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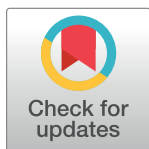
Terrestrial venomous animals, the envenomings they cause, and treatment perspectives in the Middle East and North Africa

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Abstract

The Middle East and Northern Africa, collectively known as the MENA region, are inhabited by a plethora of venomous animals that cause up to 420,000 bites and stings each year. To understand the resultant health burden and the key variables affecting it, this review describes the epidemiology of snake, scorpion, and spider envenomings primarily based on heterogenous hospital data in the MENA region and the pathologies associated with their venoms. In addition, we discuss the venom composition and the key medically relevant toxins of these venomous animals, and, finally, the antivenoms that are currently in use to counteract them. Unlike Asia and sub-Saharan Africa, scorpion stings are significantly more common (approximately 350,000 cases/year) than snakebites (approximately 70,000 cases/year) and present the most significant contributor to the overall health burden of envenomings, with spider bites being negligible. However, this review also indicates that there is a substantial lack of high-quality envenoming data available for the MENA region, rendering many of these estimates speculative. Our understanding of the venoms and the toxins they contain is also incomplete, but already presents clear trends. For instance, the majority of snake venoms contain snake venom metalloproteinases, while sodium channel–binding toxins and potassium channel–binding toxins are the scorpion toxins that cause most health-related challenges. There also currently exist a plethora of antivenoms, yet only few are clinically validated, and their high cost and limited availability present a substantial health challenge. Yet, some of the insights presented in this review might help direct future research and policy efforts toward the appropriate prioritization of efforts and aid the development of future therapeutic solutions, such as next-generation antivenoms.

1. Introduction

The total number of people that are medically affected by envenoming from snakes, scorpions, and spiders all around the globe runs into the millions. In the Middle East and North Africa (MENA), there are over 420,000 snakebites, scorpion stings, and spider bites each year [1,2]. The MENA region comprises 19 countries, i.e., Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, and Yemen. This region is home to over 30 species of venomous snakes, within the Elapidae, Viperidae, and Lamprophiidae families [1,2]. The MENA region is also home to 27 scorpion species across three families, i.e., Buthidae, Hemiscorpiidae, and Scorpionidae [3], as well as two medically important spider families, including widow spiders (*Latrodectus* spp.) and recluse spiders (*Loxosceles* spp.) [4]. Together, the venomous animals found in the MENA region present an impressive diversity of different venom toxins that can cause a range of local and systemic effects that can lead to permanent disability or death.

As is the case globally, the only effective treatment for severe venomous bites and stings in the MENA region is intravenous administration of antivenom. Antivenom is produced by immunizing large animals, such as horses and sheep, with sublethal doses of venom and then extracting and purifying the resulting polyclonal antibodies [5]. Although animal-derived antivenoms save numerous lives, many of these medicines suffer from several drawbacks, including a complicated and expensive production process, mismatch of demand–need–supply, poor quality, low specificity against small venom toxins, and often an inability to neutralize local tissue damage [6,7]. Fortunately, the rise of next-generation antivenoms based on defined recombinant cocktails of monoclonal antibodies, as well as recently investigated repurposed small molecule inhibitors and chelators, gives hope toward a substantial improvement in the treatment of envenoming victims in the near future [8–14].

However, to improve or replace current treatments and to effectively decrease the morbidity and mortality of envenomings in the MENA region, it is crucial to gain a better understanding of the magnitude of the problem and the variables involved. Therefore, in this review, we provide an overview of the epidemiology of snake, scorpion, and spider envenomings in the MENA region. Moreover, due to the relation between the venom composition and its pathophysiological effects [15], wherever possible/relevant, the key toxins of the venoms and their physiological effects are discussed. Addressing the biological activity of the venoms and their medically significant toxins not only helps to gain a comprehensive understanding of the envenomings, but also has a crucial impact on the design and development of new therapeutic approaches, such as next-generation antivenoms, to circumvent them [15,16]. Accordingly, the antivenoms that are currently in use in the MENA region to counteract animal envenomings and the future perspectives are discussed.

2. Main species responsible for severe envenomings

2.1. Snakes

There are over 731 different venomous snake species spread across the world (snakedb.org). However, the burden that these snakes cause to regions and communities is not evenly distributed. The highest burden is felt in sub-Saharan Africa and Southeast Asia, in part, due to the high number of highly venomous species found in these regions [17]. Consequently, these regions have so far received most of the international attention and resources. Conversely, the MENA region has been largely overlooked, despite numerous venomous species inhabiting this region. Indeed, according to the World Health Organization (WHO), a total of 16 Category I medically important snake species (i.e., highly venomous snakes that are prevalent in

the respective country and cause numerous bites, leading to mortality or morbidity) are spread across North Africa and the Middle East (Fig 1A) [1]. Based on a literature review and modeling study performed by Kasturiratne and colleagues [17], North Africa was estimated to have between 463 and 36,208 snakebite incidences with a death toll between 20 and 29 individuals each year; the Middle East had similar figures, with 2,306 to 31,417 incidences and between 15 and 33 deaths annually. However, these statistics are very broad estimations seen from a global perspective and are expected to be significantly underestimated due to the lack of medical information in most of the assessed countries [17]. In the last 25 years, no reliable data involving snakebites exist from Algeria, Libya, Tunisia, Qatar, Syria, and Kuwait. This significantly skews the data for the whole MENA region and, in particular, North Africa, as only Egypt and Morocco are providing the epidemiological data for the entire region. As it remains, the actual number of incidences and deaths in this region will not be fully known until the lack of data from many countries is resolved. The available epidemiological data from the MENA countries reveal many similarities consistent across incidences involving snakebites. Numerous data reports show that most snakebite cases occur in rural farmable areas [18–24]. Specifically, multiple studies conducted in Egypt, Iran, Iraq, Morocco, and Saudi Arabia found that 70% or more of cases were reported from rural farming areas. Furthermore, males constitute more than 50% of snakebite incidences in many MENA countries [18,22,24–32]. Mortality rates from these countries range significantly and are largely dependent on the amount of available data. Epidemiological data from Egypt, Iran, Jordan, Morocco, Saudi Arabia, and Yemen have shown mortality rates ranging from 0.13% up to 4.8% [18,19,22–24,26,29,32]. Disturbingly, a study conducted on snakebite incidences in Iraq found a mortality rate of 7% to 15% among adults [27].

Responsible for this morbidity and mortality are the snakes' toxins. Notably, while a great diversity in venom composition exists between and within different snake species, the key protein components that are present in these toxin cocktails often remain similar: Elapid venoms typically predominantly consist of three-finger toxins (3FTxs) and phospholipase A_2s (PLA$_2$s), whereas viper venoms often contain a substantial amount of snake venom metalloproteases (SVMPs), snake venom serine proteases (SVSPs), as well as PLA$_2$s [7,33]. Currently, proteomics or transcriptomic data exist for half of the medically important snake species (nine out of 18), and based on that, SVMPs are the most prominent (average relative abundance of 41.9%) toxins in the MENA snakes, followed by C-type lectins (CTLs; 9.7%), PLA$_2$s (9%), disintegrins (DISs; 8.5%), 3FTxs (7.5%), and SVSPs (6.4%; Fig 1B). SVMPs are important compounds of most viperid and crotalid venoms. The highest relative abundances of these toxins in the MENA snakes are found in the genera *Echis*, *Cerastes*, and *Macrovipera* (Fig 1B). They are known to cause hemorrhagic and local effects in victims through different mechanisms including disrupting extracellular matrix (ECM) of capillary endothelial cells, which, in turn, results into escaping of blood from capillaries. The second most abundant toxin family in the MENA snakes, i.e., snake venom CTLs (lectin-like proteins) [34]. CTLs are frequently found in the vipers and target clotting factors and various receptors on platelets, endothelial, and immune cells. CTL-related proteins can cause disseminated intravascular coagulopathies or severe bleedings, which both are life-threatening situations in viper envenomings [35]. Notably, PLA$_2$s are another group of abundant toxins in MENA snakes, but their relative abundance varies greatly between different species, with the highest percentages observed in *Echis pyramidum* (20.6%) and *Cerastes cerastes* (19.1%) and the lowest in *Naja haje* (4%, Fig 1B). Besides affecting the blood coagulation cascade, PLA$_2$s can have both neurotoxic and cytotoxic activities, resulting in systemic and local symptoms [36,37]. DISs constitute another group of abundant toxins in the MENA snakes and are frequently found in vipers and rattlesnakes and closely related to SVMPs. They are either produced from the proteolysis of a SVMP precursor

A)

B)

Snake family	Snake genus	Snake species	Snake specimen origin	LD$_{50}$ (mg/kg)	Dominant toxin families				Secondary toxin families						Other	Ref
					3FTxs	PLA$_2$s	SVMPs	SVSPs	LAAOs	KSPIs	CRiSPs	DISs	NPs	CTLs		
Elapidae	Naja	haje legionis	Morocco	0.29	60	4	9	-	1	1.9	10	-	-	-	14.1	[42]
Viperidae	Cerastes	cerastes	Morocco	0.25	-	19.1	63.1	6.9	-	-	0.7	8.5	-	1.7	0	[43]
			Tunisia													
	Bitis	arietans	Ghana	0.39	-	4.3	38.5	19.5	-	4.2	1.7	17.8	-	13.2	0.8	[44]
	Echis	pyramidum+	Kenya	0.84	-	20.6	45.4	2	2.6	-	-	0.1	-	24	5.3	[45]
		carinatus+	UAE	0.12	-	7.9	52.6	4.6	1.1	-	1.8	7.3	-	16.7	8	[45]
		coloratus+	Egypt	0.25	-	5.3	56.9	4.4	3.9	-	5.3	5.6	-	10.3	8.3	[45]
	Macrovipera	lebetina	Tunisia	0.57	-	5	63.1	5.5	-	3.1	-	15.1	0.8	3.2	4.2	[46]
	Daboia	mauritanica	Morocco	0.3	-	5.5	45.4	8.3	-	2.5	-	13.8	4.5	8.1	11.9	[46]

Fig 1. Medically relevant Category I snakes in North Africa and the Middle East. (A) Phylogeny and geographic distribution and **(B)** reported toxicity and available venom proteome or transcriptome (+) data are shown. Specifically, the table presents the genera, species, the origin of the reference proteome or transcriptome, and the median lethal dose in mice (LD$_{50}$; mg/kg) [42–46]. It also illustrates the relative abundance of 3FTxs, PLA$_2$s, SVMPs, SVSPs, LAAOs, KSPIs, CRiSPs, DISs, NPs, and CTLs. All components are represented as relative wet weight abundance in %. Notably, snake venom composition may vary depending on region. 3FTx, three-finger toxin; CRiSP, cysteine-rich secretory protein; CTL, C-type lectin; DIS, disintegrin; KSPI, kunitz-type serine protease inhibitor; LAAO, L-amino acid oxidase; NP, natriuretic peptide; PLA$_2$s, phospholipase A$_2$s; SVMP, snake venom metalloprotease; SVSP, snake venom serine protease.

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or synthesized from mRNAs that have lost their metalloprotease-coding region [38]. DISs induce their toxicity through interacting with integrins on platelets, which are responsible for cell–ECM interactions and intercellular signaling [39], hence interfering with clot formation.

Furthermore, while 3FTxs are only found in *Naja* species, they comprise more than half of their venom, e.g., *Naja nubiae* [40] and *N. haje* venom contains 70.9% and 60% of these toxins, respectively (Fig 1B). They are highly toxic and despite significant homology in sequence and structure, 3FTxs demonstrate a wide range of activities, from highly specific ion channel inhibition (neurotoxicity) to nonspecific membrane disruption (cytotoxicity). Finally, SVSPs are found in all viper species in the MENA region, with *Bitis arietans* presenting the highest relative abundance (19.5%; Fig 1B). In general, different SVSPs are able to both specifically activate the blood components that play a role in coagulation, fibrinolysis, and platelet aggregation (coagulant effect) and enzymatically degrade them (anticoagulant effect) [41].

The following presents an overview of all medically relevant snakes in the MENA region (see also [28]), their key toxins (Fig 1), and the role these toxins play in inducing envenoming symptoms.

2.1.1. Elapidae family. Elapids have short, hollow, and fixed fangs [47], with venoms that are predominantly neurotoxic and characterized by progressive symptoms of paralysis and respiratory failure [48]. In the MENA countries, the Elapidae family is only represented by one genus, *Naja*, otherwise known as true cobras, that contains three species of Category I and one (*N. nubiae*) of Category II (potentially dangerous, but insufficient epidemiological data) medically important venomous snakes.

***Naja* genus.** The genus *Naja* contains over 30 species of highly venomous snakes [49], of which three have been identified within the MENA region. WHO considers *Naja arabica*, *N. haje*, and *Naja oxiana* as Category I venomous snakes. While *N. arabica* is found across Oman, Saudi Arabia, and Yemen, where it especially is a problem [1], *N. oxiana* is only located in Iran. Meanwhile, *N. haje* is distributed across North Africa and is known to be highly problematic in Algeria, Egypt, Libya, and Morocco (Fig 1A) [1].

Like many cobras, *N. haje* bites result in potentially lethal neurotoxic symptoms, as well as local swelling and pain at the bite site; these effects are primarily caused by neurotoxins (NTxs) and cytotoxins (CTxs) [42,50] from the 3FTx family. The NTxs mostly act by binding to the postsynaptic nicotinic acetylcholine receptors (nAChRs) at the neuromuscular junction to produce clinically significant and potentially lethal skeletal muscle paralysis [51]. Notably, in the MENA region, snake venom 3FTxs are only found in *Naja* species and have never been identified in the venoms of other MENA snakes. Yet, in the *Naja* genus, 3FTxs constitute a significant proportion of the whole venom and the majority of the venom's toxicity. Indeed, proteomics data, which are only available for *N. haje*, reveals that 3FTxs (60%; Fig 1B) constitute the main venom component of these snakes. In addition to 3FTxs, PLA$_2$s likely also play a role in inducing some of the *N. haje* envenoming symptoms. Indeed, PLA$_2$s and CTxs from sub-Saharan African *Naja* species have been shown to act synergistically [52] and to be the primary components behind permanent tissue loss and the resultant amputations in *Naja* snakebite envenomings [53].

2.1.2. Viperidae family. Besides elapids, another family of highly venomous snakes can be found in the MENA region, i.e., the family Viperidae, more commonly known as vipers. Vipers are characterized by their long, hollow, and retractable fangs [47] and often possess myotoxic and hemotoxic venom that can cause symptoms of local or systemic bleeding in the affected limbs, coagulopathy, and extensive edema [50]. This family also encompasses 12 of the 16 species identified by WHO as Category I snakes in the MENA region. These 12 species are spread across six genera, which are further discussed below.

2.1.2.1. Bitis. The *Bitis* genus is widespread across the African continent and the southern Arabian Peninsula and consists of 17 species [49]. However, only one species, *B. arietans*, can be found within the MENA region. This species is known to inhabit Algeria and Morocco, but its distribution also extends to the Arabian Peninsula, including Oman, Saudi Arabia, and Yemen (Fig 1A) [49]. A study conducted by Eljaoudi and colleagues [50] found that *B. arietans*

is responsible for approximately 17% of all recorded snakebites in Morocco. Notably, the large amounts of venom injected during an average bite (typically between 150 and 350 mg), alongside its toxicity, renders this species highly dangerous [54]. The venom of *B. arietans* can induce severe local and systemic clinical manifestations, including bleeding, swelling, necrosis, compartment syndrome, and hypotension [54]. Furthermore, based on proteomics data, *B. arietans* possesses the highest relative abundance (19.5%; Fig 1B) of SVSPs among all MENA snakes. SVSPs can generally be found in viper venoms and are known to affect the blood coagulation cascade at different levels, resulting in the inactivation of blood clotting factors, inhibition of platelet aggregation, and a decrease in blood pressure by acting as a hypotensive agent [42,46,55]. Besides SVSPs, CTLs make up a significant amount of *Bitis* venoms. These toxins (e.g., bitiscetin) are hemostasis disruptive and consequently prevent blood clotting by interfering with platelet aggregation and the coagulation cascade [35].

2.1.2.2. Cerastes. One of the most widely distributed viper genera across the Sahara and Arabian Peninsula is the genus *Cerastes*, which consists of only three distinct species [56]. Two, i.e., *C. cerastes* and *Cerastes gasperettii*, are considered medically relevant. These species are dispersed across the MENA region (Fig 1A) and are responsible for many snakebite incidences. In particular, a study conducted by Al-Sadoon over the period from 2005 to 2010 found that in the Riyadh Province of Saudi Arabia, *C. gasperettii* was responsible for 886 snakebite cases, accounting for 86.9% of all incidences in this area [32]. In southern Morocco, *C. cerastes* is considered the most dangerous snake species [57].

A *C. gasperetti* envenoming causes local pain, swelling, edema, and tenderness in most patients [32]. Similarly, the danger from *C. cerastes* can be attributed to its venom causing mild to severe local effects, hypotension, and arterial thrombosis [50,58]. Currently, proteomics data are only available for *C. cerastes*; this suggests that SVMPs and PLA$_2$s are the main constituents of its venom. SVMPs are capable of damaging ECM components, such as proteoglycans [59], collagen, laminin, and fibronectin [60]. Thus, SVMPs are mainly involved in edema, inflammation, swelling, blistering, skin damage, tissue necrosis, myonecrosis, and cardiovascular shock. In addition, they have procoagulant, anticoagulant, and platelet aggregation inhibitory effects [60]. In the MENA region, *Cerastes*, together with *Echis* and *Macrovipera* (see Sections 2.1.2.4, 2.1.2.5, and Fig 1B), possesses the highest relative abundances of SVMPs.

2.1.2.3. Daboia. Like *Cerastes*, the genus *Daboia* only contains two medically relevant species within the MENA region, *Daboia mauritanica* and *Daboia palaestinae*. The former can be found within Algeria, Morocco, and Tunisia, whereas the latter is distributed across Israel, Jordan, Lebanon, Palestine, and Syria (Fig 1A). *D. mauritanica*, in particular, has been suggested to be responsible for most of the snakebite incidences within North Africa [49]. This species was linked to 69.4% of all the snakebite incidences that Eljaoudi and colleagues identified in Morocco [50]. Epidemiological data are scarce for *D. palaestinae*, but it has been reported that bites are associated with a death rate of 6.2% in Israel and Jordan [49].

