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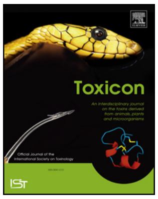

A global accounting of medically significant scorpions: Epidemiology, major toxins, and comparative resources in harmless counterparts

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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,

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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

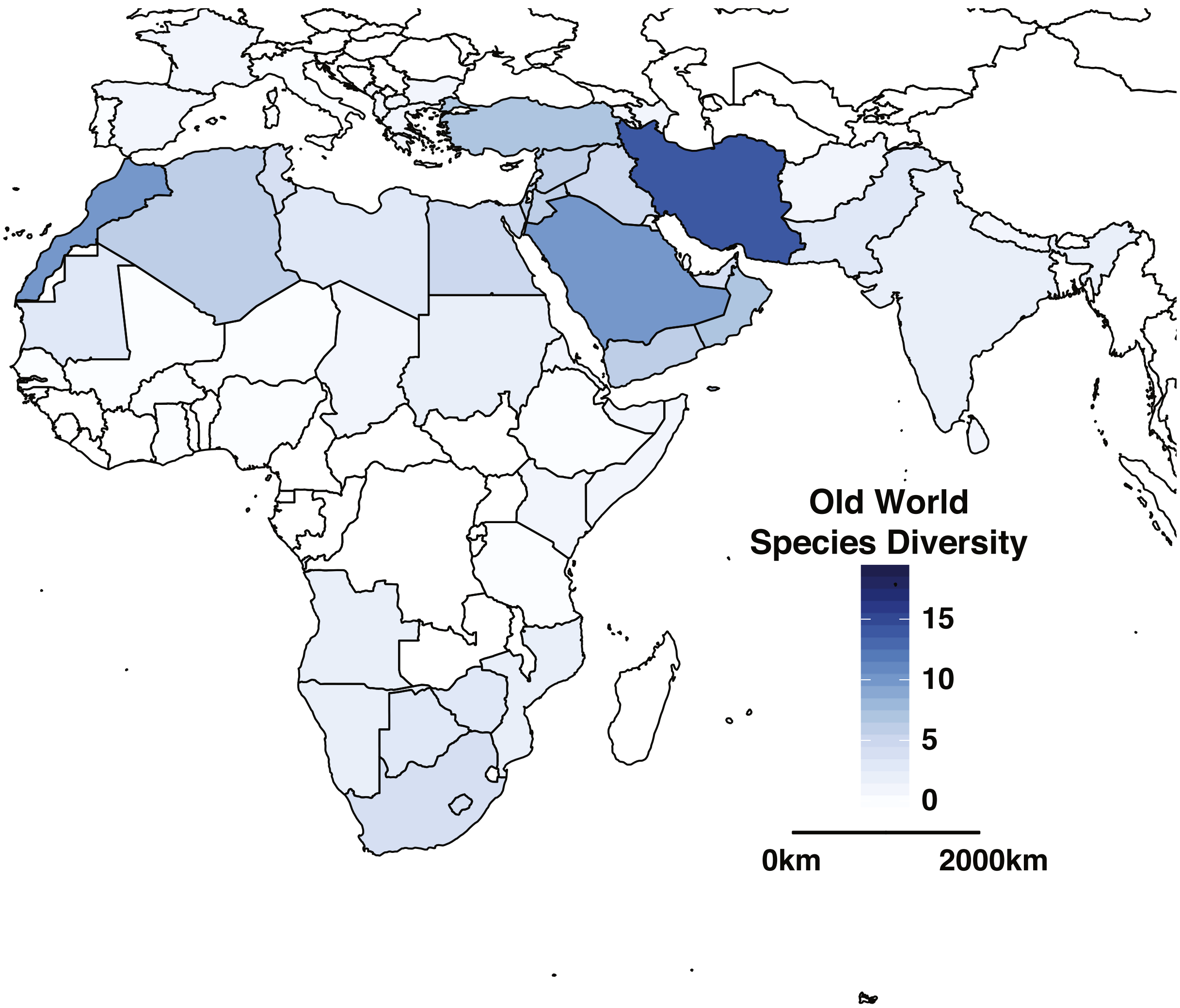

Fig. 1. Old World heat map of medically significant scorpion diversity. Higher scores (darker regions) indicate countries with a greater number of reported medically significant species, and lower scores (lighter regions) indicate countries with fewer reported medically significant species (see methods). The map does not reflect the number of envenomations or severity of symptoms by region.

this species. Dehghani and Fathi (2012) also mentioned *A. pterygocercus* as being medically significant, but with only minor importance. For these reasons, we included *A. pterygocercus* in our review with an unknown sting classification, as it is unclear whether or not this species is harmful to humans (Hauke and Herzig, 2017). We could not find any confirmed venom toxins for *A. pterygocercus*.

3.1.2. *Androctonus*

We found six species belonging to the *Androctonus* genus, *A. amoreuxi*, *A. australis*, *A. bicolor* (*A. aeneas*), *A. crassicauda*, *A. liouvillei*, and *A. mauretanicus*. Members of *Androctonus* are commonly referred to as “fat-tailed” scorpions, and are distributed in parts of Africa and Asia (Table 1). Recent taxonomy of *Androctonus* (Coelho et al., 2014) and epidemiological reports (Chakroun-Walha et al., 2018) indicate *A. bicolor* and *A. aeneas* as being the same species and are counted as such for the purposes of this review, although others have indicated that further taxonomic clarification is needed (Goyffon et al., 2012). *Androctonus amoreuxi*, *A. bicolor (A. aeneas)*, and *A. liouvillei*, have been reported as harmful to humans, however, these reports are from areas with high scorpionism rates and no symptoms were assigned to specific species (Touloun et al., 2001; Coelho et al., 2016; Amr et al., 2017). Additionally, *A. amoreuxi* has previously been reported as harmless (Goyffon et al., 2012). We therefore included *A. amoreuxi*, *A. bicolor (A. aeneas)*, and *A. liouvillei*, in our list with an unknown sting classification (Table 3). *Androctonus australis*, *A. crassicauda*, and *A. mauretanicus* have been responsible for severe envenomation symptoms, including fatalities, and were assigned to sting class III (Table 3).

Partial venom characterizations have been completed for *A. australis* (Laraba-Djebari et al., 1994), *A. crassicauda* (Caliskan et al., 2013), and *A. mauretanicus* (Martin-Eauclaire and Bougis, 2012), all of which revealed potent NaTxs and KTxs that contribute to potentially fatal stings. A complete venom characterization using transcriptomic and proteomic analyses was completed for *A. bicolor* (*A. aeneas)*, which identified NaTxs, KTxs, CaTxs, AMPs, defensins, KUNs, and Bpps (Zhang et al., 2015). Another group isolated two AMPs from the venom of *A. bicolor* (*A. aeneas*), and synthetic analogues of these peptides showed potent antimicrobial and anticancer activities (Du et al., 2015). Several toxins have also been isolated from *A. amoreuxi* including AMPs (Almaaytah et al., 2012) and ion-channel toxins (Chen et al., 2003, 2005), and this venom has been shown to be effective against multiple cancer lines (Salem et al., 2016; Akef et al., 2017). We could not find any confirmed toxins for *A. liouvillei*.

3.1.3. *Buthacus*

We identified one member of the *Buthacus* genus, *B. macrocentrus*, which is distributed throughout Middle Eastern countries of Asia (Table 1). We could not find any specific case reports or envenomation symptoms reported for this species (Table 3), however, Caliskan et al.

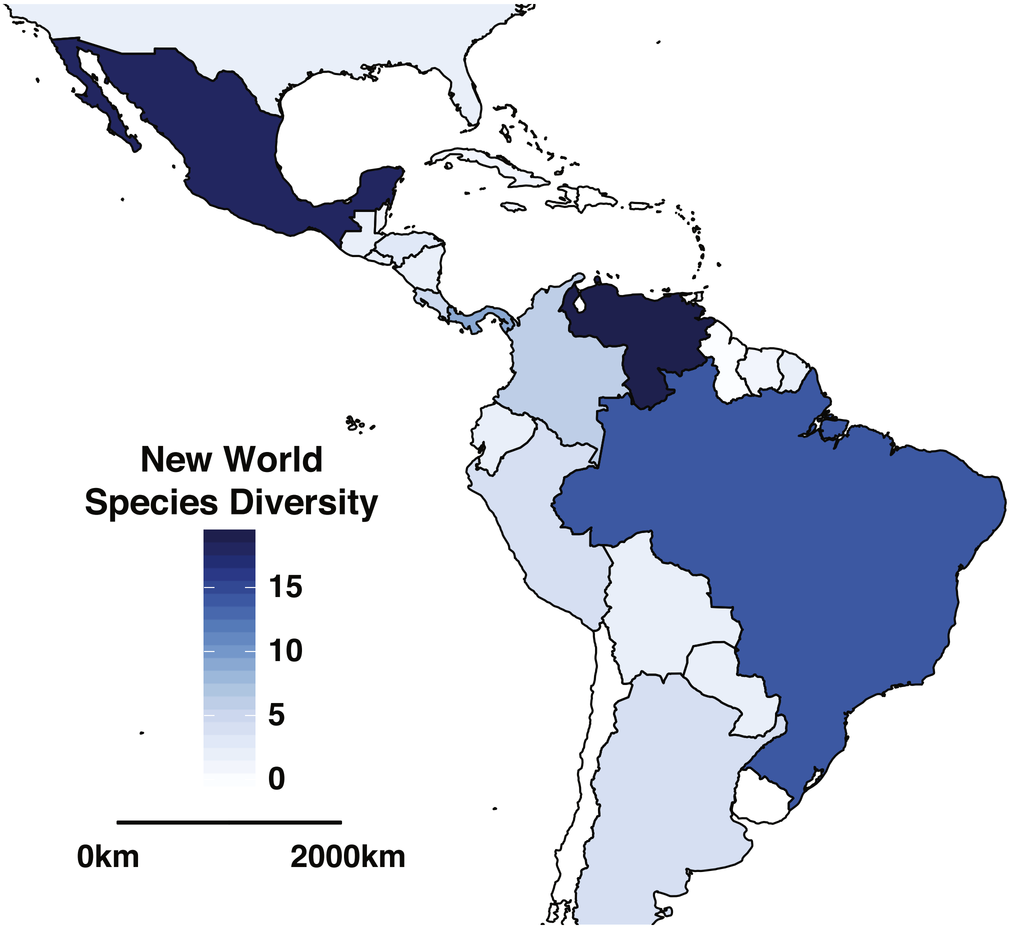

Fig. 2. New World heat map of medically significant scorpion diversity. Higher scores (darker regions) indicate countries with a greater number of reported medically significant species, and lower scores (lighter regions) indicate countries with fewer reported medically significant species (see methods). The map does not reflect the number of envenomations or severity of symptoms by region.

