicine Hygiene,* 83(5): 1084, 2010.

[117] Albuquerque, C. M. R. D., Santana Neto, P. D. L., Amorim, M. L. P. and Pires, S. C. V. Pediatric epidemiological aspects of scorpionism and report on fatal cases from *Tityus stigmurus* stings (Scorpiones: Buthidae) in State of Pernambuco, Brazil. *Revista da Sociedade Brasileira de Medicina Tropical,* 46: 484-489, 2013.

[118] Barbosa, A. D., Magalhães, D. F. D., Silva, J. a. D., Silva, M. X., Cardoso, M. D. F. E. C., Meneses, J. N. C. and Cunha, M. D. C. M. Epidemiological study of scorpion stings in Belo Horizonte, Minas Gerais state, Brazil, 2005-2009. *Cadernos de Saúde Pública,* 28: 1785-1789, 2012.

[119] Dehesa-Dávila, M. and Possani, L. D. Scorpionism and serotherapy in Mexico. *Toxicon,* 32(9): 1015-1018, 1994.

[120] Dabo, A., Golou, G., Traoré, M., Diarra, N., Goyffon, M. and Doumbo, O. Scorpion envenoming in the north of Mali (West Africa): epidemiological, clinical and therapeutic aspects. *Toxicon,* 58(2): 154-158, 2011.

[121] Goyffon, M. and Billiald, P. Envenomations VI. Scorpionism in Africa. *Medecine Tropicale: Revue du Corps de Sante Colonial,* 67(5): 439-446, 2007.

[122] Matthiensen, F. Os escorpiões e suas relações com o homem: uma revisão. *Ciência e Cultura,* 40(12): 1168-1172, 1988.

[123] Soares, M. R. M., Azevedo, C. S. D. and De Maria, M. Escorpionismo em Belo Horizonte, MG: um estudo retrospectivo. *Revista da Sociedade Brasileira de Medicina Tropical,* 35: 359-363, 2002.

[124] Bawaskar, H. and Bawaskar, P. Management of the cardiovascular manifestations of poisoning by the Indian red scorpion (*Mesobuthus tamulus*). *Heart,* 68(11): 478-480, 1992.

[125] Goyffon, M., Vachon, M. and Broglio, N. Epidemiological and clinical characteristics of the scorpion envenomation in Tunisia. *Toxicon,* 20(1): 337-344, 1982.

[126] Otero, R., Navío, E., Céspedes, F., Núñez, M., Lozano, L., Moscoso, E., Matallana, C., Arsuza, N., García, J. and Fernández, D. Scorpion envenoming in two regions of Colombia: clinical, epidemiological and therapeutic aspects. *Transactions of the Royal Society of Tropical Medicine Hygiene,* 98(12): 742-750, 2004.

[127] Wang, X., Gao, B. and Zhu, S. Exon shuffling and origin of scorpion venom biodiversity. *Toxins,* 9(1): 10, 2016.

[128] Zhang, L., Shi, W., Zeng, X.-C., Ge, F., Yang, M., Nie, Y., Bao, A., Wu, S. and Guoji, E. Unique diversity of the venom peptides from the scorpion *Androctonus bicolor* revealed by transcriptomic and proteomic analysis. *Journal of Proteomics,* 128: 231-250, 2015.

[129] Chowell, G., Díaz-Dueñas, P., Bustos-Saldaña, R., Mireles, A. A. and Fet, V. Epidemiological and clinical characteristics of scorpionism in Colima, Mexico (2000–2001). *Toxicon,* 47(7): 753-758, 2006.

[130] Abroug, F., Nouira, S., El Atrous, S., Besbes, L., Boukef, R., Boussarsar, M., Marghli, S., Eurin, J., Barthelemy, C. and El Ayeb, M. A canine study of immunotherapy in scorpion envenomation. *Intensive Care Medicine,* 29: 2266-2276, 2003.

[131] Bawaskar, H. and Bawaskar, P. Utility of scorpion antivenin vs prazosin in the management of severe *Mesobuthus tamulus* (Indian red scorpion) envenoming at rural setting. *Journal of the Association of Physicians of India,* 55: 14-21, 2007.

[132] Freire-Maia, L., Campos, J. and Amaral, C. Approaches to the treatment of scorpion envenoming. *Toxicon,* 32(9): 1009-1014, 1994.