Notably, the venom of *D. palaestinae* is cytotoxic and can induce hematuria, swelling, bleeding at the site of the bite, and significant hemorrhage [49]. Similarly, the venom of D. *mauritanica* is primarily cytotoxic and is characterized by mild to severe local effects, hypotension, and coagulopathy [50]. Proteomics data are only available for *D. mauritanica* (Fig 1B) and demonstrates that its venom predominantly contains SVSPs and DISs that inhibit platelet aggregation and integrin-dependent cell adhesion.

2.1.2.4. Echis. *Echis* constitutes another genus of vipers in the MENA region and is one of the most taxonomically problematic Viperidae genera. The number of currently recognized species ranges from 8 to 12, and potentially 20 subspecies, depending on the literature [61]. Five of these species can be found in the MENA countries: *Echis burkini*, *Echis carinatus*, and *Echis omanensis*, which are predominantly located across the Middle Eastern countries, as well

as *E. pyramidum* and *Echis coloratus*, which are mainly found in Egypt but also in the ME (Fig 1A). Indeed, a bite from this genus, without antivenom treatment, has an estimated mortality rate of up to 20% [45]. *E. coloratus*, in particular, is one of the key species contributing to this high mortality rate. It was identified as the primary species causing snakebite-related deaths in two different studies in Saudi Arabia. The first study found that *E. coloratus* accounted for 67% of all the Riyadh Province's identifiable snakebite cases [18], yet this statistic did not hold true in a later study that demonstrated that *C. gasperettii* was the primary cause of death. The second one focused on snakebites among children in the Al-Baha region and found that this species accounted for 10.8% of the identifiable cases [20]. Furthermore, *E. carinatus* was responsible for up to 9% of snakebites in Oman, and alongside *E. omanensis*, it is thought to be the primary cause for snakebites in this country [31]. *E. carinatus* has also been identified as the species which causes highest mortality and morbidities in Iran [22].

General symptoms of *Echis* bites include local swelling at the bite site, local blistering, necrosis, incoagulable blood, and spontaneous systemic bleeding. The proteomics data available for *E. carinatus*, *E. coloratus*, and *E. pyramidum* offer a possible reason. Venom from these snakes predominantly contains SVMPs and CTLs. Besides local effects, SVMPs together with CTLs, have anticoagulant and platelet-modulating activities [62].

2.1.2.5. Macrovipera. The genus *Macrovipera*, a smaller and taxonomically simpler genus than *Echis*, currently contains just three species and five subspecies [63]. *Macrovipera lebetina* is the most prominent species from this genus, with an extensive geographic range from the Middle East extending throughout central Asia (Fig 1A) [64,65]. In addition, it is the only species from this genus that is considered as a Category I medically important species by WHO. On the Iranian plateau (i.e., Afghanistan, Azerbaijan, Iran, Iraq, Pakistan, and Turkmenistan), this species is considered one of the most venomous snakes [64]. It is noteworthy that *Macrovipera razii* has recently been separated from *M. lebetina* as a new species that is endemic to Iran; however, its epidemiologic data are still not available [63].

The venom of *M. lebetina* is known to cause significant local tissue damage, necrosis, edema, and hemorrhage [64]. Nevertheless, the primary cause of death by this species has been attributed to acute renal failure [64]. The underlying toxin(s) that induce acute renal failure have not been identified. However, the venom of *M. lebetina* was found to be dominated by SVMPs (Fig 1B) that have been hypothesized to cause nephrotoxicity through secondary effects, including hypotension, hemolysis, and rhabdomyolysis [64].

2.1.2.6. Pseudocerastes. Finally, the genus *Pseudocerastes* was given its name due to its phenotypic similarity to the *Cerastes* genus, despite a lack of genetic relatedness. *Pseudocerastes* contains three species with a geographical distribution ranging from Egypt to Iran and extending to the southeastern part of the Arabian Peninsula (Fig 1A) [49]. Nonetheless, *Pseudocerastes persicus* is the only clinically relevant species recognized within the MENA region. This species' venom is thought to be highly coagulopathic, but little is known about its symptomatic effects in humans [66]. *Pseudocerastes fieldi* inhabits a similar geographic range as *P. persicus* and is classified as a Category II species by WHO. Notably, its venom substantially differs from *P. persicus* and is thought to possess neurotoxic properties [66]. This neurotoxicity is attributed to a novel PLA_2 complex that creates an irreversible neuromuscular blockade at the presynaptic site [66].

2.1.3. Lamprophiidae. The last of the represented snake families, Lamprophiidae, contains a single subfamily that is regarded as medically relevant in the MENA region. The species in the Atractaspidinae subfamily are known for their unique jaw that allows a single fang to protrude from an almost fully closed mouth [67].

This subfamily's venom is cardiotoxic, with general symptoms of mild to moderate pain, swelling, and local discoloration [67]. However, this venom has also been associated with producing lethal coronary vasospasms, i.e., intense vasoconstriction of the coronary artery [68].

Atractaspis. The genus *Atractaspis* contains 22 different species, which are distributed across Africa and the Middle East, but only two, i.e., *Atractaspis engaddensis* and *Atractaspis andersonii*, are found within the MENA countries [69]. Envenomings have been associated with anaphylactic shock, coronary vasoconstriction, and local necrosis [70]. Additionally, only *A. andersonii*, found in Oman, Saudi Arabia, and Yemen, is considered a Category I species. Clinical data are usually scarce for Category II snakes, yet three deaths due to *A. engaddensis* envenoming have been reported from Saudi Arabia. The deaths involved two children and one 30-year-old adult who all died within 1 hour from being bitten as a result of severe coronary vasospasm [71].

In humans envenomed by *A. engaddensis*, local effects are observed within minutes and are shortly followed by systemic effects of vomiting, weakness, hypoxia, liver damage, skin necrosis, and possibly fatal cardiac conduction disorders [72,73]. Species belonging to the *Atractaspis* genus are the only snakes known to produce another toxin family containing strong vasoconstrictor iso-peptides, i.e., sarafotoxins (SRTXs) [72]. This toxin constitutes around 18% of *Atractaspis microlepidota engaddensis* venom [73] and is considered to be one of the most potent vasoconstrictors described to date and is stipulated to be the primary cause of death in victims [74].

2.2. Scorpions

Compared to sub-Saharan Africa and Asia, snakebite morbidity and mortality are relatively low in the MENA region. Conversely, incidences of accidental envenoming of humans by dangerous scorpions (scorpionism) and the resultant lethality are higher than anywhere else in the world. Global estimates surpass 1.2 million cases of scorpion envenoming and 3,250 deaths each year. The number of stings in the ME and NA has been estimated to be around 146,000 and 350,000, respectively, which, together, make up 42% of the global scorpion sting burden. The morbidity and mortality rates, although not accurate due to inaccurate/scarce data, are presented as 0.42% (613) and 0.55% (803) for the ME and 0.52% (1,820) and 0.23% (805) for NA, respectively [75]; notably, since the last available study is from 2008, these numbers might differ significantly today. Compared to other regions of the world, the mortality rate for ME and the morbidity rate for NA are the highest worldwide.

Among the 19 countries of the MENA region, Algeria, Egypt, Iran, Israel, Morocco, Saudi Arabia, and Tunisia are particularly affected by scorpionism [76]. For instance, in Tunisia, 40,000 stings are reported annually, with a mortality rate of 7.5% in the southern part of the country [77,78]. In addition, 12 different Buthidae family species in Morocco are responsible for an average of 25,000 stings every year, with a lethality rate of 0.40% (100) [79,80]. In Algeria, six species of this family are found, which cause 50,000 stings with a lethality rate of 0.22% (110) each year [81].

Among the 2,200 scorpion species described to date, only a small percentage of them are known to be dangerous to humans. In the MENA region, most stings and hospitalizations can be attributed to the scorpion species belonging to *Androctonus*, *Buthus*, *Hottentotta*, *Leiurus*, and *Mesobuthus* genera of the Buthidae family and *Hemiscorpius* genus of the Hemiscorpiidae family (Fig 2A).

The Buthidae family, as the largest scorpion family, comprises 86 genera and over 900 species [82]. It is also the most widespread family of scorpions [82], occupying all six faunal regions of the world. Therefore, it is not surprising that Buthidae is the main family of medically important scorpions all around the world, including the MENA region, where 36 out of 101 venomous species of this family can be found [83]. While all of the medically important scorpion species in other parts of the world belong only to the Buthidae family, the three exceptional non-Buthidae scorpion species with medical importance can be found in the

A)

B)

Scorpion genera	Scorpion species	Specimen origin	LD$_{50}$	Neurotoxins				Enzymatic toxin					Other toxins							Other	Ref.
				NaTxs	KTxs	CaTxs	ClTxs	VSPs	VMPs	PLA$_2$s	HYALs	PIs	HDPs	La1s	CAPs	IGFBPs	BPPs	KSPIs	BmKa2s		
Androctonus	bicolor (aeneas)	Tunisia	1.21	33.5	32.6	0.3	-	-	-	-		-	3.5	-	-	-	3.2	4.8	2.6	19.5	[88]
	mauretanicus	Morocco	0.32	10.3	3.86	-	-	-	-	0.4	-	-	-	-	-	-	0.8	0.5	20.9	63.24	[89]
Hottentota	gentili	Morocco	-	13.1	5.3	9.6	4.7	-	-	1.2	-	-	-	-	-	-	0.6	1.6	13.9	50	[89]
Mesobuthus	eupeus+	Iran	1.45	21	15	-	3	1	-	-	-	18	13	1	10	7	-	-	-	11	[90]
Hemiscorpius	lepturus+	Iran	5.81	-	10.1	2.8	-	2.8	4.3	15.9	2.8	-	15.9	8.6	-	-	-	-	-	36.8	[91]
Nebo	hierichonticus	Israel		-	11.3	-	-	-	-	-	-	-	-	-	-	-	6.8	-	-	81.9	[89]

Fig 2. Medically important scorpions in North Africa and the Middle East. **(A)** Phylogeny and geographic distribution and **(B)** reported toxicity and available venom proteome or transcriptome (+) data are shown [88–91]. Specifically, the table presents the genera, species, the origin of the reference proteome or transcriptome, and the median lethal dose in mice (LD$_{50}$; mg/kg). It also illustrates the relative abundance of toxins acting on Na$^+$ channels (NaTx), toxins acting on K$^+$ channels (KTxs), toxins acting on Ca^{2+} channels (CaTxs), toxins acting on Cl$^-$ channels (ClTxs), VSPs, VMPs, PLA$_2$s, HYALs, PIs, HDPs, La1s, antigen-5 and CAPs, IGFBPs, BPPs, KSPIs, NDBPs (e.g., BmKa2s), and other (often a result of lacking data). All components are represented as relative wet weight abundance in %. Notably, scorpion venom composition may vary depending on region. BPP, bradykinin-potentiating peptide; CAP, pathogenesis-related protein; HDP, host defense peptide; HYAL, hyaluronidase; IGFBP, insulin-like growth factor binding protein; KSPI, kunitz-type serine protease inhibitor; La1, La1 peptide; NDBP, non-disulfide-bridged peptide; PI, protease inhibitor; PLA$_2$, phospholipase A$_2$; VMP, venom metalloproteinase; VSP, venom serine protease.

MENA region. These three species are members of two families, namely Hemiscorpiidae and Scorpionidae. The most venomous non-Buthidae family of scorpions is Hemiscorpiidae, which consists of one genus (*Hemiscorpius*) and 15 species [84]; two of these species are medically important (see Section 2.2.2). The family Scorpionidae contains some of the world's

largest living scorpions (up to 20 cm in length) distributed across seven genera [82]. The only medically important species of this family belongs to the genus *Nebo* (see Section 2.2.3).

In comparison to snakes, scorpion venoms are less complex. In fact, the most clinically relevant effects of scorpion venoms are caused by the inhibitory actions of two types of NTxs, namely NaTxs (Na$^+$ channel toxins) and KTxs (K$^+$ channel toxins) [85]. These two toxins also have the highest relative abundance in the MENA scorpions (average of 14.1%, ranging between 0% and 33.5%, and 13%, ranging between 5.3% and 32.6%, respectively; Fig 2B). These toxins, unlike snake NTxs, affect the voltage-gated Na$^+$- and K$^+$-channels, thus interfering with the generation and propagation of action potentials in neurons and resulting in potentially lethal paralysis in humans [85,86]. Unfortunately, to date, proteomics or transcriptomic data exist for only seven out of the 27 scorpion species (Fig 2B) [87].

An overview of the medically relevant scorpions in the MENA region and their most important toxins is presented below (Fig 2).

2.2.1. Buthidae.

2.2.1.1. Androctonus. Currently, the genus *Androctonus* (fat-tailed scorpions) comprises 22 species [92], many of which can be found in African countries north of the Equator, as well as in the ME and all the way to India [93]. However, out of the 22, only six species, namely *Androctonus liouvillei*, *Androctonus amoreuxi*, *Androctonus bicolor* (previously *Androctonus aeneas*), *Androctonus mauretanicus*, *Androctonus australis*, and *Androctonus crassicauda* are considered medically important [83].

A. liouvillei is only found in Morocco and is responsible for 9% of stings and 14% of deaths in the country's southwestern part [94]. Furthermore, *A. amoreuxi* shares the same geographical range and is responsible for approximately 17% of scorpion stings in southern Morocco [94], but its distribution also stretches to Egypt and Jordan. Another medically important species, *A. bicolor*, is distributed across a wide geographical range from NA to the ME (as far as Morocco in the west and Syria in the east) [95]. However, human contact with this scorpion appears to be rare [78]. Indeed, in Tunisia, during 2018, only seven cases of *A. bicolor* stings were recorded [96]. Conversely, *A. australis* and *A. mauretanicus* are responsible for most envenoming cases in Tunisia (86.7%) [96] and 13% of annual lethality cases in the southeast of Morocco, respectively [97]. Stings from *A. mauretanicus* can cause clinical manifestations such as respiratory disorders, including tachypnea, acute pulmonary edema, thrombocytosis, hyperglycemia, as well as hepatic and renal damage [97]. However, lethality is primarily associated with altering the mode of action in sodium and potassium channels via NaTxs and KTxs (Fig 2B) [98]. These toxins are also responsible for lethality caused by *A. crassicauda*, which is unsurprising since its venom profile is very similar to that of *A. australis* and *A. mauretanicus* [83]. Notably, *A. crassicauda* has the most prevalent distribution in the MENA region, spanning from Morocco to the Arabian Peninsula. However, its distribution also expands outside of the MENA region and also includes Armenia, Azerbaijan, and Turkey [83]. Furthermore, *A. crassicauda* is one of the two most dangerous scorpion species in Egypt, the other one being *Leiurus quinquestriatus* (see Section 2.2.1.3). These two species represent all the reported scorpion stings in Egypt (about half each) [99]. *A. crassicauda* is the most abundant and one of the most dangerous species among seven other medically important scorpion species in Iran [100]. Similarly, in Saudi Arabia, with 224 incidences per 100,000 people, the highest morbidity rate due to scorpionism is attributed to *A. crassicauda* [101], emphasizing the medical importance of this species all over the MENA region.

2.2.1.2. Buthus. *Buthus* is the fourth largest genus of the Buthidae family, with 52 species widely distributed throughout Europe, Africa, and Asia [102]. Due to a significant increase in the description of new *Buthus* species over the past 15 years, the taxonomy of this genus has dramatically changed. For instance, *Buthus occitanus*, which once was reported as the most

medically important species of the genus, causing severe/lethal envenomings in Morocco, now has been limited to France and Spain, while 17 other *Buthus* species have been assigned to Morocco [102]. As a consequence, the true epidemiology of the different species of this genus and the health burden they cause remain elusive. Nevertheless, at least five species of this genus, i.e., *Buthus lienhardi*, *Buthus malhommei*, *Buthus mardochei*, *Buthus paris*, and *Buthus tunetanus*, are considered to be medically important species [83].

2.2.1.3. Hottentotta. Similar to *Androctonus* and *Buthus*, *Hottentotta* is a large genus. Formerly known as *Buthotus*, the *Hottentotta* genus is currently divided into 27 species, which are spread across Africa, the ME, and India [103]. In the MENA region, *Hottentotta khoozestanus*, *Hottentotta zagrosensis*, *Hottentotta saulcyi*, *Hottentotta schach*, *Hottentotta jayakari*, and *Hottentotta gentili* are the main species that may pose a medical threat to humans. While *H. khoozestanus* and *H. zagrosensis* are endemic to Iran, *H. saulcyi* and *H. schach* are found both in Iran and Iraq, and *H. jayakari* is distributed across the whole Arabian Peninsula, including Oman, Saudi Arabia, UAE, and Yemen. Notably, *H. gentili* is the only species of this genus found in NA, specifically in Algeria and Morocco [103]. In 2001, an epidemiological survey based in the southwest of Morocco reported that *H. gentili* was responsible for 14% of stings (130 out of 912) and 26% of deaths (nine out of 35) [104]. Similarly, A 12-year epidemiologic study carried out between 1994 and 2006 reported 724 envenomings and 32 deaths in the same country; *H. gentili* was responsible for 11% of the stings and 32% of the deaths, making it the second-most important species in the studied area [105]. Partial characterization of *H. gentili* venom has revealed that it contains all four types of NTxs, including NaTxs, KTxs, CaTxs (calcium channel toxins), and ClTxs (chloride binding toxins; Fig 2B). Thus, it is likely that severe localized pain that is prevalent in envenomings caused by the *Hottentotta* genus is mediated by NTxs [106–108]. In addition to localized pain, severe sympathetic symptoms, such as tachypnea, convulsions, and parasympathetic symptoms with potentially fatal outcomes, have been reported for this genus [94,106].

