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A global accounting of medically significant scorpions: Epidemiology, major toxins, and comparative resources in harmless counterparts

Micaiah J. Ward*, Schyler A. Ellsworth[1], Gunnar S. Nystrom[1]

Department of Biological Science, Florida State University, Tallahassee, FL 32306, USA

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ABSTRACT

Scorpions are an ancient and diverse venomous lineage, with over 2200 currently recognized species. Only a small fraction of scorpion species are considered harmful to humans, but the often life-threatening symptoms caused by a single sting are significant enough to recognize scorpionism as a global health problem. The continued discovery and classification of new species has led to a steady increase in the number of both harmful and harmless scorpion species. The purpose of this review is to update the global record of medically significant scorpion species, assigning each to a recognized sting class based on reported symptoms, and provide the major toxin classes identified in their venoms. We also aim to shed light on the harmless species that, although not a threat to human health, should still be considered medically relevant for their potential in therapeutic development. Included in our review is discussion of the many contributing factors that may cause error in epidemiological estimations and in the determination of medically significant scorpion species, and we provide suggestions for future scorpion research that will aid in overcoming these errors.

1. Introduction

Originating approximately 450 million years ago, scorpions have since diversified into 19 recognized families and over 2200 species (Sharma et al., 2015; Lourenço, 2018). Epidemiological reviews on scorpionism have uncovered the dangerous reality of this global health problem, which results in thousands of deaths annually, and have contributed to the expansion of recognized harmful scorpion species (Müller, 1993; Al-Sadoon and Jarrar, 2003; Chippaux and Goyffon, 2008; Sari et al., 2011; Dehghani and Fathi, 2012; Borges et al., 2012; Santibáñez-López et al., 2015; Santos et al., 2016; Shahi et al., 2016; Bavani et al., 2017; Erickson and Cheema, 2017; Kang and Brooks, 2017; Riaño-Umbarila et al., 2017; Sanaei-Zadeh et al., 2017). Ten years ago, Chippaux and Goyffon (2008) listed 34 scorpion species known to cause human harm, with all but one (*Hemiscorpius lepturus*) belonging to the Buthidae family. It is now estimated that nearly 50 scorpion species are harmful to humans (Lourenço, 2018) and include the families Buthidae, Hemiscorpiidae, and Scorpionidae. The majority of scorpion species, however, have not been reported in the literature as causing human harm and are generally considered harmless.

Scorpion venoms are a rich source of protein-based toxins, many of which have been identified as responsible for the painful and often life-threatening symptoms, especially the highly expressed ion-channel toxins (Possani et al., 1999; de la Vega and Possani, 2004; de la Vega et al., 2010; Quintero-Hernández et al., 2013). Functional characterization of scorpion toxins has led to the development of life-saving medications, including a chlorotoxin found in *Leiurus hebraeus* (formerly *L. quinquestriatus hebraeus*), which can act as both an optical imaging contrast agent in the surgical removal of tumors, known as tumor paint, as well as an inhibitor of glioma cell invasion (Castle and Strong, 1986; Veiseh et al., 2007; Deshane et al., 2003). Scorpion venom characterization has also revealed that harmless scorpion species produce a plethora of toxins homologous to those found in their deadly relatives, including ion-channel toxins and antimicrobial peptides (Schwartz et al., 2007; Ma et al., 2009; Diego-García et al., 2012; He et al., 2013; Luna-Ramírez et al., 2015; Quintero-Hernández et al., 2015; Rokyta and Ward, 2017; Santibáñez-López et al., 2017; Ward et al., 2018). The term "medically significant" has been applied to scorpion species that cause human harm throughout the literature, often with the implication that venom from these species may be therapeutically useful. Harmless scorpion species, however, are just as medically relevant in drug development due to the homologous toxins ubiquitous in scorpion venoms.

The goal of this review is to provide an up-to-date global accounting of scorpion species identified as being medically significant in the literature, including geography, estimated sting frequency, symptoms,

* Corresponding author. Florida State University, Department of Biological Science, 319 Stadium Dr., Tallahassee, FL 32306-4295 USA.
E-mail address: mward@bio.fsu.edu (M.J. Ward).
[1] Contributed equally to manuscript.

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and sting class assignments based on criteria proposed by Khattabi et al. (2011). Where available, the major toxin classes identified in their venoms are also reported to provide reference of scorpion toxin diversity and identify where additional venom characterization work is needed. We also highlight a few well-characterized scorpion species that are considered harmless to humans to illustrate their potential role in medicine and in understanding the evolutionary trajectories that have led to the co-existence of extraordinarily similar venoms with drastically different consequences. We recognize that several factors make an accurate assessment on this scale nearly impossible, including the continued emergence and reclassification of species, overlapping geographical regions of species with extremely similar morphology, variation in human sensitivity, and lack of proper scorpion identification. Nevertheless, we have made every effort to provide a summary of scorpions considered to be medically significant or harmful to humans as reported throughout the literature, with notes on contributing factors that may cause error in epidemiological estimations.