(2012) suggested this species be characterized as dangerous to humans based on the likelihood of being misidentified as either a *Leiurus* or *Mesobuthus* species (these are all described as "yellow" scorpions in Turkey), the functional characterization of a NaTx in the venom, and the high toxicity of *B. macrocentrus* venom in mice. Although the lethality in one vertebrate is not necessarily an indicator of lethality in another, even when toxins are deemed mammal-specific (van der Meijden et al., 2017), we still included *B. macrocentrus* in our review with an unknown sting classification (Table 3) as it is unclear whether or not this species should be considered medically significant.

3.1.4. *Buthus*

In our initial searches, we only found one medically significant *Buthus* species, *B. occitanus*, which was widely distributed throughout the Old World (Fet et al., 2000). Recent taxonomical updates have reclassified several new species that were formerly considered *B. occitanus*, and there are currently 52 species of *Buthus* distributed throughout Europe, Africa, and Asia, with *B. occitanus* having a much more limited range (Sousa et al., 2017). Previous reports attributed severe envenomations to *B. occitanus* (Ghalim et al., 2000; Aboumaâd et al., 2014), however, these reports were based in Morocco where it is unlikely that *B. occitanus* exists. According to Sousa et al. (2017), *B. occitanus* is limited to France and Spain, and there are 17 other *Buthus* species in Morocco. El Hidan et al. (2017) lists 12 *Buthus* species in Morocco, including *B. occitanus*, and Emerich et al. (2017) performed a comparative analysis on four subspecies of *B. occitanus* from Morocco that Sousa et al. (2017) classified as full species. Because the taxonomical updates to *Buthus* by Sousa et al. (2017) were unavailable at the time El Hidan et al. (2017) and Emerich et al. (2017) were published, we elected to follow the classification and location information provided by Sousa et al. (2017) for the purposes of this review.

The recent taxonomical updates for this genus have not yet been widely incorporated into the literature and the species of medically significant *Buthus* are not yet clear. We conducted separate searches for each of the 52 *Buthus* species listed by Sousa et al. (2017), and although we did not find case reports or symptoms assigned to a specific species, we did find reports suggesting at least six *Buthus* species should be considered medically significant and have included them in our list with an unknown sting classification (Table 3). *Buthus tunetanus*, *B. paris*, *B. malhommei*, and *B. mardochei*, were all toxic at low doses when injected into mice, and all have KTxs and NaTxs present in their venoms (Emerich et al., 2017). Hmimou et al. (2008) also reported *B. malhommei* as being responsible for severe envenomations in humans in Morocco, although the report did not separate the number of scorpion envenomations caused by *B. malhommei* from other scorpions in the area. *Buthus lienhardi* (Laaradia et al., 2018) and *B. occitanus* (Martin-Eauclaire et al., 2014) venoms were also shown to be toxic at low doses when injected into mice.

NaTxs were identified as the most abundant and diverse group of toxins in the venom of *B. occitanus* from France, where the species is government protected (Martin-Eauclaire et al., 2014). In a study using *Buthus* from Egypt (formerly *B. occitanus*, now five separate *Buthus* species), Bpps were identified as one of the most abundant toxins (Meki et al., 1995).

Table 1
Old World geographic distribution of medically significant scorpions.

Species	Region	Country(ies)	Source(s)
Family Buthidae			
Apistobuthus			
A. pterygocercus	Asia	Iran, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen	Dehghani and Fathi (2012)
Androctonus			
A. amoreuxi	Africa	Egypt, Mali, Morocco	Goyffon et al. (2012); Coelho et al. (2014); Amr et al. (2017);
	Asia	Jordan	Badry et al. (2018); El Hidan et al. (2018)
A. australis	Africa	Algeria, Chad, Egypt, Libya, Mauritania, Morocco, Somalia, Sudan, Tunisia	Chippaux and Goyffon (2008); Coelho et al. (2014);
	Asia	India, Israel, Jordan, Pakistan, Saudi Arabia, Yemen	Amr et al. (2017); Badry et al. (2018)
A. bicolor (*A. aeneas*)	Africa	Algeria, Egypt, Eritrea, Libya, Morocco, Tunisia	Fet et al. (2000);
	Asia	Israel, Jordan, Lebanon, Syria	Coelho et al. (2014); Amr et al. (2017); Badry et al. (2018)
A. crassicauda	Africa	Egypt, Mauritania, Morocco	Fet et al. (2000);
	Asia	Armenia, Azerbaijan, Bahrain, Iran, Iraq, Israel, Jordan, Kuwait, Oman, Saudi Arabia, Syria, Turkey, United Arab Emirates, Yemen	Amr et al. (2017); Badry et al. (2018)
A. liouvillei	Africa	Morocco	Coelho et al. (2014); El Hidan et al. (2017)
A. mauretanicus	Africa	Algeria, Mauritania, Morocco	Fet et al. (2000); Touloun et al. (2012); Coelho et al. (2014); El Hidan et al. (2017)
Buthacus			
B. macrocentrus	Asia	Bahrain, Iran, Iraq, Israel, Jordan, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates	Yağmur et al. (2008)
Buthus			
B. lienhardi	Africa	Morocco	Sousa et al. (2017)
B. malhommei	Africa	Morocco	Sousa et al. (2017)
B. mardochei	Africa	Morocco	Sousa et al. (2017)
B. occitanus	Europe	France, Spain	Sousa et al. (2017)
B. paris	Africa	Algeria, Morocco, Tunisia	Sousa et al. (2017)
B. tunetanus	Africa	Algeria, Lybia, Morocco, Tunisia	Sousa et al. (2017)
Compsobuthus			
C. matthiesseni	Asia	Iran	Navidpour (2015)
C. persicus	Asia	Iran	Navidpour (2015)
Hottentotta			
H. gentili	Africa	Algeria, Morocco	Kovařík (2007)
H. jayakari	Asia	Iran, Oman, Saudi Arabia, United Arab Emirates, Yemen	Sari et al. (2011); Kovařík (2007)
H. saulcyi	Asia	Afghanistan, Iran, Iraq, Turkey	Kovařík (2007)
H. schach	Asia	Iran, Iraq	Kovařík (2007)
H. tamulus	Asia	India, Nepal, Pakistan, Sri Lanka	Kovařík (2007); Strong et al. (2015)
H. zagrosensis	Asia	Iran	Kovařík (2007); Sanaei-Zadeh et al. (2017)
Leiurus			
L. abdullahbayrami	Asia	Syria and Turkey	Khalil and Yağmur (2010); Lowe et al. (2014)
L. arabicus	Asia	Saudi Arabia	Lowe et al. (2014)
L. brachycentrus	Asia	Saudi Arabia, Yemen	Lowe et al. (2014)
L. haenggii	Asia	Oman, Saudi Arabia, Yemen	Lowe et al. (2014)
L. heberti	Asia	Oman	Lowe et al. (2014)
L. hebraeus	Asia	Israel, Jordan, Lebanon, Syria	Lowe et al. (2014); Amr et al. (2017)
L. jordanensis	Asia	Jordan, Saudi Arabia	Lowe et al. (2014); Amr et al. (2017)
L. macroctenus	Asia	Oman	Lowe et al. (2014)
L. quinquestriatus	Asia	Egypt, Sudan	Lowe et al. (2014); Badry et al. (2018)
Mesobuthus			
M. caucasicus complex	Asia	Iran, Turkey	Fet et al. (2018)
M. eupeus	Asia	Iran, Turkey	Karataş and Karataş (2003); Ozkan and Kat (2005); Dehghani and Fathi (2012); Navidpour (2015)
M. gibbosus	Asia	Turkey	Ozkan and Kat (2005);
	Europe	Albania, Bulgaria, Greece, Macedonia (FYROM), Montenegro	Parmakelis et al. (2006); Kaltsas et al. (2008)
Odontobuthus			
O. doriae	Asia	Iran	Lourenco and Pezier (2002)
Orthochirus			
O. scrobiculosus	Asia	Iran	Dehghani and Fathi (2012)
Parabuthus			
P. granulatus	Africa	Angola, Botswana, Kenya, Namibia, South Africa, Zimbabwe	Fet et al. (2000); Prendini and Esposito (2010)
P. mossambicensis	Africa	Botswana, Mozambique, South Africa, Zimbabwe	Fet et al. (2000)
P. transvaalicus	Africa	Botswana, Mozambique, South Africa, Zimbabwe	Fet et al. (2000)
P. villosus	Africa	Angola, Namibia, South Africa	Fet et al. (2000); Prendini and Esposito (2010)
Family Hemiscorpiidae			
Hemiscorpius			
H. acanthocercus	Asia	Iran	Navidpour (2015)
H. lepturus	Asia	Iran, Iraq, Oman, Pakistan, Saudi Arabia, United Arab Emirates, Yemen	Navidpour (2015); Dehghani et al. (2018)
Family Scorpionidae			
Nebo			
N. hierichonticus	Africa	Egypt	Rosin and Shulov (1963);
	Asia	Israel, Jordan, Saudi Arabia, Syria	Badry et al. (2018)

3.1.5. Centruroides

The *Centruroides* genus is one of the most diverse scorpion genera, currently comprised of 90 species (Esposito et al., 2017). Several *Centruroides* species are commonly referred to as bark scorpions as they are often arboreal and found under peeling tree bark (Jiménez-Jiménez and Palacios-Cardiel, 2010; Esposito et al., 2017). The majority of

Table 2
New World geographic distribution of medically significant scorpions.