2.2.1.4. Leiurus. Having an infamous reputation as the most dangerous genus of the Buthidae family, scorpions within the genus *Leiurus* are commonly found in NA, the Levant, and the Arabian Peninsula [93]. Although the *Leiurus* genus is currently divided into 12 species, it was once assumed to be represented by only a single species, *L. quinquestriatus* [83]. Therefore, most of the epidemiological data that were previously assigned to *L. quinquestriatus* must be reexamined, a situation which makes it very hard, if not impossible, to provide precise epidemiology data for different species of this genus [83]. Scorpions currently classified as *L. quinquestriatus* are restricted to Egypt and Sudan [109]. In upper Egypt, *L. quinquestriatus*, together with *A. crassicauda*, has been responsible for severe, even lethal envenomings. While the clinical manifestations were more severe in *L. quinquestriatus* stings, the death rate was higher in *A. crassicauda* stings [99]. Based on murine studies, it has been estimated that an injection of 17-mg *L. quinquestriatus* venom into an average-sized human adult might be lethal [110]. However, the average amount of venom injected in a sting is rather low (0.225 mg), which means that the risk of mortality is low in adults stung by *L. quinquestriatus* [111]. Nevertheless, the quantity of venom appears to be sufficient to pose a severe risk to children. For instance, it has been reported that *L. quinquestriatus* stings cause significant mortality among young children in Sudan [93]. The venom of *L. quinquestriatus* is extremely neurotoxic and may cause mild to severe local pain and severe systemic complications, such as vomiting, headache, disturbed consciousness, heart failure, pulmonary edema, interstitial edema, hemorrhage, and even coma [99,110,112]. In Jordan, *Leiurus hebraeus* and *Leiurus jordanensis* are considered to be dangerous to humans, with the former being the most common and widely distributed species in the country [113]. *L. hebraeus* stings are manifested by local pain of variable intensity at the site of the sting accompanied by mild swelling and tenderness. Still, systemic effects, such as vomiting, abdominal pain, sweating, salivation, tachycardia,

hypertension, restlessness, tremors, and generalized myalgia, may evolve. In more severe cases, these symptoms are followed by agitation, hypotensive collapse with peripheral cyanosis, and signs of congestive cardiac failure that may simulate early myocardial infarction. Finally, interstitial myocarditis with local necrosis is seen in fatal cases [3].

2.2.1.5. Mesobuthus. The *Mesobuthus* genus is the most widely distributed genus in the Buthidae family. It comprises 15 species dispersed across a variety of arid habitats of the Palearctic Region, from Turkey to Korea [114]. It has been reported that two species of this genus, i.e., *Mesobuthus gibbosus* and *Mesobuthus epeus*, can pose a risk of mild to severe envenoming to humans [115,116]. However, it is noteworthy that *M. eupeus* is a polytypic species complex that likely includes more than 1 valid species [117,118]. While *M. gibbosus* is mainly distributed in the eastern Mediterranean region [119], *M. epeus* has a wide geographical distribution in the ME and Central Asia. In the northwestern region of Iran, 80% of the 368 scorpion specimens collected between June 2015 and August 2016 belonged to *M. epeus* [120]. Although there are no data on scorpionism caused by *M. epeus* in this part of the country, it has been reported that 20% to 45% of all cases of scorpion stings in the Khuzestan Province (southwest) and Kashan (center) county, respectively, were caused by this species [121]. In Iran, stings by *M. epeus* are less dangerous than stings by *A. crassicauda* and *Hemiscorpius lepturus*, as so far, no deaths due to *M. epeus* stings have been reported [115,121]. However, *M. epeus* is still responsible for the majority of scorpionism cases in Iran [115]. It has been reported that local pain, hyperemia, swelling, and to a lesser extent, burning, itching, and numbness are seen among the victims. Moreover, dry mouth, thirst, sweating, hypotension, nausea, hypertension, difficulty in breathing, tachycardia, an increase of bronchial secretion, and cyanosis have also been reported [115]. It is believed that similar to other Buthids, the toxic effects of *M. epeus* are derived from various NTxs, including MeuKTx. This toxin specifically interacts with and blocks potassium ion channel subtype $K_v1.3$ in humans [122]. $K_v1.3$ is the first K^+ channel that was identified outside electrically excitable tissues and its blockers have high significance as potential drugs against immune and inflammatory diseases [123].

2.2.2. Hemiscorpiidae.

2.2.2.1. Hemiscorpius. Contrary to the widely distributed Buthidae family, scorpions belonging to the Hemiscorpiidae family are only found in Iran, Iraq, Pakistan, Saudi Arabia, Oman, UAE, and Yemen [124]. Additionally, this family is represented in Africa by three species, known only from a handful of specimens found in Egypt, Eritrea, and Somalia [125,126]. These three species all fall within the same and only Hemiscorpiidae genus, *Hemiscorpius*. Among 15 species within the *Hemiscorpius* genus, only two of them, i.e., *H. lepturus* and *Hemiscorpius acanthocercus*, have been reported to be medically important [127]. *H. lepturus* is considered to be responsible for almost all of the fatalities caused by *Hemiscorpius* stings, while only one case study has reported death due to *H. acanthocercus* envenoming [128]. However, it must be kept in mind that scorpions belonging to the *Hemiscorpius* genus look very similar in morphology, making it difficult for non-specialists to distinguish between different species [129]. Therefore, while there are many reports on the envenomings caused by *H. lepturus*, it is very likely that it is not the only species responsible for all of the cases [129–131].

Known as the only non-buthid scorpion that has the potential to be lethal to humans, *H. lepturus* is restricted to both sides of the common border between Iraq (southeast/east) and Iran (southwest), while stretching to the southern regions of the latter [118]. Annually, between 40,000 and 50,000 cases of scorpion stings (approximately 60 cases per 100,000 inhabitants) are recorded in Iran, resulting in approximately 20 fatalities [121]. It is estimated that *H. lepturus* is responsible for 10% to 25% of all sting cases and near 70% of the fatalities [121]. One possible explanation for the high lethality of *H. lepturus* stings is related to the small size of their stinger that is approximately 1 mm long (in comparison to 6 to 8 mm long stinger of

A. crassicauda) [132,133]. It is believed that since the sting of *H. lepturus* does not penetrate the inner layers of skin, it causes no or minimal pain. This is the main reason why victims do not seek medical care until the toxicity has already been established. Another explanation focuses on the unique and exceptional venom composition of this species. While almost all of the medically important scorpion species from Buthidae and Scorpionidae families have neurotoxic effects, the venom of *H. lepturus* is more similar to the venom of *Loxosceles* spiders and has cytotoxic and hemotoxic effects (see Section 2.3.2.1) [129]. In the absence of pain-inducing NTxs, the symptoms of *H. lepturus* stings are largely negligible in the first 24 to 72 hours. After this period, however, local redness, inflammation, necrosis, ecchymosis, blisters, and hematuria may manifest, with the latter being one of the main reasons forcing victims to seek medical help [133]. Hemoglobinuria has been reported for more than half of *H. lepturus* sting cases (more than 90% of children present with this clinical manifestation), which, in turn, can be a sign of acute kidney injury that is frequently seen among the victims [134,135]. It has been suggested that the venom's delayed effects and its retention in the body provides the toxins enough time to cause severe damage to vital organs, including the kidneys and, to a lesser extent, the liver. Death usually results from cardiovascular or renal failure [136]. However, even when victims survive, their hospitalization time is longer than that of victims stung by other scorpion species [137].

2.2.3. Scorpionidae family.

2.2.3.1. Nebo. The *Nebo* genus is distributed in Egypt (Sinai), Israel, Jordan, Lebanon, Oman, Saudi Arabia, Syria, and Yemen [138]. The only medically important species of this genus, *Nebo hierichonticus*, is one of the least common but largest scorpions in Egypt, Israel, Saudi Arabia, and Syria [139]. With only two relatively old studies, the envenoming data for *N. hierichonticus* are very scarce. The first study (1969) reported only mild symptoms, such as mild local burning pain, swelling, and itching in two adults [140]. However, the second study reported the death of a child due to persistent hypotension, severe pulmonary edema, and congestive heart failure that was probably caused by toxic myocarditis. Other reported clinical manifestations included coagulopathy, temporary blindness, and deafness [141]. Together these studies indicate relatively mild venom toxicity that mostly poses a risk to children, elderly people, and victims suffering allergic reactions to the venom.

2.3. Spiders

It has been estimated that around five humans die from spider envenoming each year, with no death being reported from the MENA region [4]. The low number of fatalities despite the toxic venom of spiders is typically related to their small size, their docile nature, and the inability of their fangs to penetrate deeply into human skin [142]. Spider species with medical importance to humans are limited to six genera belonging to four different families; the genera *Atrax* and *Hadronyche* from the Atracidae family (Australian funnel-web spiders), the genus *Loxosceles* from the Sicariidae family (recluse spiders), the genus *Latrodectus* from the Theridiidae family (widow spiders), and the genus *Phoneutria* from the Ctenidae family (Brazilian armed spiders) [142]. Notably, Latrodectus and Loxosceles are both present in the MENA region and can cause adult morbidity and child mortality (Fig 3A).

In spiders, the synergistic effects between various toxins are particularly important for the whole venom toxicity [142]. Although proteomics or transcriptomic studies have only been conducted for the venoms of two out of the 10 potentially medically important spider species, it seems like *Latrodectus* venoms are predominantly made up of latrotoxins (34.7% to 75.4%), cysteine-rich secretory proteins (CRiSPs; 10.2% to 15.1%), and latrodectins (α-latrotoxin–associated low molecular weight proteins; 0% to 8.2%; Fig 3B). In contrast, *Loxosceles* venoms

A)
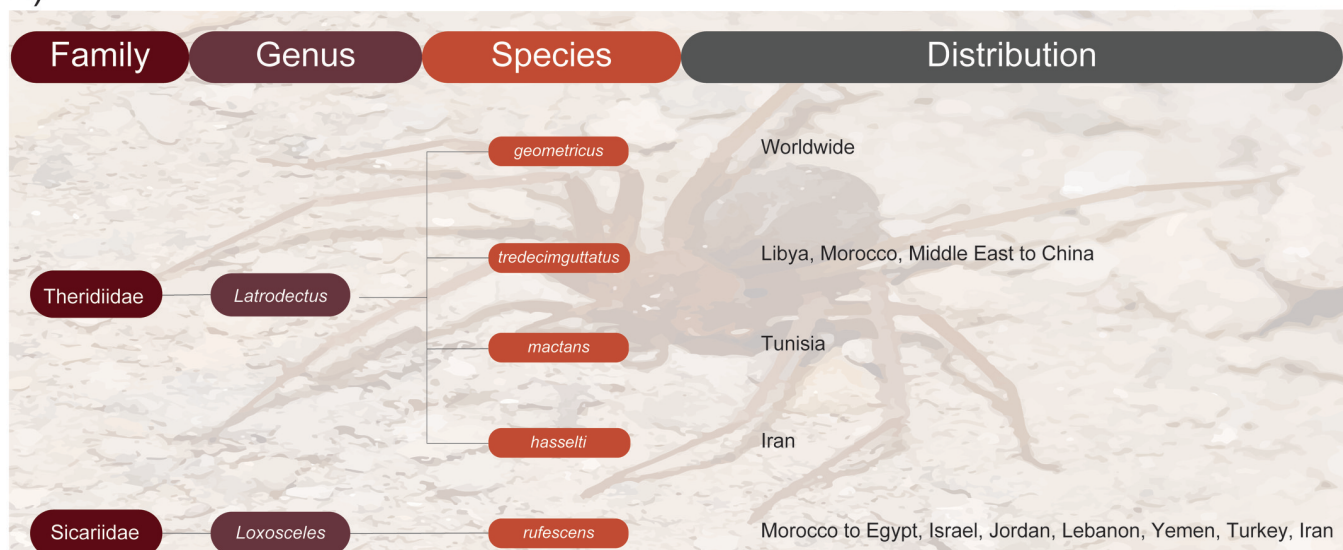
B)

Spider genera	Spider species	Specimen origin	LD50 (mg/kg)	LTxs	Latrodectins	PLDs	Knottins	CRISPs	VMPs	VSPs	HYs	Lipases	Other	Ref
Latrodectus	geometricus	USA	-	34.7	8.2	-	4.1	10.2	16.3	16.3	2	8.2	-	[145]
	tredecimguttatus	Unknown	0.9	75.4	-	-	-	15.1	-	3.2	1.3	-	4.1	[146,147]
Loxosceles	rufescens +*	Brazil	0.48	-	-	20.2	53.5	-	22.6	0.5	0.1	-	3.1	[148,149]

Fig 3. Medically relevant spiders in North Africa and the Middle East. (A) Phylogeny and geographic distribution and **(B)** reported toxicity and available venom proteome or transcriptome ([+]) data are shown [145–149]. Specifically, the table presents the genera, species, the origin of the reference proteome or transcriptome, and the median lethal dose in mice (LD$_{50}$; mg/kg). It also illustrates the relative abundance of LTxs, Latrodectins, PLDs, ICKs (Knottins), CRiSPs, VMPs, VSPs, HYALs, and lipases. All components are represented as relative wet weight abundance in %. *proxy from *Loxosceles intermedia* was used. Notably, spider venom composition may vary depending on region. CRiSP, cysteine-rich secretory protein; HYAL, hyaluronidase; LTx, latrotoxin; PLD, phospholipase-D; VMP, venom metalloproteinase; VSP, venom serine protease.

include inhibitory cysteine knot toxins (ICK peptides or Knottins; 53.5%), phospholipase-Ds (PLDs; 20.2%), and astacin-like metalloendopeptidases (MPs; 22.6%; Fig 3B) [142,143]. The synergy between spider toxins has also been demonstrated in a study that illustrated that *Loxoceles* sphingomyelinase Ds (SMDs) hydrolyze sphingomyelin (zwitterionic) to ceramide 1-phosphate (anionic); hence, they increase the affinity of NTxs for the nearby ion channels [144]. It appears that latrotoxins and PLDs are the most medically relevant toxins of the spiders found in the MENA region.

Below we present an overview of the medically relevant spiders in the MENA region and their most important toxins (Fig 3).

2.3.1. Theridiidae.

2.3.1.1. Latrodectus. So far, 30 species of *Latrodectus* have been identified, inhabiting all continents, except for Antarctica [150]. Some of the most infamous species of this genus are *Latrodectus mactans* (North American black widow), *Latrodectus tredecimguttatus* (European black widow), *Latrodectus hasselti* (Australian red-back), and *Latrodectus geometricus* (cosmopolitan brown widow) [150–152]. These species are found within the MENA region, but while bites from members of these species can be fatal, no confirmed reports exist of *Latrodectus* induced mortality or morbidity in this region. The possible clinical manifestations caused by *Latrodectus* bites, known as latrodectism, include mild to moderate symptoms with

generalized pain and muscle cramps being the most apparent. Typically, severe pain lasting for two days, on average, is observed in half of all *Latrodectus* bites. Furthermore, local effects such as redness at the bite site and swelling are also prevalent [153]. However, systemic effects such as nausea, vomiting, and headache are rare, and life-threatening symptoms generally only present in young children and elderly people [154].

Latrodectism is mainly induced by a neurotoxic component of the venom, i.e., α-latrotoxin (α-LTx) [155]. *α*-LTx is a presynaptic NTx that affects the vertebrate central nervous system through depolarizing neurons by increasing Ca^{2+} concentration and inducing a massive release of neurotransmitters [146,156,157]. Proteomics data demonstrate that latrotoxins are the main components in the venoms of *L. tredecimguttatus* (75.4%) and *L. geometricus* (34.7%), yet little data are available on the abundance of latrotoxins in other spider species found in the MENA region (Fig 3B).

2.3.2. Sicariidae family.

2.3.2.1. Loxosceles **genus.** Of about 120 described *Loxosceles* species, *Loxosceles rufescens* is the only species that has been reported to be of medical importance in the MENA region. *L. rufescens* (Mediterranean recluse) is found from Morocco to Egypt, as well as in Iran, Israel, Jordan, Lebanon, and Yemen [143]. In Iran, *L. rufescens* is widely distributed across the country [158–161]. Envenoming by these spiders can cause necrotizing-hemolytic effects, known as loxoscelism. Loxoscelism is commonly associated with skin lesions, while systemic effects such as nausea, vomiting, chills, fever, myalgia, hemolytic anemia, and acute renal failure are rarely observed [161]. In Iran, loxoscelism can be misdiagnosed as *Hemiscorpius* scorpionism, since both *Loxosceles* spiders and *Hemiscorpius* scorpions contain SMD, a necrotic toxin, in their venom [162].

SMD is a member of phospholipase D protein family that makes up to approximately 20% of *Loxosceles* venoms (Fig 3B) [163–165]. PLDs are the most studied toxic compounds of the *Loxosceles* venom and have hydrolyzing activity on the D site of phospholipids in various mammalian tissues [129]. Cleavage at the D site of phospholipids is rare and has not been identified elsewhere in the animal kingdom other than for PLDs from *Loxosceles* spiders and *Hemiscorpius* scorpions [153]. Notably, the primary causative agent in necrotic lesion formation in *Loxosceles* spider and *Hemiscorpius* scorpion envenomings are a group of PLDs and SMDs [163–165]. In addition to the dermonecrotic characteristics, PLDs are responsible for various pathologies ascribed to the whole venom of *Loxosceles* spiders, including an inflammatory response accompanied by neutrophil infiltration and complement activation, increased permeability of the endothelial lining of blood vessels, hemolysis, platelet aggregation, and renal failure. This venom toxin induces cell lysis by hydrolysis of sphingomyelin and complement-dependent hemolysis [166]. Unfortunately, the process in which the cleavage of sphingomyelin leads to necrotic lesion formation is poorly understood, although a complex immune response has been indicated as a primary instigator [167].