2. Methods

2.1. Search strategy

Our search strategy focused on scorpions that have been reported as medically significant or cause human harm in previous scorpionism literature reviews (Müller, 1993; Al-Sadoon and Jarrar, 2003; Chippaux and Goyffon, 2008; Sari et al., 2011; Borges et al., 2012; Dehghani and Fathi, 2012; Lourenço, 2015, 2018; Santibáñez-López et al., 2015; Santos et al., 2016; Shahi et al., 2016; Bavani et al., 2017; Erickson and Cheema, 2017; Kang and Brooks, 2017; Riaño-Umbarila et al., 2017; Sanaei-Zadeh et al., 2017; Salazar et al., 2018), and updating these records to include any species reported as harmful in the literature, or that required medical attention. Searches were performed in March–May of 2018 using traditional search tools such as PubMed and Google Scholar, as well as searching through literature available on the Virtual Health Library (VHL) following methods described by Santos et al. (2016), and reports publicly available from poison control centers (*i.e.* National Poison Data System annual reports). We did not limit searches to specific terms (*i.e.* "scorpion", "public health", etc.), as our goal was to find any available information, including epidemiology, geographic distribution, and venom characterization, on scorpion species that have been previously reported as medically significant. We do not include scorpion identification information as this has been discussed in many of the previously mentioned reviews and elsewhere (Lourenço, 2016; Rein, 2018), although the need for proper scorpion identification in epidemiological reporting is discussed. Due to the continued diversification of scorpion species and updated taxonomy classifications, we have retained species names as reported in the corresponding cited literature and noted taxonomic updates if available. Sting classifications, following criteria proposed by Khattabi et al. (2011), were only assigned to scorpions where symptoms attributed to that species were provided and verifiable. Sting frequencies were estimated based on the number of envenomations reported as being attributed to each species in the referenced literature and are meant to reflect the likely envenomation events for each species, although these are likely underestimations.

2.2. Map creation

All maps were generated using the ggplot2 package in R (Wickham, 2016). Mapped regions were scored as the number of species present in that location that have been reported as medically significant in the literature, such that locations with a greater number of medically significant species are darker than locations with fewer species. The maps do not reflect the number of envenomations or severity of symptoms by region.

2.3. Toxin abbreviations

Functional characterizations, descriptions, and definitions of toxin classes are outside the scope of this review and are discussed elsewhere, including Possani et al. (1999); de la Vega and Possani (2004); Zeng et al. (2005); de la Vega et al. (2010); Quintero-Hernández et al. (2013); Serrano (2013); Carmo et al. (2014); Harrison et al. (2014), as well as in many of the citations included throughout our review. We therefore only included major toxin classes that have been identified for each species by method of functional assay, individual toxin isolation, transcriptomic and/or proteomic approaches. Abbreviations are as follows: AMPs—antimicrobial peptides, Bpps—bradykinin-potentiating peptides, CaTxs—calcium-channel toxins, ClTxs—chloride-channel toxins, CRISPs—cysteine-rich secretory proteins, HYALs—hyaluronidases, KTxs—potassium-channel toxins, KUNs—Kunitz-type toxins, MPs—metalloproteases, NaTxs—sodium-channel toxins, PLA2s—phospholipases, SPs—serine proteases.

3. Results and discussion

Our search resulted in a total of 104 scorpion species considered medically significant or harmful to humans, including 101 Buthidae, 2 Hemiscorpiidae, and 1 Scorpionidae. Sting classes were assigned following definitions described by Khattabi et al. (2011). Class I describes minor, localized symptoms that rarely require medical treatment. Class II describes moderate to severe symptoms that, although not life-threatening, usually do require medical treatment. Class III describes severe, life-threatening symptoms that are likely fatal without medical treatment. All known scorpion species should be considered sting class I (harmless) unless otherwise documented. Of the 104 scorpion species identified as medically significant in the literature, only 36 species were assigned a sting class of I-III based on symptoms reported as specific to that species. Four species were assigned to sting class I, eight species to sting class II, and 24 to sting class III. The remaining 68 species were given an unknown sting class because we were unable to verify symptoms for these species.

The global distributions of the medically significant species identified by our literature review are shown in Figs. 1 and 2. In the Old World (Fig. 1), the darker locations corresponding to Iran, Saudi Arabia, and Morocco, indicate the density of medically significant scorpion species found in these areas, with fewer found in the surrounding countries of Africa, Asia, and Europe (Table 1). In the New World (Fig. 2), it appears that Mexico, Brazil, and Venezuela, are rich with harmful scorpion fauna, with fewer harmful species described from the United States, Central America, the Caribbean, and other South American countries (Table 2).

Venom characterization can include the isolation and functional characterization of individual toxins, venom-gland transcriptome sequencing, and/or venom proteomics, all of which contribute to and are necessary for the development of therapeutics from venom. Fifty-four of the 104 scorpion species we identified as medically significant had some type of venom characterization work completed, many of which were limited to the isolation of one or a handful of toxins from the venom. Only 12 species had undergone more extensive venom characterizations including transcriptomic or proteomic approaches. We could not find venom characterization studies for the remaining 51 medically significant scorpion species.

3.1. Family Buthidae

3.1.1. Apistobuthus

We found one species belonging to the *Apistobuthus* genus, *A. pterygocercus*, which is distributed throughout Middle Eastern countries of Asia (Table 1). Al-Sadoon and Jarrar (2003) referenced this species as medically significant in Saudi Arabia, however, no specific case reports were found that could associate specific envenomation symptoms with