Species	Region	Country(ies)	Source(s)
Family Buthidae			
Centruroides			
C. balsasensis	North America	Mexico	Ponce Saavedra and Francke (2004); Riaño-Umbarila et al. (2017)
C. bicolor	Central America	Panama	Salazar et al. (2018)
C. elegans	North America	Mexico	Riaño-Umbarila et al. (2017)
C. exilicauda	North America	Mexico	Jiménez-Jiménez and Palacios-Cardiel (2010)
C. gracilis	Caribbean	Cuba, Jamaica	Sissom and Lourenço (1987);
	Central America	Belize, El Salvador, Guatemala, Honduras	Fet et al. (2000); Teruel (2008);
	North America	Mexico, United States	Borges et al. (2012)
	South America	Northern regions	Otero et al. (2004); Borges et al. (2012)
C. granosus	Central America	Panama	Salazar et al. (2018)
C. hirsutipalpus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. huichol	North America	Mexico	Teruel et al. (2015)
C. infamatus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. limbatus	Central America	Costa Rica, Honduras, Nicaragua, Panama	Borges et al. (2012); Salazar et al. (2018)
C. limpidus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. margaritatus	Central America	Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama	Sissom and Lourenço (1987); Fet et al. (2000);
	North America	Mexico	Borges et al. (2012)
	South America	Western Colombia	
C. meisei	North America	Mexico	Riaño-Umbarila et al. (2017)
C. noxius	North America	Mexico	Riaño-Umbarila et al. (2017)
C. ornatus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. panamensis	Central America	Panama	Salazar et al. (2018)
C. pococki	Caribbean	Lesser Antilles	Fet et al. (2000)
C. sculpturatus	North America	United States, Mexico	Riaño-Umbarila et al. (2017); Kang and Brooks (2017)
C. suffusus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. tecomanus	North America	Mexico	Riaño-Umbarila et al. (2017)
C. testaceus	Caribbean	Lesser Antilles	Fet et al. (2000)
	South America	Venezuela	
C. villegasi	North America	Mexico	Riaño-Umbarila et al. (2017)
C. sp. *nov* A	North America	Mexico	Riaño-Umbarila et al. (2017)
C. sp. *nov* B	North America	Mexico	Riaño-Umbarila et al. (2017)
Tityus			
T. apiacas	South America	Brazil	Silva et al. (2017)
T. arellanoparrai	South America	Venezuela	D'Suze et al. (2015)
T. asthenes	Central America	Costa Rica, Ecuador, Panama	Fet et al. (2000); Otero et al. (2004); Salazar et al. (2018)
	South America	Brazil, Colombia, Peru	
T. bahiensis	South America	Argentina, Brazil, Paraguay	Brasil (2009); Lourenço (2015)
T. bastosi	Central America	Ecuador	Fet et al. (2000)
	South America	Brazil, Colombia, Peru	Costa et al. (2016)
T. breweri	South America	Venezuela	Fet et al. (2000); Borges et al. (2010); D'Suze et al. (2015)
T. carabobensis	South America	Venezuela	D'Suze et al. (2015)
T. caripitensis	South America	Venezuela	D'Suze et al. (2015)
T. cerroazul	Central America	Costa Rica, Panama	Borges et al. (2012); Salazar et al. (2018)
T. confluens	South America	Argentina, Bolivia, Brazil, Paraguay	Lourenço and da Silva (2007); Brasil (2009)
T. costatus	South America	Brazil	Fet et al. (2000); Brasil (2009); Lourenço (2015)
T. discrepans	South America	North-Central Venezuela	Borges et al. (2011)
T. falconensis	South America	Venezuela	D'Suze et al. (2015)
T. festae	Central America	Panama	Borges et al. (2012);
	South America	Colombia	Salazar et al. (2018)
T. feuhrmanni	South America	Colombia	Otero et al. (2004)
T. isabelceciliae	South America	Venezuela	Borges et al. (2010); D'Suze et al. (2015)
T. ivic-nancor	South America	Venezuela	D'Suze et al. (2015)
T. matthieseni	South America	Brazil	Costa et al. (2016)
T. metuendus	South America	Brazil, Peru	Fet et al. (2000); Lourenço (2008); Brasil (2009)
T. monaguensis	South America	Venezuela	D'Suze et al. (2015)
T. neoespartanus	South America	Venezuela	Fet et al. (2000); De Sousa et al. (2007)
T. nororientalis	South America	Venezuela	D'Suze et al. (2015)
T. obscurus	South America	Brazil, French Guiana, Suriname	Fet et al. (2000); Brasil (2009); Pardal et al. (2014); Torrez et al. (2015)
T. pachyurus	Central America	Costa Rica, Panama	Fet et al. (2000); Otero et al. (2004); Salazar et al. (2018)
	South America	Colombia, Venezuela	
T. perijanensis	South America	Venezuela	Fet et al. (2000); D'Suze et al. (2015)
T. pittieri	South America	Venezuela	D'Suze et al. (2015)
T. pusillus	South America	Brazil	Dias et al. (2006); Porto et al. (2010)
T. quirogae	South America	Venezuela	D'Suze et al. (2015)
T. sanarensis	South America	Venezuela	D'Suze et al. (2015)
T. serrulatus	South America	Argentina, Bolivia, Brazil	Fet et al. (2000); Brasil (2009); Lourenço (2015)
T. silvestris	South America	Brazil, French Guiana, Peru	Fet et al. (2000); Brasil (2009); Monteiro et al. (2016)
T. stigmurus	South America	Brazil	Brasil (2009); Bertani et al. (2018)
T. surorientalis	South America	Venezuela	D'Suze et al. (2015)
T. trinitatis	South America	Trinidad and Tobago	Daisley et al. (1999)
T. trivittatus	South America	Argentina, Brazil	de Roodt (2014)
T. valarae	South America	Venezuela	D'Suze et al. (2015)
T. zulianus	South America	Venezuela	Borges et al. (2011)

Table 3

Reported envenomations and symptoms of medically significant scorpions. Annual sting frequencies were estimated based on cited literature if available, and are likely still underestimates. A sting class was assigned if symptoms reported, based on the Khattabi et al. (2011) classification system. In brief: Class I indicates minor, localized symptoms; Class II indicates non life-threatening, moderate to severe systemic symptoms; Class III indicates severe systemic symptoms that are life-threatening if untreated. Those with a U indicate the sting class is unknown.