3. Animal envenomings in the MENA region: Country-specific impact

Estimates suggest that NA records over 36,000 snakebites (29 deaths) and 350,0000 scorpion stings (810 deaths) and the ME more than 31,000 snakebites (33 deaths) and 146,000 scorpion stings (796 deaths) each year [2,17]. However, actual country-specific epidemiological reports are scarce and fragmented, particularly for snakebite. Therefore, the following should not be seen as a comprehensive overview, but rather an indication as to where potential envenoming hotspots might be and thus, where to focus further research efforts (Fig 4 and S1 Table) [2,17–31,77,78,80,99,113,121,127,168–186].
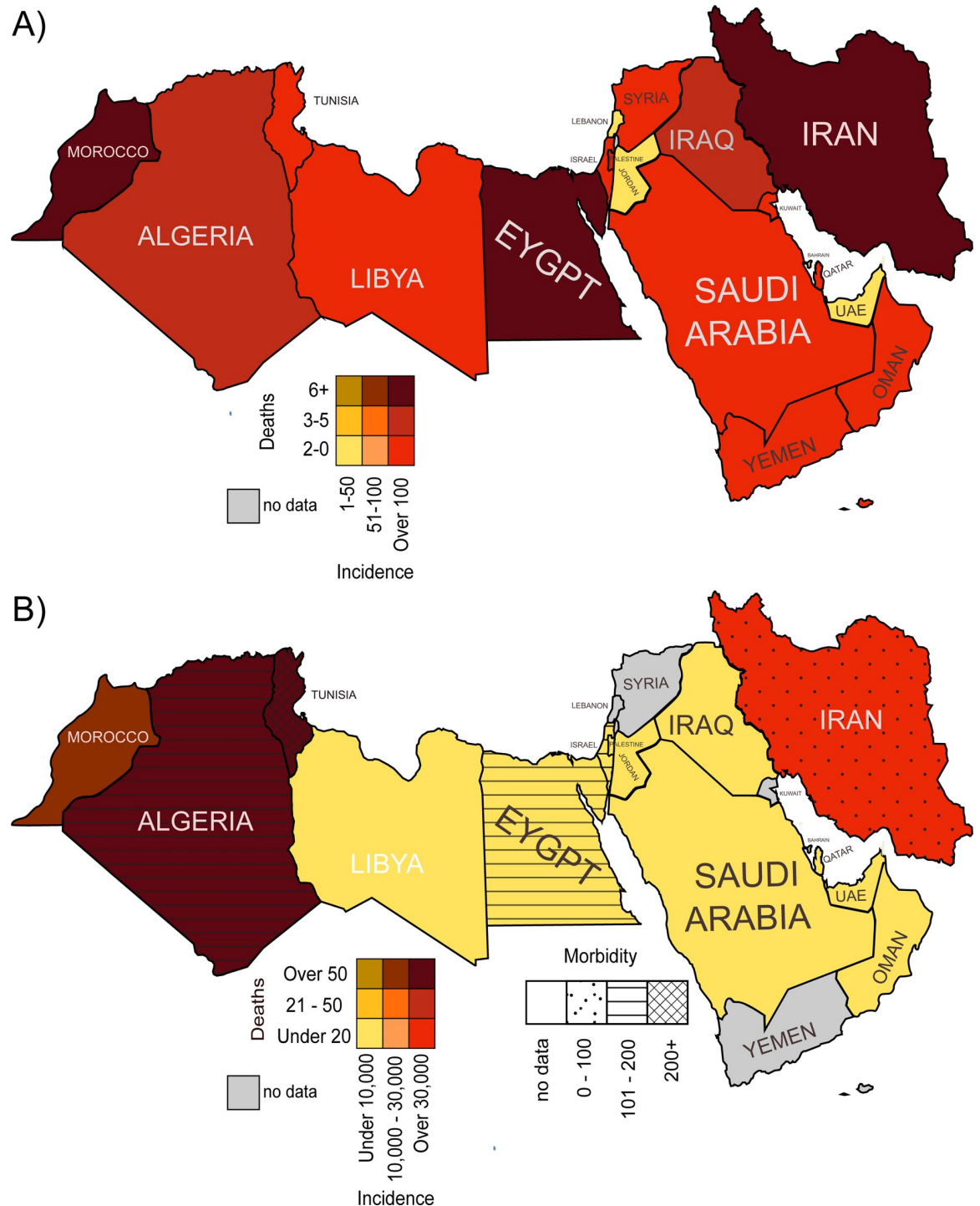
Fig 4. Country-specific overview of the epidemiology of snakebite (A) and scorpion stings (B) in the MENA region. The country-specific data were obtained from epidemiological literature covering the past 25 years (1995 to 2020). The data represent absolute numbers, and details can be found in S1 Table. MENA, Middle East and North Africa.

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Most snakebites in the MENA region occur in rural, aridic regions during the summer months and in the evening hours, with some data suggesting that primarily men are bitten. In the ME, patients are typically young and in most cases below the age of 30 (S1 Table).

According to the literature published over the past 25 years, Morrocco and Egypt suffer from most snakebites in NA, with annual incidences of 137 and 246, respectively (Fig 4A) [17,23,25]. However, these numbers are still relatively low when compared to prior estimates that were made based on a literature review and a modeling study (up to 6,349 and 21,245 bites per year, respectively) [17]. In the ME, Iran (5,379), followed by Israel (322), presents the highest incidence of snakebite (Fig 4A) [18,21,138,139]. Notably, estimates suggested that up to 11,079 bites occur in Iran each year (significantly more than reported), while Israel's estimates are lower than what is reported in the literature (155) [17]. The presence or absence of such discrepancies are often a good indication of whether snakebite is reported appropriately and comprehensively in the respective country. When there are significant differences between published data and estimates, usually estimates represent the true burden better since published data are frequently incomplete [17]. Based on epidemiological estimates, Yemen (7,949), Syria (4,651), and Iraq (4,366) should also receive further attention [17]. Morbidity data are also lacking, which in other snakebite affected regions often constitutes the majority of the overall health burden, as well as mortality data [7].

While the issue of snakebite in the MENA region should not be neglected, scorpionism constitutes a significantly larger problem. The majority of stings occur in the summer months, equally affecting men and women, with primarily children being stung (S1 Table). In NA, Algeria [187–189] and Tunisia [78] both report over 40,000 stings from scorpions each year, resulting in 73 and 10 annual deaths, respectively (Fig 4B). Furthermore, although Morocco reports fewer annual incidences than Algeria and Tunisia (21,467), it has higher annual deaths (86) [80]. This, in part, could be due to the fact that Morocco is inhabited by 12 different species of highly venomous Buthidae scorpions [80]. In terms of morbidity, Tunisia seems to be most affected in the whole MENA region, with over 425 cases recorded each year. In the ME, Iran (50,000) [121,127,172] and Saudi Arabia (14,433) [173] report the highest number of annual scorpion stings. However, similarly to the snake epidemiological data, these numbers still appear to be very low when compared to the comprehensive estimations mentioned above.

4. Treatment of severe animal envenomings in the MENA region

To date, the only effective treatment for envenoming consists of serotherapy [190]. Here, immunity is induced in a production animal (e.g., horse or sheep), and the resultant polyclonal antibodies isolated from the hyperimmunized plasma are transfused into the patient. Thus, it is also known as passive vaccination [7]. A vital advantage of this approach is that in the case of highly diverse toxin cocktails that are commonly found in animal venoms, it is not essential to know what specific toxins are present, as long as the immune system of the production animal gives rise to neutralizing antibodies against all the key toxic components [190]. Although serotherapy has been the mainstay in treatment of envenomings for over a century and has saved countless lives, the complexity and high cost of production, the decreasing number of antivenom products, and the fragility of the production systems in developing countries contribute to the risk of not having effective, safe, and affordable antivenoms in the future. Therefore, there is a global push toward development of improved envenoming therapies [191]. Efforts include the improvement of existing antivenoms via better immunization and antibody purification approaches [190,192], as well as the discovery of specific antibodies and alternative protein scaffolds that target specific toxins, among others [193]. Furthermore, small-molecule inhibitors that target phospholipase A_2s (varespladib), snake venom metalloproteinases (marimastat, batimastat, dimercaprol, and 2,3-dimercaptopropane-1-sulfonic acid), and snake venom serine proteinases (nafamastat) are particularly interesting in the context of envenomings in the MENA region [8–14].

4.1. Current treatments

Until novel types of antivenom products reach the market, prompt administration of the appropriate polyvalent antivenom in the approved dose is the best treatment following an envenoming by a venomous animal [194]. Currently, eight snake, 11 scorpion, and two spider antivenoms exist that, according to the manufacturers, cover medically relevant species that inhabit the MENA region [2,3]. All of the antivenoms are based either on either immunoglobulin G antibodies (IgGs) or are F(ab')$_2$ fragments that are generated by pepsin digestion of whole IgG antibodies to remove most of the fragment crystallizable (Fc) region (i.e., the tail region of an IgG antibody that interacts with cell surface receptors), while leaving intact some of the hinge region. Thus, like IgG antibodies, F(ab')$_2$ fragments have two antigen-binding F(ab) portions linked together by disulfide bonds, and therefore are divalent.

4.1.1. Snake antivenoms. Currently, there are 10 antivenoms marketed as efficacious against snake species found across the MENA (Table 1). A lack of clinical data necessitates the

Table 1. Snake antivenoms currently available for use in MENA.

Antivenom name	Producer	Species venoms neutralized according to manufacturer	
		Viperidae	**Elapidae**
INOSERP MENA	Inosan Biopharma, **Spain**	B. arietans, C. cerastes, C. gasperettii, C. vipera, Daboia deserti, D. mauritanica, D. palaestinae, E. carinatus sochureki, E. coloratus, E. khosatzkii, E. leucogaster, E. megalocephalus, E. omanensis, E. pyramidum, M. lebetina, M. Iebetina transmediterranea, M. Iebetina turanica, Montivipera bornmuelleri, M. raddei kurdistanica, P. fieldi, P. persicus, Vipera latastei	N. haje, N. nubiae, N. pallida, Walterinnesia aegyptia
SAIMR Polyvalent Antivenom	South African Vaccine Producers (SAVP) **South Africa**	B. arietans, B. gabonica	Hemachatus haemachatus, Dendroaspis angusticeps, D. jamesoni, D. polylepis, N. nivea, N. melanoleuca, N. annulifera, N. mossambica
Polyvalent Snake Antivenom	National Antivenom and Vaccine Production Center (NAVPC), **Saudi Arabia**	B. arietans, E. coloratus, E. carinatus, C. cerastes,	N. haje (N. arabica), W. aegyptia
Bivalent Snake Antivenom			N. haje (N. arabica), W. aegyptia
VACSERA polyvalent antivenom	Egyptian Organization for Biological Products & Vaccines, **Egypt**	C. cerastes, C. cerastes cerastes, C. vipera, P. persicus fieldi	N. haje, N. nigricollis, N. pallida, W. aegyptia
Anti-vipérin	Institut Pasteur d'Algerie, **Algeria**	C. cerastes, M. lebetina spp.	
Anti-D. palaestinae monospecific antivenom	Felsenstein Medical Research Center, **Israel**	D. palaestinae	
Gamma-Vip	Institut Pasteur de Tunis, **Tunisia**	C. cerastes, M. lebetina spp.	
Pentavalent Snake Antivenom IgG	Razi Vaccine and Serum Research Institute, **Iran**	V. lebetina, V. albicornuta, E. carinatus, P. persicus, Agkistrodon halys	
Hexavalent Snake Antivenom IgG		V. lebetina, V. albicornuta, E. carinatus, P. persicus, A. halys	N. oxiana

All listed antivenoms are produced as F(ab')$_2$s.

IgG, immunoglobulin G; MENA, Middle East and North Africa.

assessment of a wide range of efficacy evidence, including preclinical investigations, observational clinical studies, and expert opinions from clinicians with extensive experience managing African snakebites; on that basis, SAIMR Polyvalent, Inoserp MENA, and NAVPC Polyvalent Snake Antivenom are generally considered to be relatively safe and effective [195]. Notably, Inoserp MENA are lyophilized products, allowing them to be stored at ambient tropical temperatures and injected intravenously, allowing for use in poorly equipped and/or rural health centers. Conversely, while considered one of the most effective antivenoms SAIMR must be refrigerated; in addition, it is known to cause a high rate of early adverse reactions and is very expensive [196,197]. Indeed, SAIMR Polyvalent antivenom, which currently incorporates venoms from 10 species (two vipers and eight elapids) is sold at a cost of approximately $117 USD per vial. Typically, a patient will require 6 to 10 vials for successful treatment resulting in a cost of more than $600 USD for only the antivenom [198]. Thus, the resultant increased demand for cheaper antivenoms has already resulted in the sale and use of products developed for similar species from Asia, but with potentially dangerously low efficacy and no proven cross-reactivity [199,200]. For instance, at the main government hospital in Taizz (Yemen), the only antivenom in use was the imported Indian Snake Venom Antiserum I.P. VINS Bioproducts; this product covers the Indian cobra (*Naja naja*), the common Krait (*Bungarus caeruleus*), the Russell's viper (*Daboia russelii*), and the saw scaled Viper (*E. carinatus*). None of these species can be found in Yemen, but the hope for paraspecificity stems from the fact that other species from some of the same genera inhabit Yemen. Unfortunately, evidence to date suggests poor efficacy at best [199,200]. Some data suggest that Anti-*Daboia palaestinae* monospecific antivenom (Felsenstein Medical Research Center) [201], Gamma-Vip (Institut Pasteur de Tunis) [43], and the Penta/Hexavalent Snake Antivenom IgG (Razi) [202] should be efficacious, while no reliable efficacy data exist for VACSERA polyvalent antivenom, Anti-vipérin (Institut Pasteur d'Algérie) [196].

There is a need for more cost-effective antivenoms in the MENA region as well as the need to keep future treatments at a low cost (affordable to the general population) while retaining efficacy.

4.1.2. Scorpion antivenoms. Currently, 11 antivenoms to treat scorpionism exist in the MENA region (Table 2), yet the treatment of scorpion envenomings with antivenom remains debated. This might, in part, be due to inconclusive clinical trial outcomes, with studies focusing on scorpionism in the MENA region yielding conflicting results. For instance, a study in Tunisia with 875 patients showed no benefits of using bivalent antivenom (produced by Institut Pasteur de Tunis) after envenoming by what was assumed to be *A. australis* and *B. occitanus* scorpions [203]. Yet, it is noteworthy that the trial did not include a lot of cases of severe or systemic envenoming (145 patients with systemic symptoms of whom 11 had life-threatening signs), where antivenom might have had a bigger impact on clinical outcome. In comparison, a retrospective Moroccan trial with 275 patients (28 with systemic symptoms) investigated the specific use of rapid administration of a polyvalent scorpion antivenom (produced at Institut Pasteur du Maroc) following envenoming by *A. mauretanicus* and *B. occitanus* scorpions. The use of this antivenom was associate with a decrease in envenoming clinical signs in patients who received prompt and specific antivenoms [204]. Additionally, a study by the French military demonstrated that 19 patients were effectively treated with SCORPIFAV (MicroPharm) [205]. There also exists some preclinical data indicating the potential usefulness of antivenoms in treating scorpionism for Polyvalent Scorpion Antivenom (Razi) [206–209], Purified polyvalent anti-scorpion serum (VACSERA) [210], Inoscorpi (Inosan Biopharma) [211]. No data could be found for Polyvalent scorpion antivenom (Institut Pasteur du Maroc), Anti-scorpionique (Institut Pasteur d'Algérie), Anti-scorpionic sera (Institut Pasteur de Tunis) Polyvalent scorpion antivenom (NAVPC), and SAIMR Scorpion antivenom; the same is true

Table 2. Scorpion antivenoms currently available for use in the MENA.

Antivenom name	Producer	Species venoms neutralized according to product insert
Polyvalent scorpion antivenom	Institut Pasteur du Maroc, **Morocco**	*B. occitanus, Androctonus mauritanicus*
Purified polyvalent anti-scorpion serum	Egyptian Organization for Biological Products & Vaccines (VACSERA), **Egypt**	*A. amoreuxi, A. australis, A. bicolor, A. crassicauda, B. occitanus, Leiurus quinquestriatus, Scorpio maurus*
Anti-scorpionique (Monovalent)	Institut Pasteur d'Algerie, **Algeria**	*A. australis*
Bivalent scorpion antivenom	Institut Pasteur de Tunis, **Tunisia**	*A. australis, B. occitanus*
Anti-scorpionic sera		*A. australis, A. bicolor, B. occitanus, L. quinquestriatus*
Polyvalent scorpion antivenom	National Antivenom and Vaccine Production Center (NAVPC), **Saudi Arabia**	*L. quinquestriatus, A. crassicauda, Buthacus arenicola, Hottentotta minax, B. occitanus, L. hebraeus and A. amoreuxi*
SCORPIFAV	MicroPharm, **UK**	*A. australis, B. occitanus, and L. quinquestriatus*
Scorpion Venom Antiserum (VINS)	VINS Bioproducts, **India**	*Specific for L. quinquestriatus and A. ameoreuxi Paraspecific for A. crassicauda, A. aeneas, A. australis, S. marus [Sic] palmatus, and Bathus [Sic] occitanus*
Polyvalent Scorpion Antivenom	Razi Vaccine and Serum Research Institute, **Iran**	*A. crassicauda, M. eupeus, O. doriae, H. saulcyi, H. schach and H. lepturus*
Middle East & Northern Africa (MENA) Inoscorpi High Specificity Immunotherapic Polyvalent F(ab')₂ Scorpion Antivenom lyophilized	Inosan Biopharma, **Spain and Mexico**	*A. australis, A. mauritanicus, A. crassicauda, A. amourexi, A. bicolor, B. occitanus, B. mardochei, L. quinquestriatus, L. hebraeus, B. tunetanus*
SAIMR Scorpion antivenom	South African Vaccine Producers, **South Africa**	*Parabuthus* sp.

Most of the listed antivenoms are produced as F(ab')₂s, with the exception of Scorpion Venom Antiserum (VINS) and Polyvalent scorpion antivenom (NAVPC), which are IgGs.

IgG, immunoglobulin G; MENA, Middle East and North Africa.

for Scorpion Venom Antiserum (VINS), with efficacy being unlikely due to the reliance on paraspecificity.

Skepticism against the use of antivenoms to treat scorpionism also stems from their questionable cost-effectiveness, given that the treatment can be rather expensive [212]. Fortunately, unlike in the United States of America where a single vial of scorpion antivenom can cost around $3,500 USD, there are significantly cheaper products available in the MENA region. For instance, the bivalent scorpion antivenom (produced at Institut Pasteur de Tunis) costs approximately $13 USD per vial, which when taking local economics into account is not cheap, but significantly more affordable [213]. Due to the lower cost, 6,226 to 7,253 doses of just this bivalent scorpion antivenom are sold each year (2016 to 2018). Thus, when taking in to account the improved price-point of scorpion antivenom in the MENA region compared to the USA, as well as investigations of antivenom treatment of scorpionism outside of the MENA region, it is likely that antivenom can be cost-effective and useful in most, and necessary in severe, envenoming cases [214]. However, the question remains whether currently available antivenoms are able to sufficiently neutralize toxicity across all medically relevant scorpion species in the MENA region.

4.1.3. Spider antivenoms.   While spider bites do not constitute a substantial medical threat in the MENA region, this might change in the near future. This is due to the fact that many of the species, such as *L. hasselti* and *L. mactans*, are invasive and will potentially spread in the years to come. Fortunately, two antivenoms from the countries these species are native to (Australia and the USA) already exist (Table 3). In Brazil, Peru, and Mexico, there are also anti-*Loxosceles* antivenoms being produced, but none of them specifically use *L. rufescens* venom in their immunizations [215]. Regardless, similarly to antivenom treatment in cases of

Table 3. Spider antivenoms currently available for use in MENA.

