



Centipede envenomation: Clinical importance and the underlying molecular mechanisms



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ABSTRACT

Centipede bites are usually characterized by mildly to moderately painful encounters with humans, however, they are relatively infrequent. The vast majority of centipede envenomations do not cause severe symptoms and only in very rare cases more serious symptoms such as myocardial ischemia and infarction, hematuria, hemoglobinuria, rhabdomyolysis, hemorrhage, pruritus, eosinophilic cellulitis, as well as anaphylaxis are observed. More prevalent are symptoms including pain, paresthesia, lethargy, localized necrosis, headache, dizziness and nausea. The numerous symptoms and complications elicited by these envenomations indicate that centipede venom possesses an arsenal of chemical components with functional diversity. Centipede venom is a rich and complex natural source of bioactive proteins, peptides and other small molecules that aid in predation or defense. The venom can induce myotoxic, cardiotoxic, neurotoxic and other toxic effects. The constituents target different cellular processes and pathways which in turn trigger a cascade of physiological reactions in the victim. The venom components are potent and selective on peripheral targets; thus, they are valuable in studying the molecular basis of these envenomation symptoms and complications. This review highlights the clinical importance of centipede envenomation and the recent discoveries on the underlying molecular mechanisms of the resulting symptoms which is crucial in therapy.

1. Introduction

Centipedes belong to the class Chilopoda which is one of the four major Myriapoda lineages. In terrestrial habitats, the centipedes represent a significant group of predatory arthropods. Common morphological features of the Chilopoda members include the posterior genital opening, 15 to 191 trunk segments each bearing a pair of walking legs, a pair of antennae, three pairs of mouthparts and venomous appendages known as the forcipules which are modified from the first pair of legs (Edgecombe and Giribet, 2007; Lewis, 2006). The venom glands are located in the forcipules (Bucherl, 2013; Jangi, 1984). Globally, there are approximately 3500 species with abundant distribution in tropical and subtropical countries (Edgecombe and Giribet, 2007). These species are classified within five extant orders: Scutigermorpha, Lithobiomorpha, Craterostigmomorpha, Geophilomorpha, and Scolopendromorpha (Edgecombe and Giribet, 2007). Among the centipede genera, *Scolopendra* (Scolopendromorpha: Scolopendridae) is a relatively well-studied genus (Veraldi et al., 2014). A

study by Undheim et al., (2015b) indicated that the venom gland morphology of this genus may have evolved to accommodate more secretory cells and the venom production across these cells is heterogeneous.

Most of the centipede envenomations are characterized by transient symptoms, some of which may take a few days to subside (Bush et al., 2001; Lin et al., 1995; Mohri et al., 1991; Remington, 1950). These symptoms are characterized by instantaneous, localized, burning pain that varies in intensity from mild to excruciating, and in some instances, it spreads to other parts of the victim's body (Baerg, 1924, 1925; Balit et al., 2004; Remington, 1950; Sutherland and Tibballs, 2001). Allergic-like complications have also been reported following centipede envenomations, such as anaphylaxis (Supakthanasiri et al., 2004), rashes (Supakthanasiri et al., 2004), fever and chills (Lin et al., 1995), pruritus (Bush et al., 2001; Mumcuoglu and Leibovici, 1989) and eosinophilic cellulitis (Friedman et al., 1998). Other relatively common complications associated with the bites include localized necrosis, lethargy, paresthesia, dizziness, nausea, headache and burning sensation around

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the bite site (Bush et al., 2001; Coffin, 1919; Sutherland and Tibballs, 2001). Severe symptoms have also been reported in humans including myocardial ischemia and infarction (Ozsarac et al., 2004; Üreyen et al., 2015; Yildiz et al., 2006), hemorrhage (Knysak et al., 1998), rhabdomyolysis (Logan and Ogden, 1985), myoglobinuria (Logan and Ogden, 1985), hemoglobinuria and hematuria (Vazirianzadeh et al., 2007). However, it is noteworthy that these severe symptoms rarely occur.