Species	Estimated Annual Sting Frequency	Source(s)	Sting Class	Reported Symptoms	Source(s)
Family Buthidae					
Apistobuthus					
A. pterygocercus	100–1000	Al-Sadoon and Jarrar (2003)	U	unknown, no specific case reports or symptoms found, reported as being of minor importance	Dehghani and Fathi (2012)
Androctonus					
A. amoreuxi	Unknown		U	No specific case reports or symptoms found. Reported as both harmful and harmless in literature	Goyffon et al. (2012); Coelho et al. (2014); Amr et al. (2017)
A. australis	100–1000	Chakroun-Walha et al. (2018)	III	tachycardia, tachypnea, heart failure, pulmonary edema	Bahloul et al. (2004, 2005)
A. bicolor (*A. aeneas*)	10–100	Chakroun-Walha et al. (2018)	U	unknown, may be fatal but no specific case reports or symptoms found	Touloun et al. (2001); Coelho et al. (2016)
A. crassicauda	1000–10,000	Dehghani et al. (2009); Ozkan et al. (2006); Al-Sadoon and Jarrar (2003)	III	pain and burning at sting site, tachypnea, drowsiness, gastrointestinal pain, diarrhea, vomitting, increased salivation, numbness, hypotension, hypothermia, cyanosis, can be fatal within 9–36 h	Radmanesh (1990); Dehghani and Fathi (2012)
A. liouvillei	Unknown		U	reported as medically significant, formerly *A. bicolor liouvillei*, no specific case reports or symptoms found	Coelho et al. (2014)
A. mauretanicus	100–1000	Ghalim et al. (2000); Touloun et al. (2012)	III	pain and burning sensation, sweating, shivering, hyperthermia, severe cases can be fatal	Ghalim et al. (2000); Touloun et al. (2001)
Buthacus					
B. macrocentrus	Unknown		U	unknown, no specific case reports or symptoms found, may have been misidentified as *Leiurus* or *Mesobuthus* species	Caliskan et al. (2012)
Buthus					
B. lienhardi	10–100	Ghalim et al. (2000); Aboumaâd et al. (2014)	U	unknown, formerly *B. occitanus*	Ghalim et al. (2000); Aboumaâd et al. (2014); Sousa et al. (2017)
B. malhommei	10–100	Ghalim et al. (2000); Hmimou et al. (2008); Aboumaâd et al. (2014)	U	unknown, formerly *B. occitanus*	Ghalim et al. (2000); Hmimou et al. (2008); Aboumaâd et al. (2014); Sousa et al. (2017)
B. mardochei	10–100	Ghalim et al. (2000); Aboumaâd et al. (2014)	U	unknown, formerly *B. occitanus*	Ghalim et al. (2000); Aboumaâd et al. (2014); Sousa et al. (2017)
B. occitanus	< 10	Martin-Eauclaire et al. (2014)	U	unknown, no specific case reports or symptoms found after species reclassification	Martin-Eauclaire et al. (2014); Sousa et al. (2017)
B. paris	10–100	Ghalim et al. (2000); Aboumaâd et al. (2014)	U	unknown, formerly *B. occitanus*	Ghalim et al. (2000); Aboumaâd et al. (2014); Sousa et al. (2017)
B. tunetanus	10–100	Ghalim et al. (2000); Aboumaâd et al. (2014)	U	unknown, formerly *B. occitanus*	Ghalim et al. (2000); Aboumaâd et al. (2014); Sousa et al. (2017)
Compsobuthus					
C. matthiesseni	10–100	Dehghani et al. (2009); Sanaei-Zadeh et al. (2017); Shahi et al. (2016)	U	unknown, aside from requiring medical attention and some reports of hematuria that require confirmation	Dehghani et al. (2009); Sanaei-Zadeh et al. (2017); Shahi et al. (2016)
C. persicus	10–100	Shahi et al. (2016)	U	unknown, aside from requiring medical attention	Shahi et al. (2016)
Centruroides					
C. balsasensis	100–1000	Riaño-Umbarila et al. (2017)	I	pain, numbness	Ponce Saavedra and Francke (2004)
C. bicolor	100–1000	Salazar et al. (2018)	U	reported as causing severe envenomations, case reports need confirmation	Salazar et al. (2018)
C. elegans	100–1000	Riaño-Umbarila et al. (2017)	U	described as deadly, with no specific case reports or symptoms found	Riaño-Umbarila et al. (2017); Vandendriessche et al. (2010)
C. exilicauda	10–100	Chippaux and Goyffon (2008)	U	unknown, previously reported as harmful before differentiating from *C. sculpturatus*	Valdez-Cruz et al. (2004); Chippaux and Goyffon (2008)
C. gracilis	10–100	Otero et al. (2004)	II	pain, systemic symptoms, may be region-dependent	Otero et al. (2004); Borges et al. (2012)
C. granosus	100–1000	Salazar et al. (2018)	U	unknown, reported as dangerous, no specific case reports or symptoms found	Salazar et al. (2018)
C. hirsutipalpus	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. huichol	Unknown		U	unknown, formerly *C. noxius* before classified as separate species	(Teruel et al., 2015)
C. infamatus	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. limbatus	100–1000	Bush (1999); Salazar et al. (2018)	II	pain, paresthesia, flushing, hypertension, wheezing	Bush (1999)
C. limpidus	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)

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Table 3 (*continued*)

Species	Estimated Annual Sting Frequency	Source(s)	Sting Class	Reported Symptoms	Source(s)
C. margaritatus	10–100	Marinkelle and Stahnke (1965); Borges et al. (2012)	I	pain, local edema, fever, mild symptoms	Marinkelle and Stahnke (1965); Borges et al. (2012)
C. meisei	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. noxius	100–1000	Riaño-Umbarila et al. (2017)	U	described as the most toxic species in Mexico, responsible for adult human deaths, but no specific case reports or symptoms found	Teruel et al. (2015); Riaño-Umbarila et al. (2017)
C. ornatus	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. panamensis	100–1000	Salazar et al. (2018)	U	unknown, reported as dangerous, no specific case reports or symptoms found	Salazar et al. (2018)
C. pococki	< 10	Schmitt et al. (2017)	I	pain at sting site, numbness in lips and fingers	Schmitt et al. (2017)
C. sculpturatus	10–100	Chippaux and Goyffon (2008); Mowry et al. (2015, 2016); Gummin et al. (2017); Riaño-Umbarila et al. (2017)	III	pain at sting site, tachycardia, restlessness, roving eye movements, hypertension, respiratory distress, tachypnea, hypersalivation, slurred speech, stridor, can be fatal	Skolnik and Ewald (2013); Kang and Brooks (2017)
C. suffusus	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. tecomanus	100–1000	Riaño-Umbarila et al. (2017)	U	described as lethal, but no specific case reports or symptoms found	Valdez-Velazquéz et al. (2013); Olamendi-Portugal et al. (2016); Riaño-Umbarila et al. (2017)
C. testaceus	< 10	Lobo et al. (2011)	I	pain at sting site, erythema	Lobo et al. (2011)
C. villegasi	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. sp. *nov.* A	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
C. sp. *nov.* B	100–1000	Riaño-Umbarila et al. (2017)	U	no specific case reports or symptoms found	Riaño-Umbarila et al. (2017)
Hottentotta					
H. gentili	10–100	Touloun et al. (2012)	III	severe envenomations requiring medical treatment reported, including 10 fatalities	Touloun et al. (2012)
H. jayakari	< 10	Sanaei-Zadeh et al. (2017); Suresh et al. (2014)	II	infection of bone marrow reported	Suresh et al. (2014)
H. saulcyi	< 10	Dehghani et al. (2009); Shahi et al. (2016)	U	unknown, although required medical treatment	Dehghani et al. (2009); Shahi et al. (2016)
H. schach	< 10	Dehghani et al. (2009)	U	unknown, although required medical treatment	Dehghani et al. (2009)
H. tamulus	10–100	Bawaskar and Bawaskar (1998); Kularatne et al. (2015)	III	pain and numbness at sting site, swelling, tachycardia, increased blood pressure, sweating, salivation, hypotension, hypertension, piloerection and priapism, vomitting, parasternal systolic lift, cardiac arrhythmias, cold extremities, pulmonary edema, heart failure	Bawaskar and Bawaskar (1998); Kularatne et al. (2015)
H. zagrosensis	< 10	Sanaei-Zadeh et al. (2017)	U	unknown, although required medical treatment	Sanaei-Zadeh et al. (2017)
Leiurus					
L. abdullahbayrami	< 10	Seiter et al. (2016); Dokur et al. (2017)	III	pain, burning and blistering at sting site, tachycardia, nausea, sweating, hallucinations, hypotension, cardiomyopathy, pulmonary edema	Seiter et al. (2016); Dokur et al. (2017)
L. arabicus	100–1000	Al-Sadoon and Jarrar (2003)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. brachycentrus	100–1000	Al-Sadoon and Jarrar (2003)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. haenggii	100–1000	Al-Sadoon and Jarrar (2003)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. heberti	10–100	Al-Sadoon and Jarrar (2003)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. hebraeus	100–1000	Al-Sadoon and Jarrar (2003); Amr et al. (2017)	III	formerly *L. quinquestriatus*, lethargy, confusion, pulmonary edema, cardiogenic shock, severe hypertension, pancreatitis, can be fatal	Sofer and Gueron (1988); Sofer et al. (1991); Lowe et al. (2014)
L. jordanensis	100–1000	Al-Sadoon and Jarrar (2003); Amr et al. (2017)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. macroctenus	10–100	Al-Sadoon and Jarrar (2003)	U	unknown, formerly *L. quinquestriatus*	Al-Sadoon and Jarrar (2003); Lowe et al. (2014)
L. quinquestriatus	10–100	Saad et al. (2017)	U	unknown, recently reclassified into several new species	Lowe et al. (2014)
Mesobuthus					
M. caucasicus complex	Unknown		U	unknown, recently classified into several subspecies (see section 3.1.9)	
M. eupeus	100–1000	Ozkan and Kat (2005); Chippaux and Goyffon (2008); Cesaretli and Ozkan (2010)	III	pain, swelling, and burning at sting site, dry mouth, thirst, sweating, hypotension, hyperemia	Ozkan and Kat (2005)

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Table 3 (*continued*)