Antivenom name	Producer	Species venoms neutralized according to product insert
Red Back Spider Antivenom	Sequirus, **Australia**	*L. hasselti*
Antivenin *Latrodectus mactans*	Merck & Co, **USA**	*L. mactans*

All of the listed antivenoms are produced as IgGs.

IgG, immunoglobulin G; MENA, Middle East and North Africa.

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scorpionism, the use of antivenom treatment in spider envenomings has also been debated. The key criticisms are also comparable to scorpion antivenom and involve the discussion of their efficacy in neutralizing toxicity, as well as the risk of adverse reactions [216,217]. Nevertheless, the overall conclusion remains the same as in the case of scorpion stings; in cases of severe envenoming, antivenoms can significantly benefit patient outcome and can be necessary in the prevention of morbidity and mortality of the victim [215,216]. Unfortunately, the manufacture of spider antivenoms is significantly more cumbersome than similar products against scorpions and snakes, since the venom amounts required for immunization are very hard to obtain and the actual spider "milking" process is incredibly laborious [218]. Indeed, sufficient numbers of specimens for venom extraction are a key bottleneck in spider antivenom production. For instance, in 2015 and 2017, the Australian Reptile Park that is responsible for collecting and milking venom from male *Atrax robustus* spiders used for antivenom production, urged the public to catch Sydney funnel-web spiders to secure a continuous supply of antivenom [219,220]. However, novel approaches in antivenom manufacture, such as the recombinant expression of toxins for immunization [192] or RNA vaccination [206], could help circumvent such bottlenecks and help ensure a steady supply of antivenoms.

4.2. Perspectives for future treatments

While antivenoms currently constitute the only effective treatment for severe animal envenomings, these life-saving medicines also suffer from many drawbacks. Thus, researchers are investigating other avenues of treatment, such as the targeted neutralization of key medically relevant toxins using recombinant monoclonal antibodies [193,218,221,222]. In particular, two major approaches toward the discovery and development of such antibodies exist, i.e., "top-down" and "bottom-up". The former involves immunization of an animal, from which polyclonal antibody-encoding genes are derived and used for recombinant production of the antivenom [223]. Here, the development of the final product might be less costly, but the product is of undefined polyclonal nature and relatively expensive to manufacture, as it will comprise both therapeutically active and inactive antibodies, resulting in higher doses being needed for venom neutralization. Conversely, the bottom-up strategy uses in-depth knowledge on snake venom compositions (e.g., via toxicovenomics [224]), which allows for the strategic selection of a defined number of well-characterized monoclonal antibodies via *in vitro* display technologies, such as phage, ribosome, mammalian, or yeast display. The selected antibodies can then be mixed in a defined cocktail, constituting an oligoclonal recombinant antivenom [12]. These technologies can aid in the discovery of broadly neutralizing antibodies, especially when combined with other approaches, such as toxin cross-panning (i.e., different toxins are alternated during selection rounds in a display campaign) [225] or the use of consensus toxins (*in silico* design of a "consensus" toxin sequence for a set of target toxins) [226,227]; discovery of such broadly neutralizing antibodies will help minimize the total number of antibodies required for a polyvalent recombinant antivenom and thus significantly reduce the cost of the final product [223]. The hope is that these approaches will help lead to the development of

antivenoms with superior therapeutic properties (efficacy, safety, and quality) [6] composed by a low number and volume of antibodies (as all included antibodies will be broadly neutralizing and therapeutically relevant), allowing for lower cost of manufacture than the polyclonal recombinant antivenoms [198,228]. However, oligoclonal recombinant antivenoms have longer development timelines and therefore come with a higher R&D cost [229]. Besides traditional antibodies, other scaffolds, such as nanobodies [230], are also proving promising in the treatment of envenomings [193].

Based on the venom proteomes available for snakes, scorpions, and spiders inhabiting the MENA region, the development of recombinant antivenoms should particularly focus on the discovery of monoclonal antibodies against SVMPs, SVSPs, 3FTxs, and PLA$_2$s to treat snakebite, against NaTxs and KTxs for the treatment of scorpionism, and against latrotoxins and PLDs for recombinant spider antivenoms. Notably, a recombinant monoclonal antibody against α-Latrotoxin from the Mediterranean Black Widow Spider (*L. tredecimguttatus*) already exists, which has been shown to bind and neutralize this toxin *ex vivo* [231]. Supported by the comparatively small number of different toxins that require neutralization, the costly production of existing conventional antivenoms, and challenging maintenance of the venom supply chain, it thus is possible that the implementation of such recombinant therapeutics might first occur in spiders, likely followed by scorpions, and only then venomous snakes (due to the increasing complexity of their venoms).

The development of next-generation antivenoms is, however, not only driven by the discovery of recombinant toxin-targeting antibodies, but also by the repurposing of existing and sometimes even approved drugs, such as small molecule inhibitors and metal ion chelators that target phospholipase A$_2$s (varespladib) and snake venom metalloproteases (e.g., marimastat, dimercaprol, and DMPS). Indeed, initial findings have demonstrated that varespladib neutralized, *in vitro*, the vast majority of anticoagulant activities and even some procoagulant activities present across a range of snake venoms, of which some are from MENA, (i.e., *E. carinatus*, *E. ocellatus*, *D. russelii*, *B. arietans*, *Bothrops asper*, *Bothrops jararaca*, *Calloselasma rhodostoma*, and *Deinagkistrodon acutus*) [232,233]. Furthermore, a study has demonstrated that varespladib can abrogate or delay lethality induced by presynaptically acting neurotoxic snake venom in murine models; this might in part be due to the inhibition of PLA$_2$-induced anticoagulation preventing the rapid spread of the NTxs [9]. Additionally, marimastat demonstrated impressive *in vitro* neutralization of procoagulant activities in most of these venoms, while dimercaprol and DMPS were only able to partially neutralize these activities [232,233]. Together, marimastat and varespladib were even able to prevent murine lethality caused by venom from the most medically important vipers of Africa, South Asia, and Central America [13]. Due to the differences in the venom toxin families present in snakes when compared to scorpions and spiders, these small molecules have little application in the latter two animal groups.

Combined, recombinant antibody technologies and the repurposing of small molecule inhibitors give hope toward the possibility that in the future, significantly improved and cost-effective antivenom products will become available for the MENA region [8–14].

5. Outlook

Animal envenomings in the MENA region constitute a significant health burden that deserves further attention. Indeed, given the number of people affected by these neglected diseases, it is pivotal to ensure that effective and affordable treatments are readily available. Antivenoms currently available in the region are vital in preventing the health impact from worsening, yet ample room for innovation remains. While challenged with a diverse array of toxin targets,

recombinant antivenoms, consisting of defined, toxin-targeting cocktails of monoclonal antibodies, present an interesting opportunity to potentially improve future envenoming therapy in the MENA region. However, to enable the effective development of new treatments, it is pivotal to address existing gaps in epidemiological data. This will help ensure that discovery approaches are focused on the most affected areas and that scientific endeavors are aligned with actual medical needs. Furthermore, a comprehensive analysis of the venoms of all medically relevant venomous species will need to precede any such efforts, since only a fraction of the required venom proteomes is available. Nevertheless, these challenges do not present unsurmountable obstacles, but rather scientific milestones to aim for. In the future, improved and affordable envenoming treatments will hopefully become a reality for patients in the MENA region and beyond.

6. Methods

We searched for articles indexed in PubMed until February 23, 2021 using the following keywords: snake*, scorpion*, spider*, North Africa, Middle East, MENA, toxin, venom, omic, sting, bite, antiven*, envenom*, epidemiology, and treatment. This search was followed by a snowball search, manually reviewing literature reviews, and using Google Scholar/Researchgate. All the original research or review articles in either English, Persian, or Arabic that presented data directly relevant to animal envenomings in the MENA region or provided supporting information were eligible. We obtained close to 1,000 references, and which after eliminating duplicates and excluding articles that did not match the eligibility criteria, 211 of them were selected. The relevance of the epidemiological references was further assessed while a primary focus was placed on including data from the past 25 years (i.e., 1995 to 2020). From the final 59 epidemiology related references that we selected, 33 were retrospective, nine were reviews, eight were case reports, six were prospective, and three were cross-sectional studies. The variables extracted were publication identifiers (authors, journal, and year of publication); study characteristics (study design, period, country, sample size, and age groups); taxonomy of the venomous animal (species); and demographics, locality, season/time, anatomical site of bite/sting, symptoms, and the undertaken management approaches (c.f., S2 Table). In general, wherever possible, the incidences (i.e., the number of venomous animal encounters in a given period of time, disregarding the severity of symptoms) were presented as per 100,000 people per year. To supplement the scarce information on antivenoms for the MENA region available from the literature, antivenom producers were contacted. Unfortunately, only a few responded to enquiries (i.e., Inosan, Razi, and SAVP); the provided information was implemented wherever relevant.

Key Learning Points

- In the Middle East and North Africa (MENA) region, scorpion stings are significantly more common (approximately 350,000 cases/year) than snakebites (approximately 70,000 cases/year) and present the most significant contributor to overall health burden of enevenomings.

- There is a substantial lack of high-quality envenoming data available for the MENA region.

- In the MENA region, the majority of snake venoms contain snake venom metalloproteinases, while sodium channel–binding toxins and potassium channel–binding toxins are the scorpion toxins that cause most health-related challenges.

- There are a series of different antivenoms for envenoming in the MENA region, but only few are clinically validated, and their high cost and limited availability present a substantial health challenge.

- Future therapeutic solutions, such as next-generation antivenoms based on monoclonal antibodies and/or small molecule inhibitors, might help address this issue.

Top Five Papers

1. Amr ZS, Baker MAA, Warrell DA. Terrestrial venomous snakes and snakebites in the Arab countries of the Middle East. *Toxicon*. 2020;177:1–15.

2. Amr ZS, Abu Baker MA, Al-Saraireh M, Warrell DA. Scorpions and scorpion sting envenoming (scorpionism) in the Arab Countries of the Middle East. *Toxicon*. 2021;191:83–103. doi: 10.1016/j.toxicon.2020.12.017

3. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med*. 2008;5:e218. doi: 10.1371/journal.pmed.0050218

4. Chippaux J-P, Goyffon M. Epidemiology of scorpionism: A global appraisal. *Acta Trop*. 2008;107:71–79. doi: 10.1016/j.actatropica.2008.05.021

5. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. *Nat Rev Dis Primer*. 2017;3:17063. doi: 10.1038/nrdp.2017.63

Supporting information

S1 Table. Overview of the epidemiology of snakebites and scorpion stings in the MENA region. The population data for the 5 North African and 14 Middle Eastern countries as well as their allocation in "urban" and "rural" was obtained from the world development indicators database (The World Bank). The information about incidences, antivenom administration, locality of incidence, age groups, gender ratios, morbidity, and mortality were retrieved from articles published in scientific journals. The study type and the geographical region covered are also included. Due to the regional limitations of most articles, countrywide numbers were either estimated by us based on the literature of several different regions that cover the major topology of a country and are geographically evenly distributed (light green), or we used prior population adjusted (increased population since publication) estimates from Kasturiratne and colleagues for snakebites and Chippaux and Goyffon for scorpion stings (yellow), if there was insufficient literature. However, some articles gave a clear indication that the numbers are

covering the epidemiology of the entire country (dark green). Relevant publications are included in brackets. MENA, Middle East and North Africa.
(XLSX)

S2 Table. Overview of epidemiological studies included in this review. Parameters assessed included study design, country that the study was conducted in, the study period, how many patients were included (*N*), the respective patient age groups, and what venomous taxa were responsible for the envenomings. It also states whether the articles contained information on the demographics, locality, season/time, species, anatomical site of bite/sting, symptoms, and management.
(XLSX)

References

1. World Health Organization. WHO Expert Committee on Biological Standardization, sixty-seventh report. Licence: CC BY-NC-SA 3.0 IGO. Geneva; 2017. Available: https://www.who.int/publications/i/item/9789241210133

2. Amr ZS, Baker MAA, Warrell DA. Terrestrial venomous snakes and snakebites in the Arab countries of the Middle East. Toxicon. 2020; 177:1–15. https://doi.org/10.1016/j.toxicon.2020.01.012 PMID: 32001320

3. Amr ZS, Abu Baker MA, Al-Saraireh M, Warrell DA. Scorpions and scorpion sting envenoming (scorpionism) in the Arab Countries of the Middle East. Toxicon. 2021; 191:83–103. https://doi.org/10.1016/j.toxicon.2020.12.017 PMID: 33387549

4. Nentwig W, Kuhn-Nentwig L. Main components of spider venoms. Spider Ecophysiology. Springer.2013:191–202.

5. León G, Vargas M, Segura Á, Herrera M, Villalta M, Sánchez A, et al. Current technology for the industrial manufacture of snake antivenoms. Toxicon Off J Int Soc Toxinology 2018; 151:63–73. https://doi.org/10.1016/j.toxicon.2018.06.084 PMID: 29959968

6. Kini RM, Sidhu SS, Laustsen AH. Biosynthetic Oligoclonal Antivenom (BOA) for Snakebite and Next-Generation Treatments for Snakebite Victims. Toxins. 2018; 10:534. https://doi.org/10.3390/toxins10120534 PMID: 30551565

7. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017; 3:17063. https://doi.org/10.1038/nrdp.2017.63 PMID: 28905944

8. Albulescu L-O, Hale MS, Ainsworth S, Alsolaiss J, Crittenden E, Calvete JJ, et al. Preclinical validation of a repurposed metal chelator as an early-intervention therapeutic for hemotoxic snakebite. Sci Transl Med. 2020; 12. https://doi.org/10.1126/scitranslmed.aay8314 PMID: 32376771

9. Gutiérrez JM, Lewin MR, Williams DJ, Lomonte B. Varespladib (LY315920) and Methyl Varespladib (LY333013) Abrogate or Delay Lethality Induced by Presynaptically Acting Neurotoxic Snake Venoms. Toxins 2020; 12:131. https://doi.org/10.3390/toxins12020131 PMID: 32093386

10. Lewin M, Samuel S, Merkel J, Bickler P. Varespladib (LY315920) Appears to Be a Potent, Broad-Spectrum, Inhibitor of Snake Venom Phospholipase A_2 and a Possible Pre-Referral Treatment for Envenomation. Toxins 2016; 8:248. https://doi.org/10.3390/toxins8090248 PMID: 27571102

11. Oliveira ICF, Gutiérrez JM, Lewin MR, Oshima-Franco Y. Varespladib (LY315920) inhibits neuromuscular blockade induced by *Oxyuranus scutellatus* venom in a nerve-muscle preparation. Toxicon. 2020; 187:101–4. https://doi.org/10.1016/j.toxicon.2020.08.023 PMID: 32889027

12. Laustsen AH, Karatt-Vellatt A, Masters EW, Arias AS, Pus U, Knudsen C, et al. *In vivo* neutralization of dendrotoxin-mediated neurotoxicity of black mamba venom by oligoclonal human IgG antibodies. Nat Commun. 2018; 9:3928. https://doi.org/10.1038/s41467-018-06086-4 PMID: 30279409

13. Albulescu L-O, Xie C, Ainsworth S, Alsolaiss J, Crittenden E, Dawson CA, et al. A therapeutic combination of two small molecule toxin inhibitors provides broad preclinical efficacy against viper snakebite. Nat Commun. 2020; 11:6094. https://doi.org/10.1038/s41467-020-19981-6 PMID: 33323937

14. Ainsworth S, Petras D, Engmark M, Süssmuth RD, Whiteley G, Albulescu L-O, et al. The medical threat of mamba envenoming in sub-Saharan Africa revealed by genus-wide analysis of venom composition, toxicity and antivenomics profiling of available antivenoms. J Proteome. 2018; 172:173–89. https://doi.org/10.1016/j.jprot.2017.08.016 PMID: 28843532

15. Casewell NR, Jackson TNW, Laustsen AH, Sunagar K. Causes and Consequences of Snake Venom Variation. Trends Pharmacol Sci. 2020; 41:570–81. https://doi.org/10.1016/j.tips.2020.05.006 PMID: 32564899

16. Laustsen AH. Guiding recombinant antivenom development by omics technologies. New Biotechnol. 2018; 45:19–27. https://doi.org/10.1016/j.nbt.2017.05.005 PMID: 28552814

17. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. PLoS Med. 2008; 5:e218. https://doi.org/10.1371/journal.pmed.0050218 PMID: 18986210

18. Al Durihim H, Al Hussaini M, Bin Salih S, Hassan I, Harakati M, Al Hajjaj A. Snake bite envenomation: experience at King Abdulaziz Medical City, Riyadh. EMHJ-East Mediterr Health J. 16;4:438–441 2010. 2010. PMID: 20795431

19. Al-Shamsi MM, Al-Barqawi AR, Abdullah AH, Al-Jelawi MK. Venomous snakebites in Diwaniah: A Clinicoepidemiological descriptive study. Al-Qadisiyah Med J. 2014; 10:112–7.

20. Rashad M. P270 Snakebites in al-baha district, saudi arabia (Epidemiliology, clinical presentations, management and prevention). BMJ Publishing Group Ltd; 2019.

21. Mashhadi I, Kavousi Z, Peymani P. Salman Zadeh Ramhormozi S, Keshavarz K. Economic burden of scorpion sting and snake bite from a social perspective in Iran. Shiraz E-Med J. 2017; 18.

22. Dehghani R, Fathi B, Shahi MP, Jazayeri M. Ten years of snakebites in Iran. Toxicon. 2014; 90:291–8. https://doi.org/10.1016/j.toxicon.2014.08.063 PMID: 25193748

23. Abdou SF. Snake Envenomation: Should All Bites Be given Antivenom? Egypt J Forensic Sci Appl Toxicol. 2014:1–15.

24. El Hattimy F, Chafiq F, Hami H, Mokhtari A, Soulaymani A, Rachida SB. Geographical distribution of health indicators related to snake bites and envenomation in Morocco between 1999 and 2013. Epidemiol Health 2018; 40:e2018024–4. https://doi.org/10.4178/epih.e2018024 PMID: 29909610

25. Gouda AS, Elnabarawy NA, Badawy SM. A study of snakebite envenomation cases admitted to egyptian national poisoning center. Acta Medica Int. 2017; 4:34.

26. Gopalakrishnakone P, Faiz SMA, Gnanathasan CA, Habib AG, Fernando R, Yang C-C, et al. Clinical Toxinology. Springer; 2019.