[133] Yuvaraja, K., Chidambaram, N., Umarani, R., Bhargav, K. M., Kumar, S. P., Prabhu, T. and Balasubramaian, E. A study on clinical features, complications and

management of scorpion sting envenomation at a tertiary care hospital, in rural South India. *Journal of Clinical Scientific Research Volume,* 8(3): 141, 2019.

[134] Bawaskar, H. and Bawaskar, P. Indian red scorpion envenoming. *The Indian Journal of Pediatrics,* 65: 383-391, 1998.

[135] Agrawal, A., Kumar, A., Consul, S. and Yadav, A. Scorpion bite, a sting to the heart! *Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine,* 19(4): 233, 2015.

[136] Jimenez, E. C., Sasakawa, N. and Kumakura, K. Effects of sodium channel-targeted conotoxins on catecholamine release in adrenal chromaffin cells. *Philippine Journal of Science,* 137(2): 127-132, 2008.

[137] Tiwari, A. K. and Deshpande, S. B. Toxicity of scorpion (*Buthus tamulus*) venom in mammals is influenced by the age and species. *Toxicon,* 31(12): 1619-1622, 1993.

[138] Bawaskar, H. and Bawaskar, P. Severe envenoming by the Indian red scorpion *Mesobuthus tamulus*: the use of prazosin therapy. *QJM: An International Journal of Medicine,* 89(9): 701-704, 1996.

[139] Stevens, M., Peigneur, S. and Tytgat, J. Neurotoxins and their binding areas on voltage-gated sodium channels. *Frontiers in Pharmacology,* 2: 71, 2011.

[140] Ravens, U. and Cerbai, E. Role of potassium currents in cardiac arrhythmias. *Europace,* 10(10): 1133-1137, 2008.

[141] Ianzer, D., Konno, K., Marques-Porto, R., Portaro, F. C. V., Stöcklin, R., De Camargo, A. C. M. and Pimenta, D. C. Identification of five new bradykinin potentiating peptides (BPPs) from *Bothrops jararaca* crude venom by using electrospray ionization tandem mass spectrometry after a two-step liquid chromatography. *Peptides,* 25(7): 1085-1092, 2004.

[142] Fan, Z., Chen, Y. and Liu, H. Calcium channel blockers for pulmonary arterial hypertension. *Cochrane Database of Systematic Reviews,* (9), 2015.

[143] Touyz, R. M., Alves-Lopes, R., Rios, F. J., Camargo, L. L., Anagnostopoulou, A., Arner, A. and Montezano, A. C. Vascular smooth muscle contraction in hypertension. *Cardiovascular Research,* 114(4): 529-539, 2018.

[144] Madhavan, J., 2015. A study on clinical presentation and outcome of scorpion sting in children. Thanjavur Medical College, Thanjavur.

[145] Soulaymani-Bencheikh, R., Faraj, Z., Semlali, I., Khattabi, A., Skalli, S., Benkirane, R. and Badri, M. Epidemiological aspects of scorpion stings in Morocco. *Revue D'epidemiologie et de Sante Publique,* 50(4): 341-347, 2002.

[146] Prasad, R., Kumar, A., Jain, D., Das, B., Singh, U. K. and Singh, T. Echocardiography versus cardiac biomarkers for myocardial dysfunction in children with scorpion envenomation: An observational study from tertiary care center in northern India. *Indian Heart Journal,* 72(5): 431-434, 2020.

[147] Warrell, D. A. Venomous bites, stings, and poisoning: an update. *Infectious Disease Clinics,* 33(1): 17-38, 2019.

[148] Reddy, B. R. C., 2013. Scorpion Envenomation: What is New? , Medicine Update, 23ª ed. Jaypee Brothers Medical Publishers, Nova Delhi, India, pp. 421-423.

[149] Bawaskar, H. S. and Bawaskar, P. H. Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (*Mesobuthus tamulus*) sting: randomised open label clinical trial. *British Medical Journal,* 342: c7136, 2011.

[150] Barbieri, C., Caldara, R., Ferrari, C., Dal Bo, G. A., Paracchi, A., Romussi, M., Curtarelli, G. and Therapeutics. Metabolic effects of prazosin. *Clinical Pharmacology,* 27(3): 313-316, 1980.