Species	Estimated Annual Sting Frequency	Source(s)	Sting Class	Reported Symptoms	Source(s)
M. gibbosus	10–100	Chippaux and Goyffon (2008); Cesaretli and Ozkan (2010)	U	systemic manifestations and fatalities reported, case reports need confirmation	Ozkan and Ciftci (2010)
Odontobuthus					
O. doriae	< 10	Razi and Malekanrad (2008); Dehghani and Fathi (2012)	III	pain and swelling at sting site, disorientation, erythema, acute asymmetric pulmonary edema, tachypnea, tachycardia	Razi and Malekanrad (2008); Dehghani and Fathi (2012)
Orthochirus					
O. scrobiculosus	< 10	(Dehghani and Fathi, 2012)	U	unknown, reported as causing fatality as well as minor symptoms, case reports need confirmation	(Dehghani et al., 2009; Hauke and Herzig, 2017)
Parabuthus					
P. granulatus	10–100	Müller (1993); Bergman (1997)	III	pain and burning at sting site, difficulty swallowing, muscle pain and cramps, restlessness, potential respiratory failure, can be fatal	Müller (1993)
P. mossambicensis	10–100	Bergman (1997)	U	unknown, likely mild to moderate envenomation symptoms	Bergman (1997)
P. transvaalicus	100–1000	Bergman (1997)	III	pain and swelling at sting site, difficulty swallowing, muscle tremors or myoclonic jerks, fasciculation of the tongue, hypersalivation, sweating, bilateral ptosis, difficulty passing urine, can be fatal	Bergman (1997)
P. villosus	Unknown		U	unknown, likely mild envenomation symptoms, considered medically important in early literature but no other envenomation reports found	Debont et al. (1998)
Tityus					
T. apiacas	< 10	Silva et al. (2017)	II	pain and redness at sting site, systemic manifestations	Silva et al. (2017)
T. arellanoparrai	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. asthenes	100–1000	Otero et al. (2004); Borges et al. (2012); Salazar et al. (2018)	III	pain, burning and redness at sting site, edema, persistent vomiting, cerebral decortication, lack of corneal reflex, distended abdomen, peripheral cyanosis, cardio-respiratory failure, tachypnea, hypoxaemia, hyperamylasaemia, pancreatitis, can be fatal	Otero et al. (2004); Borges et al. (2015)
T. bahiensis	10–100	Bucaretchi et al. (2014)	III	cardiovascular manifestations, respiratory failure, can be fatal	de Oliveira et al. (2015)
T. bastosi	10–100	Costa et al. (2016)	U	unknown, although required medical treatment	Costa et al. (2016)
T. breweri	< 10	Borges et al. (2010); D'Suze et al. (2015)	II	pain and redness at sting site, sweating, hypersalivation, muscle tremors, fever, piloerection, tachycardia, tachypnea, abdominal pain, described as causing fatal accidents (needs confirmation)	Borges et al. (2010); D'Suze et al. (2015)
T. carabobensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. caripitensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. cerroazul	100–1000	Borges et al. (2012); Salazar et al. (2018)	U	fatalities reported, case reports need confirmation	Borges et al. (2012)
T. confluens	< 10	de Roodt et al. (2009)	III	can be fatal	de Roodt et al. (2009)
T. costatus	10–100	Diego-García et al. (2005)	U	unknown, other than symptoms require medical attention	Diego-García et al. (2005)
T. discrepans	10–100	D'suze et al. (2003); Borges et al. (2011)	III	hypertension, hypotension, tachycardia, tachypnea, hypothermia, respiratory distress, pancreatitis, gastrointestinal disorders, can be fatal	D'suze et al. (2003); Borges et al. (2011)
T. falconensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. festae	100–1000	Borges et al. (2012); Salazar et al. (2018)	U	fatalities reported, case reports need confirmation	Borges et al. (2012)
T. fuehrmanni	10–100	Otero et al. (2004)	U	unknown, described as moderate to severe requiring medical attention, but no specific symptoms reported	Otero et al. (2004)
T. isabelceciliae	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. ivic-nancor	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. matthieseni	10–100	Costa et al. (2016)	U	unknown, although required medical treatment	Costa et al. (2016)
T. metuendus	< 10	Lourenço (2016)	U	fatalities reported, case reports need confirmation	Lourenço (2016)
T. monaguensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)

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Table 3 (*continued*)

Species	Estimated Annual Sting Frequency	Source(s)	Sting Class	Reported Symptoms	Source(s)
T. neoespartanus	< 10	De Sousa et al. (2007)	II	vomiting, labored breathing, muscle tremors, hypersalivation, sweating, piloerection, tachypnea, cardiac arrhythmia, edematous pancreatitis, leukocytosis, hyperglycemia, hyperamylasemia	De Sousa et al. (2007)
T. nororientalis	< 10	D'Suze et al. (2015)	U	described as being responsible for severe and fatal accidents, no specific record or symptoms	D'Suze et al. (2015)
T. obscurus	10–100	Torrez et al. (2015); Lourenço (2016)	III	pain, burning and redness at sting site, edema, sweating, piloerection and priapism, nausea, dizziness, blurred vision, tremors, agitation, electric shock-like sensations in the body, slurred speech, lack of coordination, can be fatal	Pardal et al. (2014)
T. pachyurus	100–1000	Otero et al. (2004); Izquierdo and Buitrago (2012); Salazar et al. (2018)	III	severe systemic symptoms causing myocardial dysfunction, cardiovascular collapse, heart arrest, respiratory failure, pulmonary edema	Izquierdo and Buitrago (2012)
T. perijanensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, possible neurological manifestations, but no specific case reports	D'Suze et al. (2015)
T. pittieri	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. pusillus	< 10	Albuquerque et al. (2009)	II	pain and burning at sting site, chills, dizziness, headache and vomiting	Albuquerque et al. (2009)
T. quirogae	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. sanarensis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. serrulatus	10–100	Bucaretchi et al. (2014)	III	pain at the site of the sting, hypersalivation, vomiting, sweating, psychomotor agitation, cardiac arrhythmias, arterial hypertension, pulmonary edema, circulatory failure	Teixeira et al. (2001); Cupo and Hering (2002); Bucaretchi et al. (2014)
T. silvestris	< 10	Coelho et al. (2016); Monteiro et al. (2016)	II	pain and burning at sting site, labored breathing, agitation, tachycardia, generalized muscle spasms, hypertension	Monteiro et al. (2016)
T. stigmurus	100–1000	Batista et al. (2007)	III	pain, burning and swelling at sting site, numbness, headache, vomiting, sweating, can be fatal	Lira-da Silva et al. (2000); Batista et al. (2007)
T. surorientalis	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. trinitatis	< 10	Daisley et al. (1999)	III	tachypnea, restlessness, vomiting, hypersalivation, cerebral edema, pulmonary edema, hypovolemic shock, convulsions, myocarditis, pancreatitis	Daisley et al. (1999)
T. trivittatus	100–1000	de Roodt et al. (2003); de Roodt (2014)	III	pain, swelling, redness and burning at sting site, hyperthermia, cardiovascular and circulatory symptoms, cramps, tremors, headache, vomiting, dizziness, sweating, joint pain, can be fatal	de Roodt et al. (2003)
T. valerae	< 10	D'Suze et al. (2015)	U	described as causing severe and fatal accidents, but no specific case reports or symptoms found	D'Suze et al. (2015)
T. zulianus	10–100	Borges et al. (2011)	U	local manifestations, respiratory arrest, pulmonary edema, and fatalities reported, case reports need confirmation	Chowell et al. (2006); Borges et al. (2011)
Family Hemiscorpiidae					
Hemiscorpius					
H. acanthocercus	100–1000	Chippaux and Goyffon (2008); Shahi et al. (2016); Dehghani et al. (2018)	III	excess proteins and blood in urine, hemolysis of blood cells, severe effects on blood and kidneys, can be fatal	Shahi et al. (2015); Dehghani et al. (2018)
H. lepturus	100–1000	Jalali et al. (2010); Chippaux and Goyffon (2008); Dehghani et al. (2018)	III	toxic action on blood cells, kidney and liver function, necrosis, can be fatal	Pipelzadeh et al. (2007); Jalali et al. (2010); Dehghani and Fathi (2012); Dehghani et al. (2018)
Family Scorpionidae					
Nebo					
N. hierichonticus	< 10	Annobil (1993)	III	pain, itching and swelling at sting site, intravascular coagulopathy, intracranial hemorrhage, pulmonary edema, congestive heart failure, can be fatal	Rosin and Shulov (1963); Annobil (1993)

Centruroides considered medically significant are located in Mexico, with a small number of species found in the Southern United States, South and Central America, and throughout the Caribbean (Table 2). We found 24 *Centruroides* species that were considered medically significant in the literature, although only seven were able to be assigned a sting classification (Table 3). Recently, Riaño-Umbarila et al. (2017) performed a comprehensive median lethal dose assay, using venoms from 14 *Centruroides* species from Mexico, including two new species yet to be formally described, all of which were toxic in mice. Although toxicity in mice should not be used to indicate medical significance to humans (van der Meijden et al., 2017), Riaño-Umbarila et al. (2017) also reported the number of scorpion envenomations by region and which scorpions were responsible based on a 2016 report by the Ministry of Health of the Mexican Government. For these reasons, we included the 14 *Centruroides* species studied by Riaño-Umbarila et al. (2017) in our list of medically significant species, and assigned a sting class to those with documented case studies and symptoms (Table 3). Salazar et al. (2018) performed a similar study on *Centruroides* species in Panama, with over 33,000 scorpion stings including 47 deaths documented by the Department of Epidemiology of the Ministry of Health between 2000 and 2016, which were attributed as being caused by a handful of *Centruroides* or *Tityus* species. Venom from the four *Centruroides* species included in the Salazar et al. (2018) study were reported as dangerous and shown to be toxic in mice, although only one, *C. limbatus*, was assigned a sting class of II based on confirmed severe envenomation symptoms (Table 3).

In addition to the more comprehensive studies of *Centruroides* from Mexico and Panama discussed above, we found six other *Centruoides* species identified as being medically significant in the literature. *Centruroides exilicauda*, formerly synonymous with *C. sculpturatus*, was identified as a separate species that appears to be less harmful compared to *C. sculpturatus* (Valdez-Cruz et al., 2004). *Centruroides gracilis* has documented moderate to severe envenomations in Colombia (Otero et al., 2004), although this species has been reported as mild in Beliz (Borges et al., 2012). *Centruroides margaritatus*, which is distributed throughout Central and South America, appears to be associated with either mild or more severe envenomations depending on the region (Marinkelle and Stahnke, 1965; Borges et al., 2012). *Centruroides pococki* (Schmitt et al., 2017), and *C. testaceus* (Lobo et al., 2011) envenomations have been described as having mild to moderate symptoms. *Centruroides noxius* is considered the most toxic species in Mexico (Santibáñez-López et al., 2015; Riaño-Umbarila et al., 2017), however, we were unable to find a single case report or symptoms specifically associated with this species, and were therefore only able to assign *C. noxius* to an unknown sting class (Table 3).