27. Al-Omar DK, Al-Hammami MM, Al-Yassiri HM, Al-Asadi KH. Survival after coagulopathy induced by (Said Dakhil) snake bite in Thi–Qar (south of Iraq). Univ Thi-Qar J Med. 2012; 6:1–7.

28. Alkaabi JM, Al Neyadi M, Al Darei F, Al Mazrooei M, Al Yazedi J, Abdulle AM. Terrestrial snakebites in the South East of the Arabian Peninsula: patient characteristics, clinical presentations, and management. PLoS ONE. 2011; 6:e24637. https://doi.org/10.1371/journal.pone.0024637 PMID: 21931788

29. Haidar NA, Emran MY, Al Muslemani EA. Snakebites in Hajjah, Yemen Republic: Epidemiology, management and the relation of the degree of acuity at presentation with outcome. J Emerg Med Trauma Acute Care. 2012; 2012:2.

30. Khan YMT, Fatema N, Shekeili NAA. Snake bite envenomation: experience in a regional hospital. Oman: a retrospective observational study SM Trop Med J. 2017; 2:1015.

31. Al-Lawati A, Al-Abri SS, Lalloo DG. Epidemiology and outcome of snake bite cases evaluated at a Tertiary Care Hospital in Oman. J Infect Public Health. 2009; 2:167–70. https://doi.org/10.1016/j.jiph.2009.09.001 PMID: 20701878

32. Al-Sadoon MK. Snake bite envenomation in Riyadh province of Saudi Arabia over the period (2005–2010). Saudi J Biol Sci. 2015; 22:198–203. https://doi.org/10.1016/j.sjbs.2014.09.008 PMID: 25737653

33. Tasoulis T, Isbister GK. A Review and Database of Snake Venom Proteomes. Toxins 2017; 9:290. https://doi.org/10.3390/toxins9090290 PMID: 28927001

34. Morita T. Structures and functions of snake venom CLPs (C-type lectin-like proteins) with anticoagulant-, procoagulant-, and platelet-modulating activities. Snake Toxins Hemost. 2005; 45:1099–114. https://doi.org/10.1016/j.toxicon.2005.02.021 PMID: 15922777

35. Eble JA. Structurally robust and functionally highly versatile C-Type Lectin (-related) proteins in snake venoms. Toxins 2019; 11:136. https://doi.org/10.3390/toxins11030136 PMID: 30823637

36. Hiu JJ, Yap MKK. Cytotoxicity of snake venom enzymatic toxins: phospholipase A_2 and L-amino acid oxidase. Biochem Soc Trans. 2020; 48:719–31. https://doi.org/10.1042/BST20200110 PMID: 32267491

37. Harris JB, Scott-Davey T. Secreted phospholipases A_2 of snake venoms: effects on the peripheral neuromuscular system with comments on the role of phospholipases A_2 in disorders of the CNS and

their uses in industry. Toxins 2013; 5:2533–71. https://doi.org/10.3390/toxins5122533 PMID: 24351716

38. Juárez P, Comas I, González-Candelas F, Calvete JJ. Evolution of snake venom disintegrins by positive Darwinian selection. Mol Biol Evol. 2008; 25:2391–407. https://doi.org/10.1093/molbev/msn179 PMID: 18701431

39. Calvete JJ, Marcinkiewicz C, Sanz L. KTS and RTS-disintegrins: anti-angiogenic viper venom peptides specifically targeting the α1β 1 integrin. Curr Pharm Des. 2007; 13:2853–9. https://doi.org/10.2174/138161207782023766 PMID: 17979730

40. Petras D, Sanz L, Segura Á, Herrera M, Villalta M, Solano D, et al. Snake Venomics of African Spitting Cobras: Toxin Composition and Assessment of Congeneric Cross-Reactivity of the Pan-African Echi-TAb-Plus-ICP Antivenom by Antivenomics and Neutralization Approaches. J Proteome Res. 2011; 10:1266–80. https://doi.org/10.1021/pr101040f PMID: 21171584

41. Serrano SM, Maroun RC. Snake venom serine proteinases: sequence homology vs. substrate specificity, a paradox to be solved. Toxicon. 2005; 45:1115–32. https://doi.org/10.1016/j.toxicon.2005.02.020 PMID: 15922778

42. Malih I. Ahmad rusmili MR, Tee TY, Saile R, Ghalim N, Othman I Proteomic analysis of Moroccan cobra Naja haje legionis venom using tandem mass spectrometry. J Proteome. 2014; 96:240–52. https://doi.org/10.1016/j.jprot.2013.11.012 PMID: 24269350

43. Fahmi L, Makran B, Pla D, Sanz L, Oukkache N, Lkhider M, et al. Venomics and antivenomics profiles of North African *Cerastes cerastes* and *C. vipera* populations reveals a potentially important therapeutic weakness. J Proteome. 2012; 75:2442–53. https://doi.org/10.1016/j.jprot.2012.02.021 PMID: 22387316

44. Juárez P, Wagstaff SC, Oliver J, Sanz L, Harrison RA, Calvete JJ. Molecular Cloning of Disintegrin-like Transcript BA-5A from a Bitis arietans Venom Gland cDNA Library: A Putative Intermediate in the Evolution of the Long-Chain Disintegrin Bitistatin. J Mol Evol. 2006; 63:142–52. https://doi.org/10.1007/s00239-005-0268-z PMID: 16786436

45. Casewell NR, Harrison RA, Wüster W, Wagstaff SC. Comparative venom gland transcriptome surveys of the saw-scaled vipers (Viperidae: Echis) reveal substantial intra-family gene diversity and novel venom transcripts. BMC Genomics. 2009; 10:564–4. https://doi.org/10.1186/1471-2164-10-564 PMID: 19948012

46. Makran B, Fahmi L, Pla D, Sanz L, Oukkache N, Lkhider M, et al. Snake venomics of *Macrovipera mauritanica* from Morocco, and assessment of the para-specific immunoreactivity of an experimental monospecific and a commercial antivenoms. J Proteome. 2012; 75:2431–41. https://doi.org/10.1016/j.jprot.2012.02.022 PMID: 22387317

47. Vonk FJ, Admiraal JF, Jackson K, Reshef R, de Bakker MA, Vanderschoot K, et al. Evolutionary origin and development of snake fangs. Nature. 2008; 454:630–3. https://doi.org/10.1038/nature07178 PMID: 18668106

48. Ward MJ, Ellsworth SA, Rokyta DR. Venom-gland transcriptomics and venom proteomics of the Hentz striped scorpion (*Centruroides hentzi*; Buthidae) reveal high toxin diversity in a harmless member of a lethal family. Toxicon. 2018; 142:14–29. https://doi.org/10.1016/j.toxicon.2017.12.042 PMID: 29248469

49. Spawls S, Branch B. The dangerous snakes of Africa. Bloomsbury Publishing; 2020.

50. Eljaoudi R, Larréché S, Chakir S, Chafiq F, Hmyene A, Mion G, et al. Snake bites in morocco: Progress and challenges. Adv Toxicol Toxic Eff. 2019; 3:009–14.

51. Nirthanan S, Awal W, Niranjan NR. Snake α-Neurotoxins and the Nicotinic Acetylcholine Receptor. Gopalakrishnakone P, Inagaki H, Mukherjee AK, Rahmy TR, Vogel C-W, editors. Snake Venoms. Dordrecht: Springer Netherlands; 2015. pp. 1–39. Available. https://doi.org/10.5115/acb.2015.48.3.205 PMID: 26417481

52. Pucca MB, Ahmadi S, Cerni FA, Ledsgaard L, Sørensen CV, McGeoghan FT, et al. Unity makes strength: Exploring intraspecies and interspecies toxin synergism between phospholipases A_2 and cytotoxins. Front Pharmacol. 2020; 11:611. https://doi.org/10.3389/fphar.2020.00611 PMID: 32457615

53. Theakston RDG. Snake bite: the kinetics of envenoming and therapy. Envenomings Their Treat. 1996:117–26.

54. Mallow D, Ludwig D, Nilson G. True vipers: natural history and toxinology of old world vipers. Krieger Publishing Company; 2003.

55. de Costa J, Fonseca KC, Garrote-Filho MS, Cunha CC, de Freitas MV, Silva HS, et al. Structural and functional comparison of proteolytic enzymes from plant latex and snake venoms Biochimie. 2010; 92:1760–5. https://doi.org/10.1016/j.biochi.2010.09.002 PMID: 20868725

56. Phelps T. Old world vipers: a natural history of the Azemiopinae and Viperinae. Edition Chimaira; 2010.

57. Argaz H, Fahd S, Brito JC. Venomous snakes in Morocco: biogeography and envenomation Serpents venimeux du Maroc: biogéographie et envenimation. Sci Ed Mersenne. 2013; 5.

58. Razok A, Shams A, Yousaf Z. Cerastes cerastes snakebite complicated by coagulopathy and cardio-toxicity with electrocardiographic changes. Toxicon. 2020; 188:1–4. https://doi.org/10.1016/j.toxicon.2020.10.003 PMID: 33035563

59. Asega AF, Menezes MC, Trevisan-Silva D, Cajado-Carvalho D, Bertholim L, Oliveira AK, et al. Cleavage of proteoglycans, plasma proteins and the platelet-derived growth factor receptor in the hemorrhagic process induced by snake venom metalloproteinases. Sci Rep. 2020; 10:12912. https://doi.org/10.1038/s41598-020-69396-y PMID: 32737331

60. Olaoba OT, Karina dos Santos P, Selistre-de-Araujo HS, Ferreira de Souza DH. Snake Venom Metalloproteinases (SVMPs): A structure-function update. Toxicon X. 2020:100052. https://doi.org/10.1016/j.toxcx.2020.100052 PMID: 32776002

61. Todehdehghan F, Salemi A, Fathinia B. Identification key for Echis snakes (Serpents: Viperidae) of the East, South East, and South West of Iran. 2019.

62. Lu Q, Navdaev A, Clemetson JM, Clemetson KJ. Snake venom C-type lectins interacting with platelet receptors. Structure–function relationships and effects on haemostasis. Toxicon. 2005; 45:1089–98. https://doi.org/10.1016/j.toxicon.2005.02.022 PMID: 15876445

63. Oraie H. Genetic evidence for occurrence of *Macrovipera razii* (Squamata, Viperidae) in the central Zagros region. Iran Herpetozoa. 2020; 33:27.

64. ESMAEILI JH, ZARE MA, Kamalzadeh M. Evaluation of Iranian snake '*Macrovipera lebetina*'venom cytotoxicity in kidney cell line HEK-293. 2016.

65. Bazaa A, Marrakchi N, El Ayeb M, Sanz L, Calvete JJ. Snake venomics: comparative analysis of the venom proteomes of the Tunisian snakes *Cerastes cerastes*, *Cerastes vipera* and *Macrovipera lebetina*. Proteomics. 2005; 5:4223–35. https://doi.org/10.1002/pmic.200402024 PMID: 16206329

66. Ali SA, Jackson TNW, Casewell NR, Low DHW, Rossi S, Baumann K, et al. Extreme venom variation in Middle Eastern vipers: A proteomics comparison of *Eristicophis macmahonii*, *Pseudocerastes fieldi* and *Pseudocerastes persicus*. J Proteome. 2015; 116:106–13. https://doi.org/10.1016/j.jprot.2014.09.003 PMID: 25241240

67. Wagner P, Townsend E, Barej M, Rödder D, Spawls S. First record of human envenomation by *Atractaspis congica* Peters, 1877 (Squamata: Atractaspididae). Toxicon. 2009; 54:368–72. https://doi.org/10.1016/j.toxicon.2009.04.019 PMID: 19393678

68. Lee S-Y, Lee CY, Chen YM, Kochva E. Coronary vasospasm as the primary cause of death due to the venom of the burrowing asp. *Atractaspis engaddensis* Toxicon. 1986; 24:285–91. https://doi.org/10.1016/0041-0101(86)90153-4 PMID: 3715898

69. Chippaux J-P, Jackson K. Snakes of central and western Africa. JHU Press; 2019.

70. Warrell DA. Venomous bites and stings in Saudi Arabia. Saudi Med J. 1993; 14:196–202.

71. Abd-Elsalam MA. Bosentan, a selective and more potent antagonist for *Atractaspis* envenomation than the specific antivenom. Toxicon. 2011; 57:861–70. https://doi.org/10.1016/j.toxicon.2011.03.002 PMID: 21392521

72. Mahjoub Y, Malaquin S, Ducancel F. Structural and Functional Diversity of Snake Sarafotoxins. Snake Venoms. 2017; 253.

73. Weiser E, Wollberg Z, Kochva E, Lee SY. Cardiotoxic effects of the venom of the burrowing asp, *Atractaspis engaddensis* (Atractaspididae, Ophidia). Toxicon. 1984; 22:767–74. https://doi.org/10.1016/0041-0101(84)90159-4 PMID: 6523505

74. Mahjoub Y, Malaquin S, Mourier G, Lorne E, Abou Arab O, Massy ZA, et al. Short-versus Long-Sarafotoxins: Two structurally related snake toxins with very different *in vivo* haemodynamic effects. PLoS ONE. 2015; 10:e0132864. https://doi.org/10.1371/journal.pone.0132864 PMID: 26176218

75. Chippaux J-P, Goyffon M. Epidemiology of scorpionism: A global appraisal. Acta Trop. 2008; 107:71–9. https://doi.org/10.1016/j.actatropica.2008.05.021 PMID: 18579104

76. Amitai Y. Middle East and North African Scorpions. In: Brent J., Burkhart K., Dargan P., Hatten B., Megarbane B., Palmer R. (eds) Critical Care Toxicology. 2016. Springer, Cham. https://doi.org/10.1007/978-3-319-20790-2_104-1

77. Njah M, Abdelaziz AB, Abdouli M, Zaher M, Garaoui A. Health program and use of community health workers: the example of scorpion envenomation in Tunisia. Cah Détudes Rech Francoph. 2001; 11:57–62. PMID: 11313233

78. Bouaziz M, Bahloul M, Kallel H, Samet M, Ksibi H, Dammak H, et al. Epidemiological, clinical characteristics and outcome of severe scorpion envenomation in South Tunisia: multivariate analysis of 951 cases. Toxicon. 2008; 52:918–26. https://doi.org/10.1016/j.toxicon.2008.09.004 PMID: 18930073

79. Soulaymani Bencheikh R, Idrissi M, Tamim O, Semlali I, Mokhtari A, Tayebi M, et al. Scorpion stings in one province of Morocco: epidemiological, clinical and prognosis aspects. J Venom Anim Toxins Trop Dis 2007; 13:462–71.

80. El Oufir R, Semlali I, Idrissi M, Soulaymani A, Benlarabi S, Khattabi A, et al. Scorpion sting: a public health problem in El Kelaa des Sraghna (Morocco). J Venom Anim Toxins Trop Dis. 2008; 14:258–73.

81. Selmane S, L'Hadj M. Forecasting and prediction of scorpion sting cases in Biskra province, Algeria, using a seasonal autoregressive integrated moving average model. Epidemiol Health. 2016; 38: e2016044–4. https://doi.org/10.4178/epih.e2016044 PMID: 27866407

82. Al-Asmari AK, Al-Saif AA, Abdo NM. Morphological identification of scorpion species from Jazan and Al-Medina Al-Munawara regions, Saudi Arabia. J Venom Anim Toxins Trop Dis 2007; 13:821–43.

83. Ward MJ, Ellsworth SA, Nystrom GS. A global accounting of medically significant scorpions: Epidemiology, major toxins, and comparative resources in harmless counterparts. Toxicon. 2018; 151:137–55. https://doi.org/10.1016/j.toxicon.2018.07.007 PMID: 30009779

84. Lourenço WR. Scorpion diversity and distribution; past and present patterns. Scorpion Venoms Toxinology Springer Bus Media Dordr. 2015:3–23.

85. Ortiz E, Possani LD. Scorpion toxins to unravel the conundrum of ion channel structure and functioning. Toxicon. 2018; 150:17–27. https://doi.org/10.1016/j.toxicon.2018.04.032 PMID: 29723550

86. Dehesa-Davila M, Alagon AC, Possani LD. Clinical toxicology of scorpion stings. Handbook of: Clinical Toxicology of Animal Venoms and Poisons. CRC press; 2017. pp. 221–238.