[151] Murashita, M., Kusumi, I., Hosoda, H., Kangawa, K. and Koyama, T. Acute administration of clozapine concurrently increases blood glucose and circulating plasma ghrelin levels in rats. *Psychoneuroendocrinology,* 32(7): 777-784, 2007.

[152] Bahloul, M., Turki, O., Chaari, A., Bouaziz, M. and Metabolism. Incidence, mechanisms and impact outcome of hyperglycaemia in severe scorpion-envenomed patients. *Therapeutic Advances in Endocrinology Metabolism,* 9(7): 199-208, 2018.

[153] Bahloul, M., Chaari, A., Dammak, H., Samet, M., Chtara, K., Chelly, H., Hamida, C. B., Kallel, H. and Bouaziz, M. Pulmonary edema following scorpion envenomation: mechanisms, clinical manifestations, diagnosis and treatment. *International Journal of Cardiology,* 162(2): 86-91, 2013.

[154] Kokki, H. Nonsteroidal anti-inflammatory drugs for postoperative pain: a focus on children. *Pediatric Drugs,* 5: 103-123, 2003.

[155] Abroug, F., Nouira, S., Haguiga, H., Elatrous, S., Belghith, M., Boujdaria, R., Touzi, N. and Bouchoucha, S. High-dose hydrocortisone hemisuccinate in scorpion envenomation. *Annals of Emergency Medicine,* 30(1): 23-27, 1997.

[156] Rang, H. P., 2003. Anthelmintic Drugs, in: H. P. Rang, M.M.D., J. M. Ritter, P. K. Moore (Ed.), Pharmacology.

[157] Reader, T., Briere, R. and Grondin, L. Alpha-1 and alpha-2 adrenoceptor binding in cerebral cortex: Competition studies with [3 H] prazosin and [3 H] idazoxan. *Journal of neural transmission,* 68): 79-95, 1987.

[158] Yugandhar, B., Radha Krishna Murthy, K. and Sattar, S. Insulin administration in severe scorpion envenoming. *Journal of Venomous Animals Toxins,* 5: 200-219, 1999.

[159] Birdsall, H. H., 2015. Adaptive immunity: antibodies and immunodeficiencies, Mandell, douglas, and bennett's principles and practice of infectious diseases. Elsevier, pp. 34-49. e32.

[160] Akella, A., Tiwari, A. K., Rai, O. P. and Deshpande, S. B. Morphine blocks the *Mesobuthus tamulus* venom-induced augmentation of phenyldiguanide reflex and pulmonary edema in anesthetized rats. *Indian Journal of Pharmacology,* 48(1): 74, 2016.

[161] Bawaskar, H. and Bawaskar, P. Vasodilators: scorpion envenoming and the heart (an Indian experience). *Toxicon,* 32(9): 1031-1040, 1994.

[162] Bhoite, R. R., Bhoite, G. R., Bagdure, D. N. and Bawaskar, H. S. Anaphylaxis to scorpion antivenin and its management following envenomation by Indian red scorpion, *Mesobuthus tamulus*. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine,* 19(9): 547, 2015.

[163] Devi, C. S., Reddy, C. N., Devi, S. L., Subrahmanyam, Y., Bhatt, H. V., Suvarnakumari, G., Murthy, D. P. and Reddy, C. Defibrination syndrome due to scorpion venom poisoning. *British Medical Journal,* 1(5692): 345-347, 1970.

[164] Gueron, M., Ilia, R. and Sofer, S. The cardiovascular system after scorpion envenomation. A review. *Journal of Toxicology: Clinical Toxicology,* 30(2): 245-258, 1992.

[165] Pandurang, K. S., Singh, J., Bijesh, S. and Singh, H. Effectiveness of anti scorpion venom for red scorpion envenomation. *Indian Pediatrics,* 51: 131-133, 2014.

[166] Rahimtoola, S. H., Raphael, M. J., Pitney, W. R., Olsen, E. J. and Webb-Peploe, M. Therapeutic defibrination and heparin therapy in the prevention and resolution of experimental venous thrombosis. *Circulation,* 42(4): 729-737, 1970.

[167] Sibley, D. R., Monsma Jr, F. J. and Shen, Y. Molecular neurobiology of dopaminergic receptors. *International Review of Neurobiology,* 35: 391-415, 1993.