Individual toxins isolated from *C. elegans* (Vandendriessche et al., 2010; Santibáñez-López et al., 2015; Olamendi-Portugal et al., 2005; Restano-Cassulini et al., 2008), *C. exilicauda* (Valdez-Cruz et al., 2004), *C. gracilis* (Possani et al., 2000), *C. infamatus* (Dehesa-Dávila et al., 1996), *C. limbatus* (Koschak et al., 1998), *C. limpidus* (Lebreton et al., 1994; Dehesa-Dávila et al., 1996; Santibáñez-López et al., 2016), *C. margaritatus* (Garcia-Calvo et al., 1993), *C. sculpturatus* (Wang and Strichartz, 1983; Corona et al., 2001; Valdez-Cruz et al., 2004), and *C. suffusus* (Martin et al., 1987; Estrada et al., 2007; Corzo et al., 2008), revealed a rich diversity of NaTxs and KTxs with both insect and mammal specificity. NaTxs were also detected in the electrophoretic profiles of *C. hirsutipalpus*, *C. meisei*, *C. ornatus*, *C. villegasi*, *C.* sp. *nov.* A, and *C.* sp. *nov.* B (Riaño-Umbarila et al., 2017).

A limited number of *Centruroides* venoms have been more well-characterized using venom-gland transcriptomic and proteomic approaches. *Centruroides noxius* venom has been characterized using high-throughput transcriptomic and proteomic methods (Rendón-Anaya et al., 2012) and isolation of individual toxins (Possani et al., 1982; Zamudio et al., 1992), which have confirmed NaTxs and KTxs, as well as AMPs, MPs, and protease inhibitors. A partial venom-gland transcriptome and proteomic characterization of *C. tecomanus* also identified NaTxs, KTxs, AMPs, and MPs (Valdez-Velazquéz et al., 2013, 2016), some of which have been individually isolated and functionally characterized (Ramírez et al., 1988; Olamendi-Portugal et al., 2016).

3.1.6. *Compsobuthus*

We found two species belonging to the *Compsobuthus* genus, *C. matthiesseni* and *C. persicus*, both of which are present in Iran (Table 1). *Compsobuthus matthiesseni* was identified in several epidemiological and biodiversity reports (Dehghani et al., 2009; Dehghani and Fathi, 2012; Nejati et al., 2014; Navidpour, 2015; Sanaei-Zadeh et al., 2017) and was found to be responsible for over 20% of confirmed scorpion stings in Iran (Dehghani et al., 2009), although the severity of symptoms was not reported beyond requiring medical attention (Table 3). More recent studies have reported symptoms such as hematuria (Dehghani and Fathi, 2012), but the degree of harm this species has on humans is still unclear. *Compsobuthus persicus* was responsible for nearly 20% of scorpion stings in the south of Iran from 2014 to 2016 (Shahi et al., 2016), with no symptoms reported as being specific to this species. Both *C. matthiesseni* and *C. persicus* were assigned to an unknown sting class (Table 3), and we could not find any confirmed venom components for either species.

3.1.7. *Hottentotta*

We found six species belonging to the *Hottentotta* genus, *H. gentili*, *H. jayakari*, *H. saulcyi*, *H. schach*, *H. tamulus* (formerly *Mesobuthus tamulus*), and *H. zagrosensis*, all of which are found in parts of Asia, aside from *H. gentili*, which is found in Northern Africa (Table 1). Envenomations by *H. gentili* were assigned to sting class III due to the manifestation of life-threatening symptoms and at least 10 fatalities (Table 3). Very few *H. jayakari* envenomations have been reported (Table 3), but those that have, have required extensive medical treatment, which assigns *H. jayakari* to sting class II. We found documented envenomation reports for both *H. saulcyi* and *H. schach*, although these did not include symptoms specific to these species other than requiring medical treatment (Table 3). Of the five *Hottentotta* species identified, *H. tamulus* has the highest number of documented envenomations, including multiple deaths (Bawaskar and Bawaskar, 1998; Kularatne et al., 2015), and was assigned to sting class III (Table 3). Venom composition and symptoms caused by *H. tamulus* seem to vary depending on habitat and geography, where the coastal populations tend to cause more harm than those found in semi-arid inland plateaus (Strong et al., 2015). We found one confirmed case report of *H. zagrosensis* with no specific symptoms reported (Table 3).

We could not find any confirmed venom components for *H. jayakari* or *H. saulcyi*. In a partial venom characterization of *H. gentili* venom, SPs and PLA2s were confirmed and functionally characterized (Estrada-Gómez et al., 2017). NaTxs, KTxs, ClTxs, PLA2s, and pulmonary edema causing toxins, have all been confirmed in the venom of *H. tamulus* (Strong et al., 2001, 2015; Deshpande et al., 2005). We also found a study that functionally characterized NaTxs in the venom of *Buthotus schach* (Aboutorabi et al., 2016), which was said to be synonymized with *H. zagrosensis* in this reference. However, Kovařík (2007) synonymized *B. schach* with *H. schach* (not *H. zagrosensis*) and classified *H. schach* and *H. zagrosensis* as separate species. We have retained the position that *H. schach* and *H. zagrosensis* are separate species for the purposes of this review, and it is unclear which species was used in the study by Aboutorabi et al. (2016).

3.1.8. *Leiurus*

The *Leiurus* genus, once considered monospecific under *L. quinquestriatus*, has undergone extensive taxonomic reclassification over the last several years and is now comprised of 12 species, each with fairly distinct geographical ranges in North Africa and the Levant and Arabian Peninsula (Table 1). *Leiurus quinquestriatus* is the only *Leiurus* found in Egypt, where epidemiological studies have included *L. quinquestriatus* as one of the most probable culprits of severe scorpion envenomations

(Saad et al., 2017). However, other medically significant species are also found in Egypt and Saad et al. (2017) did not include specimen identification. Venom from *L. quinquestriatus* was shown to be toxic when injected into rats (Salman and Hammad, 2017), but the degree of severity in humans is difficult to assess without confirmed case reports. Based on the classifications by Lowe et al. (2014), many of the previous case reports attributed to *L. quinquestriatus* should now be reclassified. Sofer and Gueron (1988) and Sofer et al. (1991) case reports are from a specific hospital in Israel (Soroka Medical Center) which is located in the distribution range of *L. hebraeus*, making this species the most probable culprit of these envenomations (Table 3). Al-Sadoon and Jarrar (2003) also identified *L. quinquestriatus* as one of the three offending scorpions in Saudi Arabia, and based on the regions represented in their report, stings attributed to *L. quinquestriatus* should now be shared among *L. arabicus*, *L. brachycentrus*, *L. haenggii*, *L. hebraeus*, *L. jordanensis*, *L. macroctenus*, and *L. heberti* (Table 3). More recent reports cite *L. abdullahbayrami* as being medically significant and responsible for severe, but rare, envenomations (Seiter et al., 2016; Dokur et al., 2017). Amr et al. (2017) lists *L. hebraeus* and *L. jordanensis* as being two of the five harmful species in Jordan, with *L. hebraeus* being the most common, but could not specify the identity of scorpions responsible for the 1205 stings reported in Jordan between 2006 and 2012. Based on these reports, nine *Leiurus* species are included in our list of medically significant scorpion species, although only *L. abdullahbayrami* and *L. hebraeus* were assigned a sting classification (Table 3). We could not find any envenomation records or notes of medical significance for the three remaining African *Leiurus* species (Lourenço et al., 2006, 2018; Lourenço and Rossi, 2016), and these should be further investigated.

The reclassification of *Leiurus* species also has implications in medical development. The *Leiurus* chlorotoxin used as an optical imaging contrast agent, in the surgical removal of tumors (tumor paint), and as an inhibitor of glioma cell invasion, was originally identified by Castle and Strong (1986), who listed the venom source as being from *L. quinquestriatus hebraeus*, which is now *L. hebraeus*. Following the isolation of *Leiurus* chlorotoxin, the exact species from which the toxin was isolated was not always specified (Deshane et al., 2003; Veiseh et al., 2007), and some refer to isolation from an Israeli scorpion (Dardevet et al., 2015), which also implies *L. hebraeus*.

Peptidomic and functional characterization of *L. abdullahbayrami* venom suggests the presence of NaTxs, ClTxs, and AMPs (Dokur et al., 2017). In *L. hebraeus*, KTxs and ClTxs have been purified and functionally characterized (Castle and Strong, 1986; Garcia et al., 1994; Kumar et al., 2015). We did not find venom characterization information for any of the other *Leiurus* species.

3.1.9. *Mesobuthus*

We found three species belonging to the *Mesobuthus* genus, *M. caucasicus*, *M. eupeus* and *M. gibbosus*. *Mesobuthus caucasicus* has recently been reclassified into several species (Fet et al., 2018) which are sympatric with *M. eupeus* and *M. gibbosus* in Iran and Turkey (Table 1). Although we did not find specific envenomation reports or venom characterization for members of the *M. caucasicus* complex, some have suggested that these species may be harmful to humans and that comparative lethality assays and venom characterization should be completed (Adiguzel, 2010; Ozkan et al., 2008; Bavani et al., 2017). Both *M. eupeus* and *M. gibbosus* are likely responsible for hundreds of envenomations annually with severe envenomation symptoms reported (Table 3), although case reports for *M. gibbosus* need confirmation.