87. Cid-Uribe JI, Veytia-Bucheli JI, Romero-Gutierrez T, Ortiz E, Possani LD. Scorpion venomics: a 2019 overview. Expert Rev Proteomics. 2020; 17:67–83. https://doi.org/10.1080/14789450.2020.1705158 PMID: 31834817

88. Zhang L, Shi W, Zeng X-C, Ge F, Yang M, Nie Y, et al. Unique diversity of the venom peptides from the scorpion *Androctonus bicolor* revealed by transcriptomic and proteomic analysis. J Proteome. 2015; 128:231–50. https://doi.org/10.1016/j.jprot.2015.07.030 PMID: 26254009

89. Grashof DGB, Kerkkamp HMI, Afonso S, Archer J, Harris DJ, Richardson MK, et al. Transcriptome annotation and characterization of novel toxins in six scorpion species. BMC Genomics. 2019; 20:645. https://doi.org/10.1186/s12864-019-6013-6 PMID: 31409288

90. Baradaran M, Jalali A, Naderi-Soorki M, Jokar M, Galehdari H. First transcriptome analysis of Iranian scorpion. *Mesobuthus eupeus* venom gland Iran J Pharm Res IJPR. 2018; 17:1488. PMID: 30568706

91. Kazemi-Lomedasht F, Khalaj V, Bagheri KP, Behdani M, Shahbazzadeh D. The first report on transcriptome analysis of the venom gland of Iranian scorpion. *Hemiscorpius lepturus* Toxicon. 2017; 125:123–30. https://doi.org/10.1016/j.toxicon.2016.11.261 PMID: 27914888

92. Coelho P, Sousa P, Harris DJ, van der Meijden A. Deep intraspecific divergences in the medically relevant fat-tailed scorpions (Androctonus, Scorpiones). Acta Trop. 2014; 134:43–51. https://doi.org/10.1016/j.actatropica.2014.02.002 PMID: 24524948

93. Lourenço WR. Scorpion incidents, misidentification cases and possible implications for the final interpretation of results. J Venom Anim Toxins Trop Dis 2016;22. https://doi.org/10.1186/s40409-016-0075-6 PMID: 27398081

94. El Hidan MA, Touloun O, El Hiba O, Boumezzough A. Pathophysiological and neurobehavioral injuries in mice experimentally envenomed with *Androctonus liouvillei* (Pallary, 1928) scorpion venom. Exp Toxicol Pathol. 2016; 68:133–41. https://doi.org/10.1016/j.etp.2015.11.005 PMID: 26651916

95. El Hidan MA, Touloun O, Bouazza A, Laaradia MA, Boumezzough A. Androctonus genus species in arid regions: Ecological niche models, geographical distributions, and envenomation risk. Vet World. 2018; 11:286. https://doi.org/10.14202/vetworld.2018.286-292 PMID: 29657418

96. Chakroun-Walha O, Karray R, Jerbi M, Nasri A, Issaoui F, Amine BR, et al. Update on the Epidemiology of Scorpion Envenomation in the South of Tunisia. Wilderness Environ Med. 2018; 29:29–35. https://doi.org/10.1016/j.wem.2017.09.011 PMID: 29338987

97. Aboumaâd B, Lahssaini M, Tiger A, Benhassain SM. Clinical comparison of scorpion envenomation by *Androctonus mauritanicus* and *Buthus occitanus* in children. Toxicon. 2014; 90:337–43. https://doi.org/10.1016/j.toxicon.2014.09.001 PMID: 25218169

98. Caliskan F, Quintero-Hernández V, Restano-Cassulini R, Coronas-Valderrama FI, Corzo G, Possani LD. Molecular cloning and biochemical characterization of the first Na$^+$-channel α-type toxin peptide (Acra4) from *Androctonus crassicauda* scorpion venom. Biochimie. 2013; 95:1216–22. https://doi.org/10.1016/j.biochi.2013.01.015 PMID: 23395751

99. Abd El FE-ZA, El Shehaby DM, Elghazally SA, Hetta HF. Toxicological and epidemiological studies of scorpion sting cases and morphological characterization of scorpions (*Leiurusquin questriatus* and Androctonus crassicauda) in Luxor, Egypt Toxicol Rep 2019; 6: 329–335. https://doi.org/10.1016/j.toxrep.2019.03.004 PMID: 31049294

100. Dehghani R, Djadid ND, Shahbazzadeh D, Bigdelli S. Introducing *Compsobuthus matthiesseni* (Birula, 1905) scorpion as one of the major stinging scorpions in Khuzestan. Iran Toxicon. 2009; 54:272–5. https://doi.org/10.1016/j.toxicon.2009.04.011 PMID: 19393258

101. Jarrar BM, Al-Rowaily MA. Epidemiological aspects of scorpion stings in Al-Jouf province. Saudi Arabia Ann Saudi Med. 2008; 28:183–7. https://doi.org/10.5144/0256-4947.2008.183 PMID: 18500184

102. Sousa P, Arnedo MA, Harris DJ. Updated catalogue and taxonomic notes on the Old-World scorpion genus *Buthus* Leach, 1815 (Scorpiones, Buthidae). ZooKeys. 2017;15.

103. Kovařík F. A revision of the genus Hottentotta Birula, 1908, with descriptions of four new species (Scorpiones, Buthidae). Euscorpius 2007; 2007:1–107.

104. Touloun O, Slimani T, Boumezzough A. Epidemiological survey of scorpion envenomation in south-western Morocco. J Venom Anim Toxins. 2001; 7:199–218.

105. Touloun O, Boumezzough A, Slimani T. Scorpion envenomation in the region of Marrakesh Tensift Alhaouz (Morocco): epidemiological characterization and therapeutic approaches. Serket. 2012; 13:38–50.

106. Yağmur EA, Özkan Ö, Karaer KZ. Determination of the median lethal dose and electrophoretic pattern of *Hottentotta saulcyi* (Scorpiones, Buthidae) scorpion venom. J Arthropod-Borne Dis. 2015; 9:238. PMID: 26623435

107. Estrada-Gómez S, Gomez-Rave L, Vargas-Muñoz LJ, Van der Meijden A. Characterizing the biological and biochemical profile of six different scorpion venoms from the Buthidae and Scorpionidae family. Toxicon. 2017; 130:104–15. https://doi.org/10.1016/j.toxicon.2017.02.007 PMID: 28209477

108. Sanaei-Zadeh H, Marashi SM, Dehghani R. Epidemiological and clinical characteristics of scorpionism in Shiraz (2012–2016); development of a clinical severity grading for Iranian scorpion envenomation. Med J Islam Repub Iran. 2017; 31:27. https://doi.org/10.18869/mjiri.31.27 PMID: 29445656

109. Badry A, Younes M, Sarhan MMH, Saleh M. On the scorpion fauna of Egypt, with an identification key (Arachnida: Scorpiones). Zool Middle East. 2018; 64:75–87. https://doi.org/10.1080/09397140.2017.1414976

110. Omran MAA. Cytotoxic and apoptotic effects of scorpion *Leiurus quinquestriatus* venom on 293T and C2C12 eukaryotic cell lines. J Venom Anim Toxins Trop Dis 2003; 9:255–76.

111. Shalita EA, Wells RD. Treatment of yellow scorpion (*Leiurus quinquestriatus*) sting: a case report. J Am Pharm Assoc. 2007; 47:616–9. https://doi.org/10.1331/JAPhA.2007.07051 PMID: 17848352

112. Omran MA, Abdel-Rahman MS, Nabil ZI. Effect of scorpion *Leiurus quinquestriatus* (H&E) venom on rat's heart rate and blood pressure. Toxicol Lett. 1992; 61:111–21. https://doi.org/10.1016/0378-4274(92)90069-v PMID: 1609434

113. Amr ZS, Al Zou'bi R, Abdo N, Bani HR. Scorpion Stings in Jordan: An Update. Wilderness Environ Med. 2017; 28:207–12. https://doi.org/10.1016/j.wem.2017.05.003 PMID: 28689960

114. Shi C-M, Huang Z-S, Wang L, He L-J, Hua Y-P, Leng L, et al. Geographical distribution of two species of *Mesobuthus* (Scorpiones, Buthidae) in China: insights from systematic field surveys and predictive models. J Arachnol. 2007; 35:215–26.

115. Ozkan O, Kat I. *Mesobuthus eupeus* scorpionism in Sanliurfa region of Turkey. J Venom Anim Toxins Trop Dis 2005; 11:479–91.

116. Ozkan O, Uzun R, Adiguzel S, Cesaretli Y, Ertek M. Evaluation of scorpion sting incidence in Turkey. J Venom Anim Toxins Trop Dis. 2008; 14:128–40.

117. Kazemi SM, Sabatier J-M. Venoms of Iranian scorpions (Arachnida, Scorpiones) and their potential for drug discovery. Molecules. 2019; 24:2670.

118. Mirshamsi O, Sari A, Elahi E, Hosseinie S. Mesobuthus eupeus (Scorpiones: Buthidae) from Iran: A polytypic species complex. Zootaxa. 2011; 2929:1–21.

119. Yigit N, Benli M. The sting of *Mesobuthus gibbosus* (Scorpiones: Buthidae): morphological and ultra-structural characterization. Euscorpius. 2007; 2007:1–5.

120. Bavani MM, Rafinejad J, Hanafi-Bojd AA, Oshaghi MA, Navidpour S, Dabiri F, et al. Spatial distribution of medically important scorpions in north west of Iran. J Arthropod-Borne Dis. 2017; 11:371. PMID: 29322054

121. Dehghani R, Fathi B. Scorpion sting in Iran: a review. Toxicon. 2012; 60:919–33. https://doi.org/10.1016/j.toxicon.2012.06.002 PMID: 22750221

122. Gao B, Peigneur S, Tytgat J, Zhu S. A potent potassium channel blocker from *Mesobuthus eupeus* scorpion venom. Biochimie. 2010; 92:1847–53. https://doi.org/10.1016/j.biochi.2010.08.003 PMID: 20713119

123. Wang X, Li G, Guo J, Zhang Z, Zhang S, Zhu Y, et al. Kv1.3 channel as a key therapeutic target for neuroinflammatory diseases: state of the art and beyond. Front Neurosci. 2020; 13:1393. https://doi.org/10.3389/fnins.2019.01393 PMID: 31992966

124. Lowe G. Two new Hemiscorpius Peters, 1861 (Scorpiones: Hemiscorpiidae) from Northern Oman. Euscorpius. 2010; 2010:1–24.

125. Kovařík F, Mazuch T. *Hemiscorpius novaki* sp. n. from Somaliland (Scorpiones: Hemiscorpiidae). Euscorpius. 2011; 2011:1–9.

126. Lourenço WR. More about the afican species of *Hemiscorpius* Peters, 1861 (Scorpiones: Hemiscorpiidae), and description of a new species from Egypt. Bol SEA. 2011:23–6.

127. Dehghani R, Kamiabi F, Mohammadi M. Scorpionism by Hemiscorpius spp. in Iran: a review. J Venom Anim Toxins Trop Dis. 2018; 24. https://doi.org/10.1186/s40409-018-0145-z PMID: 29507581

128. Shahi M, Rafinejad J, Az-Khosravi L, Moosavy SH. First report of death due to *Hemiscorpius acanthocercus* envenomation in Iran: Case report. Electron Physician. 2015; 7:1234. https://doi.org/10.14661/1234 PMID: 26435822

129. Monod L, Lourenco WR. Hemiscorpiidae (Scorpiones) from Iran, with descriptions of two new species and notes on biogeography and phylogenetic relationships. Rev Suisse Zool. 2005; 112:869–942.

130. Shahbazzadeh D, Amirkhani A, Djadid ND, Bigdeli S, Akbari A, Ahari H, et al. Epidemiological and clinical survey of scorpionism in Khuzestan province, Iran (2003). Toxicon. 2009; 53:454–9. https://doi.org/10.1016/j.toxicon.2009.01.002 PMID: 19708123

131. Karataş A, Gharkheloo MM. A new hemiscorpius Peters, 1861 (Scorpiones: Hemiscorpiidae) from southwestern Iran. Turk J Zool. 2013; 37:15–23.

132. Radmanesh M. Androctonus crassicauda sting and its clinical study in Iran. J Trop Med Hyg. 1990; 93:323–6. PMID: 2231840

133. Pipelzadeh MH, Dezfulian A-R, Jalali MT, Mansouri A-K. *In vitro* and *in vivo* studies on some toxic effects of the venom from *Hemiscorpious lepturus* scorpion. Toxicon. 2006; 48:93–103. https://doi.org/10.1016/j.toxicon.2006.04.017 PMID: 16777163

134. Valavi E, Amuri P, Ahmadzadeh A, Cheraghian B, Ahankoob E. Acute kidney injury in *Hemiscorpius lepturus* scorpion stung children: risk factors and clinical features. Saudi J Kidney Dis Transpl. 2016; 27:936. https://doi.org/10.4103/1319-2442.190841 PMID: 27752001

135. Valavi E, Ansari MJA, Hoseini S. ADAMTS-13 deficiency following *Hemiscorpius lepturus* scorpion sting. Saudi J Kidney Dis Transpl. 2011; 22:792. PMID: 21743232

136. Radmanesh M. Clinical study of Hemiscorpion lepturus in Iran. J Trop Med Hyg. 1990; 93:327–32. PMID: 2231841

137. Rahmani AH, Jalali A. Symptom patterns in adult patients stung by scorpions with emphasis on coagulopathy and hemoglubinuria. J Venom Anim Toxins Trop Dis 2012; 18:427–31.

138. Mullen GR, Durden LA. Medical and veterinary entomology. Academic press; 2009.

139. Rosin R, Shulov A. Studies on the scorpiont nebo hierochonticus. Proc Zool Soc London. Wiley Online Library; 1963. pp. 547–575.

140. Rosin R. Sting of the scorpion *Nebo hierichonticus* in man. Toxicon Off J Int Soc Toxinology. 1969; 7:75–5. https://doi.org/10.1016/0041-0101(69)90167-6 PMID: 5804770

141. Annobil SH. Scorpion stings in children in the Asir Province of Saudi Arabia. J Wilderness Med. 1993; 4:241–51.

142. Langenegger N, Nentwig W, Kuhn-Nentwig L. Spider Venom: Components, Modes of Action, and Novel Strategies in Transcriptomic and Proteomic Analyses. Toxins. 2019; 11:611. https://doi.org/10.3390/toxins11100611 PMID: 31652611

143. Chaves-Moreira D, Matsubara FH, Schemcczssen-Graeff Z, De Bona E, Heidemann VR, Guerra-Duarte C, et al. Brown Spider (Loxosceles) venom toxins as potential biotools for the development of novel therapeutics. Toxins. 2019; 11:355. https://doi.org/10.3390/toxins11060355 PMID: 31248109

144. Ramu Y, Xu Y, Lu Z. Enzymatic activation of voltage-gated potassium channels. Nature. 2006; 442:696–9. https://doi.org/10.1038/nature04880 PMID: 16799569

145. Haney RA, Clarke TH, Gadgil R, Fitzpatrick R, Hayashi CY, Ayoub NA, et al. Effects of Gene Duplication, Positive Selection, and Shifts in Gene Expression on the Evolution of the Venom Gland Transcriptome in Widow Spiders. Genome Biol Evol. 2016; 8:228–42. https://doi.org/10.1093/gbe/evv253 PMID: 26733576

146. Duan Z, Yan X, Cao R, Liu Z, Wang X, Liang S. Proteomic analysis of *Latrodectus tredecimguttatus* venom for uncovering potential latrodectism-related proteins. J Biochem Mol Toxicol. 2008; 22:328–36. https://doi.org/10.1002/jbt.20244 PMID: 18972397

147. He Q, Duan Z, Yu Y, Liu Z, Liu Z, Liang S. The Venom Gland Transcriptome of *Latrodectus tredecimguttatus* Revealed by Deep Sequencing and cDNA Library Analysis. PLoS ONE. 2013; 8:e81357. https://doi.org/10.1371/journal.pone.0081357 PMID: 24312294

148. Gremski LH, da Silveira RB, Chaim OM, Probst CM, Ferrer VP, Nowatzki J, et al. A novel expression profile of the *Loxosceles intermedia* spider venomous gland revealed by transcriptome analysis. Mol BioSyst. 2010; 6:2403–16. https://doi.org/10.1039/c004118a PMID: 20644878

149. Barbaro KC, Ferreira ML, Cardoso DF, Eickstedt VR, Mota I. Identification and neutralization of biological activities in the venoms of *Loxosceles* spiders. Braz J Med Biol Res Rev Bras Pesqui Medicas E Biol. 1996; 29:1491–7. PMID: 9196551

150. Rafijenad J, Tirgari S, Biglarian F, Shemshad K. Systematics, bioecology, and medical importance of widow spiders (*Lathrodectus* spp.) in Khorasan Province, Iran. J Arthropod-Borne Dis. 2007; 1:52–7.

151. Mohammadi Bavani M, Shafaie S, Chavshin A, Dabiri F, Badakhshan M, Naghian A, et al. New data on *Latrodectus tredecimguttatus* Rossi, 1790, the medically important spider species from Iran (Araneae: Theridiidae). Arch Razi Inst. 2020.

152. Al-Hadlak KS, Najim SA. First record of red-back spider *Latrodectus hasselti* Thorell, 1870 (Araneae: Theridiidae) from Basrah, South of Iraq. J Purity Util React Environ. 2015; 4:91–8.

153. Isbister GK, Churchill TB, Hirst DB, Gray MR, Currie BJ. Clinical effects of bites from formally identified spiders in tropical Northern Territory. Med J Aust. 2001; 174:79–82. https://doi.org/10.5694/j.1326-5377.2001.tb143159.x PMID: 11245508

154. Shahi M, Hosseini A, Shemshad K, Rafinejad J. The occurrence of red-back spider *Latrodectus hasselti* (Araneae: Theridiidae) in Bandar Abbas, southern Part of Iran. Iran J Arthropod-Borne Dis. 2011; 5:63. PMID: 22808411

155. Williams M, Anderson J, Nappe TM. Black Widow Spider Toxicity. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2020. PMID: 29763163.

156. Fesce R, Segal JR, Ceccarelli B, Hurlbut WP. Effects of black widow spider venom and Ca2$^+$ on quantal secretion at the frog neuromuscular junction. J Gen Physiol. 1986; 88:59–81. https://doi.org/10.1085/jgp.88.1.59 PMID: 3488369

157. Duan ZG, Yan XJ, He XZ, Zhou H, Chen P, Cao R, et al. Extraction and protein component analysis of venom from the dissected venom glands of *Latrodectus tredecimguttatus*. Comp Biochem Physiol B Biochem Mol Biol. 2006; 145:350–7. https://doi.org/10.1016/j.cbpb.2006.08.006 PMID: 17029995

158. Zamani A, Rafinejad J. First record of the Mediterranean recluse spider *Loxosceles rufescens* (Araneae: Sicariidae) from Iran. J Arthropod-Borne Dis. 2014; 8:228. PMID: 26114138

159. Sadeghi S, Dashan M, Malek-Hosseini MJ. Mediterranean Recluse Spider, *Loxosceles rufescens* (Araneae: Sicariidae) from Charkhab Cave Southern Iran. J Arthropod-Borne Dis. 2017; 11:156. PMID: 29018831

160. Mirshamsi O, Zamani A, Hatami M. New record of the Mediterranean recluse spider *Loxosceles rufescens* (Dufour, 1820) and its bite from Khorasan Province, northeast of Iran (Aranei: Sicariidae). Iran J Anim Biosyst. 2013; 9.

161. Shahi M, Shahi A, Khademi Z, Zamani AR, Nakhaii AR, Rafinejad J. Loxoscelism: a case report from Bandar Abbas in south of Iran. 2015.