The multiple symptoms and complications that result from centipede envenomation suggest that the venom constitutes a diverse mixture of toxins (Undheim and King, 2011). Centipede venom is a rich and complex natural source of bioactive proteins and peptides with a variety of biological functions. Some of the protein components possess enzymatic activity whereas others are non-enzymatic. The enzymes include general esterases (Mohamed et al., 1983), acid and alkaline phosphatases (Mohamed et al., 1983), phospholipase A₂ (Gonzalez-Morales et al., 2009; Malta et al., 2008), metalloproteases and non-metalloproteases (Gonzalez-Morales et al., 2009; Malta et al., 2008; Mohamed et al.). Hyaluronidase and PLA₂ activities have also been detected in scolopendrid centipede venom (Malta et al., 2008). The non-enzymatic proteins are the cardiotoxins (Gomes et al., 1983), cysteine-rich secretory proteins (Rates et al., 2007) and haemolysins (Malta et al., 2008; Peng et al., 2010). Disintegrin (Bhagirath et al., 2006), haemolytic (Malta et al., 2008; Peng et al., 2010), myotoxic (Malta et al., 2008) and neurotoxic (Gutierrez, 2003; Mohamed et al., 1983; Rates et al., 2007; Stankiewicz et al., 1999) activities have likewise been detected in centipede venom. However, all the above studies on toxins and toxic activities were reported only on scolopendromorph venom. The first study on non-Scolopendromorpha, *Thereuopoda longicornis* (Scutigeroformorpha), suggested that their venom possess lower protein and peptide diversity compared to the scolopendromorphs (Undheim et al., 2014). In spite of the plethora of toxins in centipede venom, the bites cannot be broadly considered life-threatening and vast majority only result in mild to moderate local pain. Currently, there are approximately 50 constituents of centipede venom that have been reported to have different biological activities (Kong et al., 2013; Liu et al., 2012; Yang et al., 2012). Using a combination of transcriptomic, proteomic and biological functional analyses, studies suggest that ion channels may be one of the major targets of centipede toxins (Liu et al., 2012).

Extensive research has been carried out on venomous animals such as snakes and scorpions, however, centipedes still remain less explored regardless of their frequent encounters with humans as well as the array of clinical manifestations resulting from their bites. The in-depth mechanism of centipede venom toxicity is also not yet fully elucidated. However, recently, there have been noteworthy advances in centipede venom studies with specific research geared towards revealing the underlying molecular mechanisms of the clinical symptoms. In this review, we further focus on the clinical symptoms and complications resulting from centipede bites and the corresponding current knowledge on the molecular mechanisms.

2. Clinical importance of centipede envenomation

Bush et al. (2001) attributed the scarcity of literature on centipede envenomation to few studies carried out to assess the effect of the venom in humans regardless of the occurrence of frequent bites. Besides, it has also been suggested that available statistics on envenomation may be underestimated due to its general benign pathogenesis which usually contributes to frequent home-based therapeutic care (Knysak et al., 1998). However, based on the findings from case reports on envenomation with verified species identification, approximately 0.43% of all centipede species are potentially clinically important among which the majority of those implicated are the *Scolopendra* species (Table 2).

The order Scolopendromorpha comprises the largest centipedes in the world, and bites from different families such as Cryptopidae,

Scolopocryptopidae and Scolopendridae have been reported. Some severe cases of centipede attacks have been reported in victims bitten by *Scolopendra* species (Acosta and Cazorla, 2004; Harada et al., 1999; Hasan and Hassan, 2005; Ozsarac et al., 2004; Wang et al., 2004; Yildiz et al., 2006). The skew of this statistics is probably due to the less cryptic nature of scolopendrid centipedes which are usually encountered foraging at night in warmer climates or the greater severity of their bites, thus they are more likely to be reported to health personnel (Undheim et al., 2015a).

There are three well-documented mortalities due to centipede envenomation. Lewis et al. (2010) reported a fatal case of possible asphyxiation in Mauritius following centipede bite in the back of the throat. The other two cases are that of a 7-year old girl in the Philippines who died after a bite on the head presumptively by *S. subspinipes* (Pineda, 1923; Remington, 1950), and a 21-year old female bitten by a centipede in Thailand (Balit et al., 2004). However, in spite of the presence of numerous neurotoxins, cytotoxins, proteases and allergens (Undheim and King, 2011), few human fatalities that have been reported. Other venomous arthropods cause a significantly higher mortality compared to centipedes. In the United States of America, human deaths due to hymenopterans were reported to be 533 between the years 1991–2001, and 509 between the years 1997–2007, compared to merely five and two respectively over similar duration due to centipede envenomation (Forrester et al., 2012; Langley, 2005). In the two studies, envenomation by other solitary arthropods, for instance spiders, accounted for 66 and 70 deaths, whereas 5 was reported for scorpions in both studies. However, in social hymenopterans, mass envenomation and associated multiple stings could partly contribute to the relatively high statistics (Schmidt, 2018).