KTxs and antimalarial peptides have been identified in *M. eupeus* (Gao et al., 2010a,b; Kuzmenkov et al., 2015), and KTxs, ClTxs, and AMPs, have been identified in *M. gibbosus* (Diego-García et al., 2013, 2014).

3.1.10. *Odontobuthus*

We found one species belonging to the *Odontobuthus* genus, *O. doriae*, which is a burrowing species distributed in Iran (Table 1). Although we could only find one case report for *O. doriae*, it was included as a medically significant species causing moderate to severe envenomation symptoms by others (Dehghani and Fathi, 2012; Sanaei-Zadeh et al., 2017). Based on reported symptoms, *O. doriae* was assigned to a sting class of III (Table 3).

KTxs and NaTxs have been isolated and functionally characterized from the venom of *O. doriae* (Jalali et al., 2005; Abdel-Mottaleb et al., 2006), and the venom-gland transcriptome revealed the presence of KTxs, NaTxs, AMPs, and MPs (NaderiSoorki et al., 2016).

3.1.11. *Orthochirus*

We found one species belonging to the genus *Orthochirus*, *O. scrobiculosus*, which is distributed throughout Iran (Table 1). This species is described as docile with very low envenomation risk, even when directly handled (Dehghani and Fathi, 2012) and has been classified as not likely to cause severe human harm (Hauke and Herzig, 2017). This species has been reported to cause at least one fatality, with other symptoms being minor, although envenomation reports were unable to be verified (Dehghani and Fathi, 2012). We therefore included *O. scrobiculosus* in our review with an unknown sting classification (Table 3).

KTxs have been isolated and functionally characterized from the venom of *O. scrobiculosus* (Dudina et al., 2001), and were shown to be lethal when injected into mice (Mouhat et al., 2005).

3.1.12. *Parabuthus*

We found four species belonging to the *Parabuthus* genus, *P. granulatus*, *P. mossambicensis*, *P. transvaalicus*, and *P. villosus*, all of which are distributed in central and southern countries of Africa (Table 1). *Parabuthus villosus* was identified as medically important by Debont et al. (1998), although we could not find any verified case reports for this species (Table 3). Envenomation symptoms caused by *P. mossambicensis* could also not be verified, but are likely mild to moderate (Table 3). Severe envenomation symptoms have been caused by *P. granulatus* and *P. transvaalicus*, assigning them to sting class III (Table 3). Prendini and Esposito (2010) updated the taxonomy of *Parabuthus* in South Africa and Namibia and found that several other *Parabuthus* species are sympatric with *P. granulatus*, which may indicate that some envenomation reports for *P. granulatus* could be misclassified. We could not find reports suggesting other *Parabuthus* species should be considered medically significant. NaTxs and KTxs have been identified in the venom from all four of the included *Parabuthus* species (Debont et al., 1998; Dyason et al., 2002).

3.1.13. *Tityus*

Tityus is the most diverse genus in Buthidae with over 200 described species widely distributed throughout Central and South America as well as in the Caribbean (Ojanguren-Affilastro et al., 2017). Unlike many of the other species described here, most *Tityus* species are accustomed to habitats with higher levels of moisture and humidity, such as tropical, coastal and rainforest habitats (Lourenço, 2008; Diego-García et al., 2012; Monteiro et al., 2016). Although we only list species that we found to be medically significant in the literature, our results are likely an underestimation due to the vast diversity and distribution of *Tityus*, with new species continuing to be classified (Lourenço, 2017; Teruel and de los Santos, 2018). We found 37 *Tityus* species of medical significance, 14 of which we were able to assign a sting class of either II or III based on reported symptoms (Table 3). Among those with unknown sting classifications were those described as causing severe or fatal accidents, but we could not find specific case reports to provide confirmation. In some cases, the severity of symptoms caused by members of the same species is dependent on the region. For example, *T. obscurus*, which is a senior synonym for both *T. paraensis* and *T. cambridgei* (Lourenço and Leguin, 2008), is found in both eastern and western regions of Parà, Brazil, with notable differences in venom composition and envenomation symptoms between these populations

(Pardal et al., 2014; Torrez et al., 2015; Santos et al., 2016). Both populations of *T. obscurus* can cause severe symptoms that require medical treatment, but the western population causes more neurological symptoms compared to the eastern population (Pardal et al., 2014; Torrez et al., 2015).

Much like *Centruroides*, members of the *Tityus* genus exhibit a diversity of NaTxs and KTxs, although we did not find venom characterization information for most species reported. Individual ion-channel toxins have been identified and/or functionally characterized from *T. caripitensis* (D'Suze et al., 2015), *T. discrepans* (Borges et al., 2006; Trejo et al., 2012; D'Suze et al., 2015), *T. pachyurus* (Barona et al., 2006; Guerrero-Vargas et al., 2012), *T. perijanensis* (D'Suze et al., 2015), *T. quirogae* (D'Suze et al., 2015), *T. trivittatus* (Coronas et al., 2003), and *T. zulianus* (Trejo et al., 2012; D'Suze et al., 2015).

Venom characterizations using transcriptomic, proteomic, or both approaches have also been completed for several *Tityus* species. NaTxs and KTxs were confirmed in the venom-gland transcriptome and proteome of *T. costatus* (Diego-García et al., 2005). In the venom-gland transcriptome and proteome of *T. stigmurus*, NaTxs, KTxs, AMPs and HYALs were present (Batista et al., 2007; Almeida et al., 2012). The venom of *T. metuendus* was proteomically characterized by Batista et al. (2018), who confirmed NaTxs, KTxs, MPs, HYALs, lectins and CRISPs. High-throughput transcriptomic methods were used to sequence the venom-gland transcriptome of *T. bahiensis*, which revealed a high abundance of MPs and confirmed the presence of NaTxs, KTxs, AMPs, Bpps, SPs, and CRISPs (de Oliveira et al., 2015). The most well-characterized *Tityus* venoms belong to *T. obscurus* and *T. serrulatus*. NaTxs, KTxs, AMPs, Bpps, HYALs, CRISPs, and MPs are among the venom components confirmed in the venom of *T. obscurus* using venom-gland transcriptomic and proteomic approaches (de Oliveira et al., 2018), some of which have been functionally characterized (Batista et al., 2000, 2002, 2004). The venom-gland transcriptome of *T. serrulatus* also revealed the presence of NaTxs, KTxs, AMPs and MPs (Alvarenga et al., 2012), most of which were later proteomically confirmed in the venom along with CRISPs and HYALs (de Oliveira et al., 2018). Several isolated *T. serrulatus* toxins have also been functionally characterized (Zoccal et al., 2011, 2013; Guo et al., 2013; Pucca et al., 2015b,c; 2016a, 2016b; Cerni et al., 2017).

3.2. Family Hemiscorpiidae

3.2.1. Hemiscorpius

The *Hemiscorpius* genus currently consists of 15 species, several of which are found in Iran, Iraq, Oman, Saudi Arabia, Yemen, Pakistan, and the United Arab Emirates (Dehghani et al., 2018). We found two medically significant species belonging to the *Hemiscorpius* genus, *H. acanthocercus* and *H. lepturus*, although other members of this genus may be harmful to humans and mistakenly identified as *H. lepturus*. A sting from either *H. acanthocercus* or *H. lepturus* can be fatal, assigning them to sting class III, and they are each likely responsible for hundreds of envenomations annually (Table 3). Unlike medically significant Buthidae envenomations, the symptoms of *Hemiscorpius* envenomation often do not present immediately, and sometimes several days pass before severe symptoms begin, resulting in a delay in seeking available treatment that likely contributes to the severity of symptoms (Dehghani et al., 2018).

We could not find any confirmed venom toxins for *H. acanthocercus* in the literature, but the high-throughput venom-gland transcriptome of *H. lepturus* revealed a high abundance of AMPs, PLA2s, MPs, and HYALs, as well as a number of KTxs (Kazemi-Lomedasht et al., 2017). Several phospholipase D sequences were also identified in *H. lepturus*, one of which was isolated from the venom and was nearly identical in sequence and structure to the phospholipase D assumed to be responsible for high levels of toxicity and lethality of *Loxosceles* (brown recluse) spider venom (Torabi et al., 2017).

3.3. Family Scorpionidae

3.3.1. Nebo

One species from the genus *Nebo*, *N. hierichonticus*, was identified as medically significant and is distributed throughout the Middle Eastern countries of Asia (Table 1). Reported life-threatening symptoms and fatalities caused by *N. hierichonticus* assigned this species to a sting class of III, although we only found a small number of cases reported (Table 3). We could not find any confirmed venom toxins for *N. hierichonticus* in the literature, however, we did find contradicting family classifications for the *Nebo* genus. Originally considered Scorpionidae, Prendini and Wheeler (2005) reclassified *Nebo* as belonging to the Diplocentridae family. Later that same year, Fet and Soleglad (2005) reclassified *Nebo* back to the Scorpionidae family. Recent literature has retained the Scorpionidae classification (Badry et al., 2018), so we have retained this position for the purpose of this review.