162. da Silveira RB, dos Santos Filho JF, Mangili OC, Veiga SS, Gremski W, Nader HB, et al. Identification of proteases in the extract of venom glands from brown spiders. Toxicon. 2002; 40:815–22. https://doi.org/10.1016/s0041-0101(02)00078-8 PMID: 12175619

163. Tambourgi DV, Gonçalves-de-Andrade RM, van den Berg CW. Loxoscelism: From basic research to the proposal of new therapies. Toxicon. 2010; 56:1113–9. https://doi.org/10.1016/j.toxicon.2010.01.021 PMID: 20144641

164. da Silva PH, da Silveira RB, Helena Appel M, Mangili OC, Gremski W, Veiga SS. Brown spiders and loxoscelism. Toxicon. 2004; 44:693–709. https://doi.org/10.1016/j.toxicon.2004.07.012 PMID: 15500846

165. Chaim OM, Trevisan-Silva D, Chaves-Moreira D, Wille ACM, Ferrer VP, Matsubara FH, et al. Brown Spider (*Loxosceles* genus) Venom Toxins: Tools for Biological Purposes. Toxins. 2011; 3:309–44. https://doi.org/10.3390/toxins3030309 PMID: 22069711

166. Binford GJ, Wells MA. The phylogenetic distribution of sphingomyelinase D activity in venoms of Haplogyne spiders. Comp Biochem Physiol B Biochem Mol Biol. 2003; 135:25–33. https://doi.org/10.1016/s1096-4959(03)00045-9 PMID: 12781970

167. Binford GJ, Cordes MH, Wells MA. Sphingomyelinase D from venoms of *Loxosceles* spiders: evolutionary insights from cDNA sequences and gene structure. Toxicon. 2005; 45:547–60. https://doi.org/10.1016/j.toxicon.2004.11.011 PMID: 15777950

168. Adawi SHAA Adawi SHAA, Adawi DHAA. The Scorpion sting: Epidemiology, clinical symptoms, treatment, surveillance and reporting obstacles in the Salfit district (West Bank)(2014–2015). Int J Trop Dis Health. 2016:1–10.

169. Albaba I. Venomous snakes and envenomation in Palestine. J Entomol Zool Stud. 2017; 493:493–5.

170. Al Abri S, Al Rumhi M, Al Mahruqi G, Shakir AS. Scorpion Sting Management at Tertiary and Secondary Care Emergency Departments. Oman Med J. 2019; 34:9–13. https://doi.org/10.5001/omj.2019.02 PMID: 30671178

171. Elmoheen A, Salem WA, Haddad M, Bashir K, Thomas SH. Experience of Snakebite Envenomation by a Desert Viper in Qatar. Abdel-Daim MM, editor. J Toxicol. 2020; 2020: 8810741. https://doi.org/10.1155/2020/8810741 PMID: 33101406

172. Rafizadeh S, Rafinejad J, Rassi Y. Epidemiology of scorpionism in Iran during 2009. J Arthropod-Borne Dis. 2013; 7:66. PMID: 23785696

173. Al-Sadoon MK, Jarrar BM. Epidemiological study of scorpion stings in Saudi Arabia between 1993 and 1997. J Venom Anim Toxins Trop Dis. 2003; 9:54–64.

174. Bentur Y, Lurie Y, Cahana A, Bloom-Krasik A, Kovler N, Neuman G, et al. Poisoning in Israel: Annual Report of the Israel Poison Information Center, 2017. Isr Med Assoc J IMAJ. 2019; 21:175–82. PMID: 30905103

175. Shashar S, Yitshak-Sade M, Sonkin R, Novack V, Jaffe E. The association between heat waves and other meteorological parameters and snakebites: Israel national study. J Emerg Med. 2018; 54:819–26. https://doi.org/10.1016/j.jemermed.2018.02.002 PMID: 29661659

176. Khadem-Rezaiyan M, Moallem SR, Afshari R. Epidemiology of Snake, Spider and Scorpion Envenomation in Mashhad, Khorasan Razavi, Iran (2004–2011). Iran J Toxicol. 2018; 12:27–31.

177. Hameed FA, Ansari HK, Al-Najjar FJ. Prevalent poisonings in adolescents and adults in Dubai: A compendium from Rashid Hospital. Asia Pac J Med Toxicol. 2014; 3:115–9.

178. Alkahlout BH, Abid MM, Kasim MM, Haneef SM. Epidemiological review of scorpion stings in Qatar: the need for regional management guidelines in emergency departments. Saudi Med J. 2015; 36:851. https://doi.org/10.15537/smj.2015.7.11749 PMID: 26108591

179. Al-Ramahi M, Al-Hasnawi H. Diagnostic and epidemiologic Study of fat tail scorpion (*Androctonus crassicuada*) in Mid-Euphrates region/Iraq. J Kerbala Univ. 2012; 8:263–9.

180. Kachel H. Scorpion fauna and scorpionism in Zakho Province of Northern Iraq. Commagene J Biol. 2020; 4:22–7.

181. Morad MS. Identification study and some biological aspects of two families from Order: Scorpiones in Basrah Province Southern of Iraq. Basrah University; 2016.

182. Lall SB, Al Wahaibi SS, Al Riyami MM, Al Kharusi K. Profile of acute poisoning cases presenting to health centres and hospitals in Oman. EMHJ-East Mediterr Health J 9 5–6 944–954 2003. 2003. PMID: 16450524

183. Maher H. Evaluation of scorpion sting incidence in Alkufra city during 1993 and 1994. International Journal of Bioassays. 2013; 338:440–1442.

184. Amr ZS, Disi AM. Venomous Snakes and Snakebites in Jordan. In: Gopalakrishnakone P, Faiz A, Fernando R, Gnanathasan CA, Habib AG, Yang C-C, editors. Clinical Toxinology in Asia Pacific and Africa. Dordrecht: Springer Netherlands; 2015. pp. 251–273. https://doi.org/10.1007/978-94-007-6386-9_55

185. Farghly WMA, Ali FA. A clinical and neurophysiological study of scorpion envenomation in Assiut. Upper Egypt Acta Paediatr. 1999; 88:290–4. https://doi.org/10.1080/08035259950170042 PMID: 10229039

186. Miranda RH. Algunas consideraciones sobre lapicadura de escorpiones. Rev Cubana Med Trop. 1986; 38:343–7. PMID: 3299552

187. Benguedda AC, Laraba-Djébari F, Ouahdi M, Hellal H, Griene L, Guerenik M, et al. Expérience de quinze années de lutte contre l'envenimation scorpionique en Algérie. Bull Soc Pathol Exot. 2002; 95:205–8. PMID: 12404873

188. Laïd Y, Boutekdjiret L, Oudjehane R, Laraba-Djebari F, Hellal H, Guerinik M, et al. Incidence and severity of scorpion stings in Algeria. J Venom Anim Toxins Trop Dis. 2012; 18:399–410.

189. Hellal H, Guerinik M, Griene L, Laid Y, Mesbah S, Merad R, et al. Données épidémiologiques sur l'envenimation scorpionique en Algérie. Bull Soc Pathol Exot. 2012; 105:189–93. https://doi.org/10.1007/s13149-012-0234-4 PMID: 22555670

190. Pucca MB, Cerni FA, Janke R, Bermúdez-Méndez E, Ledsgaard L, Barbosa JE, et al. History of envenoming therapy and current perspectives. Front Immunol. 2019; 10:1598. https://doi.org/10.3389/fimmu.2019.01598 PMID: 31354735

191. Williams DJ, Faiz MA, Abela-Ridder B, Ainsworth S, Bulfone TC, Nickerson AD, et al. Strategy for a globally coordinated response to a priority neglected tropical disease: Snakebite envenoming. PLoS Negl Trop Dis. 2019; 13:e0007059. https://doi.org/10.1371/journal.pntd.0007059 PMID: 30789906

192. Bermúdez-Méndez E, Fuglsang-Madsen A, Føns S, Lomonte B, Gutiérrez JM, Laustsen AH. Innovative Immunization Strategies for Antivenom Development. Toxins. 2018; 10:452. https://doi.org/10.3390/toxins10110452 PMID: 30400220

193. Jenkins TP, Fryer T, Dehli RI, Jürgensen JA, Fuglsang-Madsen A, Føns S, et al. Toxin Neutralization Using Alternative Binding Proteins. Toxins. 2019; 11:53. https://doi.org/10.3390/toxins11010053 PMID: 30658491

194. WHO | WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins. [cited 1 Oct 2021]. Available: http://www.who.int/bloodproducts/snake_antivenoms/snakeantivenomguide/en/

195. Benjamin JM. Abo BN. Brandehoff N snake envenomation in Africa Curr Trop Med Rep. 2020; 7:1–10.

196. Potet J, Smith J, McIver L. Reviewing evidence of the clinical effectiveness of commercially available antivenoms in sub-Saharan Africa identifies the need for a multi-centre, multi-antivenom clinical trial. PLoS Negl Trop Dis. 2019; 13:e0007551. https://doi.org/10.1371/journal.pntd.0007551 PMID: 31233536

197. Harrison RA, Oluoch GO, Ainsworth S, Alsolaiss J, Bolton F, Arias A-S, et al. Preclinical antivenom-efficacy testing reveals potentially disturbing deficiencies of snakebite treatment capability in East Africa. PLoS Negl Trop Dis. 2017; 11:e0005969. https://doi.org/10.1371/journal.pntd.0005969 PMID: 29045429

198. Laustsen AH, Johansen KH, Engmark M, Andersen MR. Recombinant snakebite antivenoms: A cost-competitive solution to a neglected tropical disease? PLoS Negl Trop Dis. 2017; 11:e0005361. https://doi.org/10.1371/journal.pntd.0005361 PMID: 28158193

199. Krause KE, Jenkins TP, Skaarup C, Engmark M, Casewell NR, Ainsworth S, et al. An interactive database for the investigation of high-density peptide microarray guided interaction patterns and antivenom cross-reactivity. PLoS Negl Trop Dis. 2020; 14:e0008366. https://doi.org/10.1371/journal.pntd.0008366 PMID: 32579606

200. Ainsworth S, Menzies SK, Casewell NR, Harrison RA. An analysis of preclinical efficacy testing of antivenoms for sub-Saharan Africa: Inadequate independent scrutiny and poor-quality reporting are barriers to improving snakebite treatment and management. PLoS Negl Trop Dis. 2020; 14. https://doi.org/10.1371/journal.pntd.0008579 PMID: 32817682

201. Bentur Y, Raikhlin-Eisenkraft B, Galperin M. Evaluation of antivenom therapy in *Vipera palaestinae* bites. Toxicon. 2004; 44:53–7. https://doi.org/10.1016/j.toxicon.2004.04.006 PMID: 15225562

202. Seyedian R, Hosseini SM, Seyyedian N, Gharibi S, Sepahy N, Naserinejad S, et al. Neutralization effects of Iranian Vipera lebetina biological properties by Razi institute antivenom. 2013.

203. Abroug F, ElAtrous S, Nouria S, Haguiga H, Touzi N, Bouchoucha S. Serotherapy in scorpion envenomation: a randomised controlled trial. Lancet. 1999; 354:906–9. https://doi.org/10.1016/s0140-6736(98)12083-4 PMID: 10489950

204. el Hafny B, Ghalim N. Clinical evolution and circulating venom levels in scorpion envenomations in Morocco. Bull Soc Pathol Exot. 1990; 2002 (95):200–4.

205. Bomba A, Favaro P, Haus R, Aigle L, Jean F-X, Dauphin I, et al. Review of scorpion stings and snakebites treated by the French military health service during overseas operations between 2015 and 2017. Wilderness Environ Med. 2020; 31:174–80. https://doi.org/10.1016/j.wem.2020.01.006 PMID: 32331950

206. Razi Jalali M, Jalali MT, Mapar Z. Evaluation of plasma cytokine levels in Mesobuthus Eupeus (Scorpionida: Buthidae) scorpion envenomation in rats treated with polyvalent antivenom. Jundishapur J Health Sci. 2015; 7.

207. Jalali A, Bavarsad-Omidian N, Babaei M, Najafzadeh H, Rezaei S. The pharmacokinetics of *Hemiscorpius lepturus* scorpion venom and Razi antivenom following intramuscular administration in rat. J Venom Res. 2012; 3:1. PMID: 22826800

208. Zare MA. *Hemiscorpius lepturus* envenomation: manifestations and management with specific antivenom. 2013.

209. Jalali A, Moazen S, Babaee M, Dadashzade S, Droudi A. The pharmacokinetics of Iranian scorpion *Odonthubuthus doriae* venom and the available antivenom. J Venom Res 2010; 1:48. PMID: 21544182

210. Elfiky AA, Attia HR, Abd Elaziz MR. Cross neutralization of some kinds of scorpion venoms from Africa and South East using VACSERA Polyvalent Scorpion Antisera. J Egypt Soc Parasitol. 2019; 49:443–9.

211. Oukkache N, Rusmili MRA, Othman I, Ghalim N, Chgoury F, Boussadda L, et al. Comparison of the neurotoxic and myotoxic effects of two Moroccan scorpion venoms and their neutralization by experimental polyclonal antivenom. Life Sci. 2015; 124:1–7. https://doi.org/10.1016/j.lfs.2014.12.031 PMID: 25623852

212. Armstrong EP, Bakall M, Skrepnek GH, Boyer LV. Is scorpion antivenom cost-effective as marketed in the United States? Toxicon. 2013; 76:394–8. https://doi.org/10.1016/j.toxicon.2013.09.001 PMID: 24055550

213. Institut Pasteur de Tunis. Rapport IPT 2018. [cited 25 Feb 2021]. Available: http://www.pasteur.tn/index.php?option=com_content&view=article&id=310&Itemid=639

214. Isbister GK, Bawaskar HS. Scorpion envenomation. N Engl J Med. 2014; 371:457–63. https://doi.org/10.1056/NEJMra1401108 PMID: 25075837

215. Pauli I, Puka J, Gubert IC, Minozzo JC. The efficacy of antivenom in loxoscelism treatment. Toxicon. 2006; 48:123–37. https://doi.org/10.1016/j.toxicon.2006.05.005 PMID: 16808942

216. Isbister GK, Graudins A, White J, Warrell D. Antivenom treatment in arachnidism: antivenoms. J Toxicol Clin Toxicol. 2003; 41:291–300. https://doi.org/10.1081/clt-120021114 PMID: 12807312

217. Isbister GK, Page CB, Buckley NA, Fatovich DM, Pascu O, MacDonald SPJ, et al. Randomized Controlled Trial of Intravenous Antivenom Versus Placebo for Latrodectism: The Second Redback Antivenom Evaluation (RAVE-II) Study. Ann Emerg Med. 2014; 64: 620–628.e2. https://doi.org/10.1016/j.annemergmed.2014.06.006 PMID: 24999282

218. Laustsen AH, Solà M, Jappe EC, Oscoz S, Lauridsen LP, Engmark M. Biotechnological Trends in Spider and Scorpion Antivenom Development. Toxins. 2016; 8:226. https://doi.org/10.3390/toxins8080226 PMID: 27455327

219. Wong T. Desperately seeking deadly spiders in Australia. Available: https://www.bbc.com/news/world-australia-34513177

220. Hrala J. This Australian Zoo Is Urging The Public to Catch Deadly Spiders For Them. Available: https://www.sciencealert.com/this-australian-zoo-is-urging-the-public-to-bring-them-deadly-spiders

221. Knudsen C, Ledsgaard L, Dehli RI, Ahmadi S, Sørensen CV, Laustsen AH. Engineering and design considerations for next-generation snakebite antivenoms. Toxicon. 2019; 167:67–75. https://doi.org/10.1016/j.toxicon.2019.06.005 PMID: 31173790

222. Laustsen AH, Engmark M, Milbo C, Johannesen J, Lomonte B, Lohse JMG and B. From Fangs to Pharmacology: The Future of Snakebite Envenoming Therapy. In: Current Pharmaceutical Design. 2016. PMID: 27339430

223. Mackessy SP. Reptile Venoms and Toxins: Unlimited Opportunities for Basic and Applied Research. Handbook of Venoms and Toxins of Reptiles. CRC Press; 2021. pp. 3–18.

224. Laustsen AH, Lohse B, Lomonte B, Engmark M, Gutiérrez JM. Selecting key toxins for focused development of elapid snake antivenoms and inhibitors guided by a Toxicity Score. Toxicon. 2015; 104:43–5. https://doi.org/10.1016/j.toxicon.2015.07.334 PMID: 26238171

225. Ahmadi S, Pucca MB, Jürgensen JA, Janke R, Ledsgaard L, Schoof EM, et al. An *in vitro* methodology for discovering broadly-neutralizing monoclonal antibodies. Sci Rep. 2020; 10:10765. https://doi.org/10.1038/s41598-020-67654-7 PMID: 32612183

226. de la Rosa G, Corrales-García LL, Rodriguez-Ruiz X, López-Vera E, Corzo G. Short-chain consensus alpha-neurotoxin: a synthetic 60-mer peptide with generic traits and enhanced immunogenic properties. Amino Acids. 2018; 50:885–95. https://doi.org/10.1007/s00726-018-2556-0 PMID: 29626299

227. de la Rosa G, Olvera F, Archundia IG, Lomonte B, Alagón A, Corzo G. Horse immunization with short-chain consensus α-neurotoxin generates antibodies against broad spectrum of elapid venomous species. Nat Commun. 2019; 10:1–8. https://doi.org/10.1038/s41467-018-07882-8 PMID: 30602773

228. Jenkins TP, Laustsen AH. Cost of Manufacturing for Recombinant Snakebite Antivenoms. Front Bioeng Biotechnol. 2020; 8. https://doi.org/10.3389/fbioe.2020.00703 PMID: 32766215

229. Laustsen AH, Dorrestijn N. Integrating Engineering, Manufacturing, and Regulatory Considerations in the Development of Novel Antivenoms. Toxins. 2018; 10. https://doi.org/10.3390/toxins10080309 PMID: 30065185

230. Fernandes CF, Pereira SS, Luiz MB, Silva NK, da Silva MC, ACM M, et al. Engineering of single-domain antibodies for next generation snakebite antivenoms. Int J Biol Macromol. 2021. https://doi.org/10.1016/j.ijbiomac.2021.06.043 PMID: 34118288

231. Føns S, Ledsgaard L, Nikolaev MV, Vassilevski AA, Sørensen CV, Chevalier MK, et al. Discovery of a Recombinant Human Monoclonal Immunoglobulin G Antibody Against α-Latrotoxin From the

Mediterranean Black Widow Spider (*Latrodectus tredecimguttatus*). Front Immunol. 2020; 11. https://doi.org/10.3389/fimmu.2020.587825 PMID: 33262768

232. Xie C, Albulescu L, Bittenbinder MA, Somsen G, Vonk F, Casewell NR, et al. Neutralizing effects of small molecule inhibitors and metal chelators on coagulopathic Viperinae snake venom toxins. bioRxiv. 2020; 2020.06.02.129643. https://doi.org/10.3390/biomedicines8090297 PMID: 32825484

233. Xie C, Slagboom J, Albulescu L-O, Somsen GW, Vonk FJ, Casewell NR, et al. Neutralising effects of small molecule toxin inhibitors on nanofractionated coagulopathic Crotalinae snake venoms. Acta Pharm Sin B. 2020; 10:1835–45. https://doi.org/10.1016/j.apsb.2020.09.005 PMID: 33163338