Generally, the centipede venom components such as cardiotoxins, myotoxins and neurotoxins likely target specific body systems. Thus, the symptoms resulting from the bites can as well be classified accordingly (Table 1). However, some of the symptoms overlap because they are probably involved in more than one system.

2.1. Nervous system

Centipede venom causes symptoms regulated by the nervous system which can result in serious and fatal effects such as paralysis in natural prey, whereas others are milder and temporal. Centipede attack on humans can cause localized neurological symptoms characterized by sensory disorders and generalized symptoms such as lethargy, anxiety, headache and vagotonia (Mavridis et al., 2016). Virtually all centipede envenomations are characterized by burning pain with an instant onset which lasts for 30 min to about 3 days (Remington, 1950). However, the intensity of the resulting pain seems to vary taxonomically. The *Cormocephalus* species usually induces moderate pain whereas extremely sharp pain is inflicted by *Ethmostigmus* and *Scolopendra* species whose larger size corresponds with the quantity of venom injected (Undheim and King, 2011). Centipede venom causes instant rigid paralysis in crickets, houseflies and cockroaches (Rates et al., 2007). The swift arthropods are known to utilize venom to paralyze their prey prior to eating (Bush et al., 2001). The neurotoxic proteins and peptides of arthropod venom are the critical components required to achieve rapid paralysis of prey. However, up to the present time, there are no cases of paralysis that have been reported in humans.

The neurological symptoms observed following centipede envenomation are considered to be caused by the release of neurotransmitters such as histamine and serotonin besides other agents present in the venom. These agents affect the autonomic nervous system (Bush et al., 2001; Fung et al., 2011). These symptoms are also induced after an attack by other venomous animals such as snakes, sea anemones, spiders, scorpions and cone snails whose venoms target the ion channels (Catterall et al., 2007; Kalia et al., 2015). In arachnids, the rapid paralytic response is also elicited by the venom neurotoxins.

Table 1

A summary of clinical symptoms observed after centipede envenomation and the implicated species.