3.4. Medical importance of harmless scorpions

Potential uses of scorpion venom toxins in medicine include AMPs in the development of novel antibiotics and effective malaria treatments (Conde et al., 2000; Zeng et al., 2005; Díaz et al., 2009; Fang et al., 2011; Guo et al., 2013; Harrison et al., 2014), Bpps in the treatment of hypotension (Camargo et al., 2012; Ortiz et al., 2015), and ion-channel toxins in the treatment of auto-immune diseases and cancer (Guo et al., 2013; Ortiz et al., 2015), including glioma tumors (DeBin and Strichartz, 1991; Deshane et al., 2003; Veiseh et al., 2007). An overwhelming majority of known scorpion species are considered harmless to humans and have not been considered as medically significant throughout the literature. Available venom characterizations of harmless scorpion species, however, suggest that these venoms may be just as medically useful as those that cause human harm, especially in the development of antibiotics and drugs with ion-channel specificity. In fact, many of the potential treatments listed above are based on toxins isolated from harmless species (Conde et al., 2000; Zeng et al., 2005; Fang et al., 2011; Harrison et al., 2014; Ortiz et al., 2015). Discussed here are a few more examples of well-characterized harmless scorpion venoms for the purpose of illustrating their potential in medicine.

Quintero-Hernández et al. (2015) characterized the venom-gland transcriptomes for four species belonging to the *Vaejovis* genus (Family Vaejovidae), *Vaejovis mexicanus*, *V. intrepidus*, *V. subcristatus*, and *V. punctatus*, which are largely distributed in Mexico. Although precursor coding sequences for NaTxs, KTxs, and CaTxs were detected in the *Vaejovis* transcriptomes, including potent KTxs shown to affect human potassium-channels (Gurrola et al., 2012), the most abundant transcripts present were those that code for AMPs of the non-disulfide bridge peptide (NDBP) class. The same group had previously isolated and functionally characterized some *Vaejovis* NDBPs and found them to be effective against both Gram-positive and Gram-negative bacterial strains (Ramírez-Carreto et al., 2012).

Santibáñez-López et al. (2017) characterized the venom-gland transcriptome and proteome of the Mexican scorpion, *Megacormus gertschi* (family Euscorpiidae). Transcripts coding for NaTxs, KTxs, and CaTxs were present, however, these transcripts accounted for approximately 10% of the annotated toxin sequences combined. The NDBP class of AMPs also accounted for approximately 10% of annotated transcripts in *M. gertschi*, and the most abundant toxins present were enzymes such as MPs, SPs, PLA2s, and HYALs, where MPs alone accounted for nearly 20% of the annotated transcripts. Venom from *M. gertschi* was also demonstrated to be toxic in crickets and shrimp, and did not exhibit toxicity in mice, suggesting the toxins present are insect and crustacean specific.

Rokyta and Ward (2017) characterized the venom-gland transcriptome and proteome of *Hadrurus spadix*, a member of the Caraboctonidae family found in deserts of the eastern United States. The most abundant and diverse toxins present in the venom of *H. spadix* were KTxs and AMPs (both NDBPs and cysteine-containing). A number of peptidases, PLA2s, and SPs were also detected, along with 66 venom protein (VP) transcripts with unknown function. The same group later characterized the venom-gland transcriptome and proteome of *Centruroides hentzi*, a harmless Buthidae species found in the southeastern United States (Ward et al., 2018). Similar to the harmful *Centruroides* species discussed above, the venom of *C. hentzi* primarily consisted of NaTxs and KTxs, although only one NaTx in *C. hentzi* was identified as mammal-specific.

3.5. Assessing the true medical significance of scorpions: problems and prospects

We identified 104 scorpion species considered medically significant in the literature, however, we could only assign 32 of these to a severe sting class of II or III based on specific symptoms attributed to these species. We found a handful of species that were implicated as being medically significant or harmful to humans in the literature, although documented case reports for these species indicated only class I symptoms. Of the 104 medically significant species identified, 68 were given an unknown sting class due to unverifiable symptoms or lack of symptoms reported. Several species were assigned an unknown sting classification because recent taxonomical updates have not yet been incorporated into the literature and it is unclear whether or not these reclassified species should be considered medically significant (*i.e. Buthus* and *Leiurus* species in particular).

The number of envenomations and severity of symptoms reported may depend on either human or scorpion population density (*i.e.* the likelihood of envenomation, Lourenço, 2018), as well as variation in sensitivity to envenomation, which may be age or health dependent (Pucca et al., 2015a; Hauke and Herzig, 2017). Several of the species presented here were assigned a sting classification based on symptoms reported in a single case study or in studies focused on envenomations in children and do not necessarily reflect a typical reaction in a healthy adult. It should therefore be noted that the term “medically significant” as it relates to scorpions in the literature does not necessarily equal a statistical significance in terms of the number of severe cases reported in proportion to the general population. Although thousands of deaths due to scorpion envenomation are reported annually, the majority of sting incidents, even by medically significant species, likely go unreported. Much larger and more comprehensive case studies that include both children and adults need to be completed to assess the true degree of harm a given species may have on humans. These studies should include proper specimen identification and those envenomated should be encouraged to bring in the offending scorpion (if safe to do so), especially in areas with high envenomation rates and diverse scorpion fauna. These same concerns have been addressed in the case of spider envenomations, leading to a strict standard of requirements for an apparent spider bite to be classified as such (Isbister and White, 2004). The importance of these standards was recently demonstrated by Stuber and Nentwig (2016), who indicated that only 22% of 134 medical spider bite case reports could be accurately verified. Although the reported species are not considered harmful to humans, the study of Australian scorpion stings by Isbister et al. (2003) is one such example of a more comprehensive case study that will ideally become the rule, rather than the exception, in the assessment of scorpion envenomations. Another consideration is the availability and access to scorpion envenomation treatment (Chippaux and Goyffon, 2008). Although treatment may effect the overall outcome of the patient (especially in the case of fatalities), any scorpion envenomation that requires medical treatment for survival or management of symptoms, even if only a single case study, should be classified as such (*i.e.* sting class II or III) to reflect the ability of the scorpion species to cause severe human harm and encourage those envenomated to seek appropriate treatment.

The reported medical significance of scorpions often implies that the same toxins responsible for causing human harm may also be useful in therapeutic development. As such, we were surprised to find that only 54 of the 104 medically significant species we identified had undergone some form of venom characterization. Within these 54 species, most had partial characterizations with few individual toxins isolated and functionally characterized, and only 12 had more extensively characterized venoms using venom-gland transcriptomic and/or proteomic approaches. Although partial characterizations have contributed to therapeutic development (*i.e* chlorotoxin, discussed above), these characterizations are likely missing key functional elements of the venom considering some toxins require activation by another to exhibit higher levels of toxicity (Undheim et al., 2014, 2015; Whittington et al., 2018). The complete characterization of venom, using venom-gland transcriptomic and proteomic approaches, will better ensure we are capturing the full potential of these powerful venoms. Additionally, many harmless species have already demonstrated their relevance in medicine, and they may hold the key in understanding the evolution of lethal toxins. Comparing harmful and harmless scorpion venoms will assist in our ability to decipher the differences in function, sequence, and abundance of similar toxins with varying consequences across multiple species. Therefore, more extensive venom characterizations should be a prioritized research effort in the study of both harmful and harmless scorpion species.

In the process of conducting our literature review, we found a seemingly large disconnect between those who encounter and/or provide treatment for scorpion envenomations (usually medical professionals), researchers who primarily focus on venom characterization or drug development, and researchers who focus on taxonomy and the identifying characteristics of scorpion species. Each of these contributing groups focus on a different area of scorpion research, all of which need to be integrated if we aim to grasp the true severity of scorpionism as well as develop medications from their venoms. Taxonomical classifications in particular are not readily or ubiquitously incorporated into other areas of the literature, making it difficult to decipher which species are truly medically significant or responsible for causing human harm. For the purposes of our review, we retained species names as reported in corresponding literature and noted where taxonomical updates should be applied, however, this does not account for species that were misidentified and therefore not accurately reported. Proper scorpion identification should be considered in any future scorpion studies encompassing all research areas and include the submission of voucher specimens for species confirmation. In cases where venom is not directly harvested by the researcher, as is common in studies focused on the characterization of isolated toxins, the researcher should clearly state the originating species and make every effort to obtain the venom from a source in which a voucher specimen has been submitted. The submission of voucher specimens would also leave room for future taxonomical updates that may impact results of previous studies. For example, *C. huichol* was classified as a new species after detailed examination of specimens thought to be *C. noxius* (Teruel et al., 2015). As a result, some envenomations that were attributed to *C. noxius* may actually belong to *C. huichol*.

4. Conclusions

In consideration of the many contributing factors discussed throughout this review, we have provided an updated, global list of scorpion species described as medically significant throughout the literature. Because scorpions are rapidly diversifying and new species are continuing to be described, the number of species, estimated sting frequencies, geographical boundaries, and sting classifications reported here should be considered a guideline only. Proper scorpion identification should become a priority in all future scorpion research, especially in the assessment of scorpionism and in work aimed at characterizing venoms for the purpose of drug development.

Ethical statement

Reporting standards: The authors declare that our manuscript describes original research and every effort was made to ensure the accuracy of the results and the account.

Data Access and Retention: The authors declare that all data is reported and provided within the manuscript and there is no additional data to make available.

Originality and Plagiarism: The authors declare that our manuscript is an original work with proper citations as needed.

Multiple, Redundant or Concurrent Publication: The authors declare tha the data and work described in our manuscript has not and will not be submitted for consideration to another journal.

Acknowledgment of Sources: The authors have provided proper acknowledgment of sources to the best of their abilities.

Authorship of Paper: All three authors of the manuscript made significant contributions, and no one making significant contributions was excluded from authorship. All three authors have seen and read the submitted version of the manuscript and have approved submission.

Hazards and Human or Animal Subjects: This review study did not involve the use of vertebrate animals.

Disclosure and Conflicts of Interest: The authors declare no conflicts of interest.

Fundamental Errors in Published Works: If a fundamental error or inaccuracy is discovered in the results described by our literature review, the authors will immediately notify the editor or publisher.

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