Body System	Symptoms	Species	Reference
Nervous system	Pain	Unknown, <i>Lithobius forficatus</i> , <i>Otocryptops</i> sp., <i>Theatops spinicaudus</i> , <i>Cryptops</i> spp., <i>Otostigmus</i> spp., <i>Ethmostigmus rubripes</i> , <i>Cormocephalus</i> spp., <i>Scolopendra</i> spp.	(Coffin, 1919; Fung et al., 2011; Lewis et al., 2010; Logan and Ogden, 1985; Remington, 1950; Vazirianzadeh et al., 2007)
	Paresthesia	<i>Scolopendra</i> spp.	(Acosta and Cazorla, 2004)
	Headache	<i>Cryptops</i> , spp., <i>Otostigmus</i> spp., <i>Scolopendra heros</i> , <i>S. subspinipes</i>	(Bush et al., 2001; Ozsarac et al., 2004; Supakthanasiri et al., 2004; Sutherland and Tibballs, 2001; Yildiz et al., 2006)
	Anxiety	Unknown	(Bush et al., 2001; Fung et al., 2011; Ozsarac et al., 2004; Yildiz et al., 2006)
	Flushing	<i>Scolopendra</i> spp	
	Vagotonia		
	Dizziness		
	Hypotension	Unknown, <i>Cryptops</i> , spp., <i>Otostigmus</i> spp., <i>Scolopendra heros</i> , <i>S. subspinipes</i>	(Bush et al., 2001; Ozsarac et al., 2004; Supakthanasiri et al., 2004; Sutherland and Tibballs, 2001; Yildiz et al., 2006)
	Tachypnea	Unknown	(Ozsarac et al., 2004; Supakthanasiri et al., 2004; Sutherland and Tibballs, 2001; Üreyen et al., 2015; Yildiz et al., 2006)
	Palpitations	<i>Scolopendra heros</i>	
Cardiovascular system	Vasospasm		
	Acute ischemia	Unknown	(Fenderson, 2014; Ozsarac et al., 2004; Senthikumar et al., 2011; Yildiz et al., 2006)
	Acute myocardial infarction	<i>Scolopendra</i> spp.	
Musculoskeletal system	Rhabdomyolysis	Unknown <i>Scolopendra</i> spp. <i>S. cingulata</i> , <i>S. heros</i> , <i>S. valida</i>	(Acosta and Cazorla, 2004; Bush et al., 2001; Coffin, 1919; Harada et al., 1999; Hasan and Hassan, 2005; Ozsarac et al., 2004; Rouvin et al., 2008; Sutherland and Tibballs, 2001; Wang et al., 2004; Yildiz et al., 2006)
	Erythema	<i>Scolopendra</i> sp. <i>S. gigantea</i> , <i>S. heros</i> , <i>S. morsitans</i> , <i>S. sumichrasti</i> , <i>S. subspinipes</i> , <i>S. valida</i>	(Mumcuoglu and Leibovici, 1989; Rodriguez-Acosta et al., 2000; Serinken et al., 2005; Shattock, 1968; Sutherland and Tibballs, 2001; Vazirianzadeh et al., 2007; Yildiz et al., 2006)
	Skin reactions; swelling	Unknown	(Bush et al., 2001; Coffin, 1919; Lewis et al., 2010; Lin et al., 1995; Mohri et al., 1991; Rouvin et al., 2008; Serinken et al., 2005; Supakthanasiri et al., 2004; Uzel et al., 2009; Vazirianzadeh et al., 2007)
	Bruises	<i>Scolopendra</i> spp.	
	Skin lesions	<i>S. cingulata</i> <i>S. morsitans</i> <i>S. subspinipes</i> <i>S. valida</i>	
	Localized tissue necrosis	Unknown <i>Scolopendra</i> spp. <i>S. heros</i> <i>Scolopendra valida</i>	(Bush et al., 2001; Fung et al., 2011; Logan and Ogden, 1985)
	Hematuria and hemoglobinuria		(Vazirianzadeh et al., 2007)
Blood System	Lymphangitis	<i>Scolopendra heros</i>	(Essler et al., 2017)
	Eosinophilic cellulitis	Unknown	(Friedman et al., 1998)
	Localized hemorrhage	<i>Cryptops</i> spp. <i>S. subspinipes</i>	(Bush et al., 2001; Knysak et al., 1998)
	Edema	<i>Scolopendra</i> sp., <i>S. abnormis</i> , <i>S. cingulata</i> , <i>S. gigantea</i> , <i>S. heros</i> , <i>S. morsitans</i> , <i>S. subspinipes</i> <i>S. valida</i>	(Acosta and Cazorla, 2004; Bush et al., 2001; Coffin, 1919; Fung et al., 2011; Harada et al., 1999; Hasan and Hassan, 2005; Lin et al., 1995; Logan and Ogden, 1985; McFee et al., 2002; Medeiros et al., 2008; Mohri et al., 1991; Mumcuoglu and Leibovici, 1989; Ozsarac et al., 2004; Rodriguez-Acosta et al., 2000; Rouvin et al., 2008; Serinken et al., 2005; Wang et al., 2004; Yildiz et al., 2006)

2.2. Cardiovascular system

Cases of cardiovascular abnormalities such as hypotension, tachypnea and palpitations following centipede envenomation have been reported, however, they are uncommon (Bush et al., 2001; Ozsarac et al., 2004; Yildiz et al., 2006). In a case report described by Ozsarac et al. (2004), a 60-year-old male with no previously known ischemic heart illness was stung by a 12 cm centipede. The victim experienced dizziness, diaphoresis, bradycardia and hypotension. The electrocardiogram demonstrated new ST-T wave alterations indicating an acute ischemia. This was the first case report on the occurrence of coronary vasospasm following a centipede bite.

Yildiz et al. (2006) also reported a case whereby an envenomed 20-

year old man developed chest pain in which the clinical findings showed abnormal electrocardiographic recordings and elevated level of cardiac troponin T; a cardiac enzyme which is an indicator of acute myocardial infarction. The diagnosis revealed altered levels of inflammatory mediators, elevated capillary permeability, vasospasm and hypotension. Other case reports presented almost similar cases of acute myocardial infarction, however, the patients had normal coronary angiography (Fenderson, 2014; Senthikumar et al., 2011). In another case presented by Üreyen et al. (2015), a 31-year old male experienced chest pain after centipede bite and later developed cardiopulmonary arrest during electrocardiography. Afterward, acute infero-posterolateral myocardial infarction was detected in the same patient. Nonetheless, according to the documented case reports, the

Table 2

Species and estimated number of centipede species that can be regarded as potentially clinically important. The data is based only on verified case reports.

Family	Genus	Species	No. of species	References
Scolopendridae	<i>Scolopendra</i>	<i>S. gigantea</i> ,	8	(Rodriguez-Acosta et al., 2000)
		<i>S. heros</i> ,		(Baerg, 1924; Bush et al., 2001; Essler et al., 2017; Logan and Ogden, 1985)
		<i>S. morsitans</i> ,		(Balit et al., 2004; Lewis et al., 2010; Serinken et al., 2005)
		<i>S. sumichrasti</i> ,		(Baerg, 1925)
		<i>S. subspinipes</i>		(Bush et al., 2001; McFee et al., 2002; Mohri et al., 1991; Shattock, 1968; Remington, 1950; Veraldi et al., 2014; Wang et al., 2004)
	<i>Ethmostigmus</i>	<i>S. abnormis</i>	1	(Lewis et al., 2010)
		<i>S. cingulata</i> ,		(Rouvin et al., 2008)
		<i>S. valida</i>		(Vazirianzadeh et al., 2007)
		<i>E. rubripes</i>		(Balit et al., 2004)
		<i>Cormocephalus</i>		(Balit et al., 2004)
	<i>Otostigmus</i>	<i>C. aurantiipes</i>	3	
		<i>C. westwoodi</i>		
		<i>C. monteithi</i>		
Cryptopidae	<i>Cryptops</i>	<i>O. pradoi</i>	1	(Medeiros et al., 2008)
	<i>Theatops</i>	<i>C. iheringi</i>	1	(Medeiros et al., 2008)
		<i>T. spinicaudus</i>	1	(Baerg, 1924)
Potentially clinically important centipede species			15	
Total centipede species			3500	
% of potentially clinically important centipedes			0.43%	

development of myocardial infarction and cardiopulmonary arrest following centipede bite are rare symptoms.

Medical personnel has associated the cardiovascular disorders resulting from centipede envenomation to be as a result of cardiotoxins, histamine and serotonin-like substances released as mediators of myocardial injury (Yildiz et al., 2006). These cases of cardiovascular complications resulting from centipede envenomation emphasize the need for cardiac evaluation and close monitoring of the bite victims due to hypotension, vasospasm as well as other toxic myocardial effects of centipede venom. Similar envenomations in children could potentially pose greater risks (Ozsarac et al., 2004).

Cardiovascular disorders resulting from envenomation are more prevalent in arthropods such as spiders, hymenopterans and scorpions. Hymenopterans induce anaphylactic manifestations which are commonly observed in victims with previous coronary artery illness although myocardial disorders have also been associated with victims without previous heart illness (Brasher and Sanchez, 1974; Franca et al., 1994; Jones and Joy, 1988; Levine, 1976; Rowe et al., 1979; Sanghvi et al., 1997). In scorpion envenomation, the clinical signs of cardiovascular system involvement are tachycardia with hypertension in most of the patients (Abroug et al., 1991; Hood and Johnson, 1975; Reid, 1961).

2.3. Musculoskeletal system

Animal venoms are known to affect the musculoskeletal system which often causes disintegration of the skeletal muscle (Gabow et al., 1982; Schulze, 1982). Centipede envenomation has been implicated in rhabdomyolysis associated with acute renal failure due to muscle injury (Logan and Ogden, 1985). The *Scolopendra heros* envenomation in the lower extremity has been reported to induce myonecrosis with an associated increase in the leg-compartmental pressure which eventually led to a neurological dysfunction (Logan and Ogden, 1985).

Localized tissue necrosis is another myotoxicity symptom occasionally encountered in humans following centipede envenomation (Undheim and King, 2011). Skin reactions at the bite site are the most frequent symptoms (Veraldi et al., 2014). A case of a centipede bite was detailed by Fung et al. (2011), in which pain and swelling subsided after a few days but bruises were still persistent. 6 days after the bite, bruises developed into skin necrosis down to the subcutaneous layer which was still observed after two weeks. The necrosis was as a result of secondary infection associated with centipede envenomation rather than due to the venom. In another report, Serinken et al. (2005) described a rare case whereby secondary infection following *S. morsitans*

bite resulted in mortal necrosis of the skin fascia.

In the same study, by Fung et al. (2011), there were seven other cases of localized edema. Usually, small lesions resulting from centipede attack heal spontaneously (Bush et al., 2001; Uzel et al., 2009). Hematuria and hemoglobinuria, an evidence of musculoskeletal injury, following envenomation have also been reported in victims (Vazirianzadeh et al., 2007). The myotoxicity symptoms observed in centipede envenomation victims have not been precisely attributed to the venom components but it is believed to be caused by phospholipase A₂ present in scolopendromorph venoms (Gomes et al., 1983; Koestner, 1968). Additionally, a toxin from the *Scolopendra* genus which is a cytotoxin is thought to be responsible for cell breakdown (Smith, 1982).

Several cases of rhabdomyolysis involving myoglobinuria and acute renal failure have also been reported following envenomation by wasps, hornets, bees, and snakes (Akdur et al., 2013; Brigden and Sutherland, 1981; Hood and Johnson, 1975; Humblet et al., 1982; Reid, 1961; Rowlands et al., 1969; Shilkin et al., 1972; Sitprijia and Boonpucknavig, 1972). Hymenopteran venom is believed to contain histamine-like active amines, melittin, serotonin, hyaluronidase, phospholipase A₂ which induces toxicity reactions in sting victims (Habermann, 1972; Sakhuja et al., 1988). These venom components induce neurotoxic, hemolytic and vasoactive symptoms that potentially cause intravascular hemolysis and rhabdomyolysis (Bhatta et al., 2005; Gunasekera et al., 2008).

2.4. Blood system

Edema (Balit et al., 2004; Bush et al., 2001; McFee et al., 2002; Mohri et al., 1991; Veraldi et al., 2014) and hemorrhage from bite sites (Knysak et al., 1998), have been reported following envenomation. Additionally, the following secondary symptoms; lymphangitis, lymphadenitis (Essler et al., 2017), eosinophilic cellulitis (Friedman et al., 1998) and formation of hemorrhagic vesicles blisters (Fung et al., 2011; Veraldi et al., 2014) have also been reported.

Venom from *S. viridicornis*, *O. pradoi* and *C. iheringi* (Malta et al., 2008), *S. multidentis* (Peng et al., 2010), *S. s. mutilans* (Peng et al., 2010) and *Scolopendra* species (McFee et al., 2002) have been shown to induce hemolytic activity in erythrocytes and other cultured cells. Centipede venom exhibits hemolytic and anticoagulant activities which are believed to be responsible for the toxicity on the blood system (Bush et al., 2001; Liu et al., 2012). Although the observed cytotoxicity may be partly induced by the myotoxins such as PLA₂s, cytotoxic peptides which may also contribute to some of the observed symptoms (Undheim and King, 2011). A more recent study identified diverse β-

pore-forming toxins in centipedes which may potentially target different tissue and cell types, and may induce a range of toxic reactions following envenomation (Undheim et al., 2014).

The clinical symptoms observed after centipede envenomation as well as the implicated species have been summarized in Table 1. Furthermore, the percentage of the potentially clinically important centipede species has been derived in Table 2. Using data from case reports, approximately 0.43% of the centipede species can be considered as clinically important. However some of the implicated species rarely cause envenomation and only mild reactions such as transient pain are observed. Interestingly, this finding is almost similar to that observed in other venomous arthropods such as spider whereas it was significantly lower when compared to 23% observed in scorpions (Hauke and Herzig, 2017). The deduced proportion of 0.43% of the clinically important centipede species could be attributed to their relatively small body size as well as their cryptic nature. Additionally, the reported serious clinical symptoms following their envenomation are less frequent compared to other venomous arthropods. On the other hand, scorpions utilize their venom for prey incapacitation which are primarily arthropods as well as defense against predators which majorly include the vertebrates (van der Meijden et al., 2017). Scorpion venoms may have evolved to target the receptors of insectivorous mammals, therefore they potentially possess adequate toxicity to as well target humans which is evidenced by the comparatively higher statistics in scorpions.

3. Mechanism of centipede venom toxicity

Symptoms induced by centipede envenomation are generally benign in nature and rarely serious. Nevertheless, limited research has been done to gain an in-depth understanding of the mechanisms involved. Studies have been carried to explore the venom components as well as venom apparatus (Liu et al., 2012; Undheim et al., 2015b, 2016; Yang et al., 2012), however, critical information vital for elucidating the basis of venom toxicity still remain inadequate. The peptide toxins target different cellular processes, exhibiting neurotoxic, cardiotoxic, myotoxic and cytotoxic activities. Ion channels, a diverse category of membrane proteins, are among the targets of peptide toxins. They are essential in cellular physiology, as they play pivotal roles in critical processes such as muscle contractility and neuronal signaling (Catterall, 1995). Toxins from the venomous animals such as snakes, spiders, centipedes, hymenopterans, scorpions, sea anemones and cone snails have therefore evolved to either block or activate these functionally significant ion channels with high selectivity and potency (Bergeron and Bingham, 2012; Bohlen et al., 2010; Chow et al., 2015; Diochot et al., 2012; Klint et al., 2012; Possani et al., 1999; Quintero-Hernández et al., 2013; Salinas et al., 2014; Sollod et al., 2005; Takacs et al., 2014). Investigation of these toxins' activity is critical for the elucidation of the molecular mechanism of the clinical symptoms induced by envenomation. Current knowledge on the centipede toxins has been applied to partially explain the basis of occurrence of some clinical symptoms, which is significant in the discovery of diagnostic and therapeutic interventions following bites.

3.1. Pain

The venomous animals utilize toxins to inflict pain to ward-off competitors/predators. (Chahl and Kirk, 1975; Schmidt, 1982). Pain is one of the most common symptoms induced by centipede bites. The bioactive compounds in venom which induce pain have been extensively characterized, however, the mechanism of action still remains unclear. The channel transient receptor potential vanilloid 1, TRPV1, has been identified as a polymodal nociceptor responsive to a wide spectrum of chemical and physical stimuli that interact with different regions of the channel protein to facilitate channel activation (Caterina et al., 1997; Ramsey et al., 2006; Zheng, 2013). Also referred to as the

capsaicin receptor, TRPV1 is a heat-sensing channel associated with the detection of an ambient environment so as to maintain steady body temperature and heat pain transduction (Caterina et al., 1997; Gavva et al., 2008).

A recent study has demonstrated that centipedes utilize the activation mechanism of TRPV1 in pain induction. Yang et al. (2015) discovered a novel peptide toxin, RhTx, from the Chinese red-headed centipede, which potentially activates TRPV1 to elicit excruciating pain. RhTx, a compact polarized toxin consists of a 27-amino acid peptide which exhibits rapid binding kinetics and high affinity for TRPV1. The peptide, RhTx, activates TRPV1 with high potency exhibiting similar efficacy and binding affinity with capsaicin. RhTx targets TRPV1's outer pore to cause heat activation at body temperature. The interaction between RhTx and TRPV1 is facilitated by the peptide's charge-rich C-terminus which binds tightly to the highly charged outer pore region of the channel where it can directly interact with the pore helix and turret. This study suggested that centipede venom has evolved to hijack the gating machinery of TRPV1 which is reserved for heat to elicit intense burning pain.

Similar mechanism of pain infliction has also been explained in other venomous animals such as scorpions (Geron et al., 2017; Hakim et al., 2015), snakes (Geron et al., 2017) and spiders (Bae et al., 2016; Bohlen et al., 2010; Cao et al., 2013). For instance, in spider venom, toxin DkTx activates TRPV1 channel via the heat-activated pathway. DkTx interacts intimately with TRPV1 by binding to the outer edge of the channel's external pore while inserting hydrophobic residues into the surrounding bilayer (Bae et al., 2016). DkTx activates the TRPV1 channel on the sensory nerve fibres to produce pain. DkTx's TRPV1-binding strategy is distinct from that of RhTx because DkTx contains 75 amino acids and achieves high affinity by using two active knots (Bohlen et al., 2010; Cao et al., 2013).

Scorpions, on the other hand, seem to target multiple channels such as TRPV1, voltage-gated potassium channels (K_v) and the voltage-gated sodium channels (Na_v) to induce pain. For instance, Bmp01, a pain-inducing peptide from scorpion (*Mesobuthus martensii*) venom evokes pain by targeting TRPV1 (Hakim et al., 2015; Wu et al., 2000; Yang et al., 2017). Interestingly, Bmp01 and the proton packed in venom utilize a “one-two punch” mechanism to activate TRPV1 synergistically (Yang et al., 2017). Snake venom contains TRPV1-activated peptides as well. A recent study on *Echis coloratus* viper venom suggests that it contains proteins which can activate the pain pathway by directly targeting TRPV1 (Geron et al., 2017).

Centipedes, as well as other venomous animals, have evolved a pain-inducing strategy to activate TRPV1, suggesting a convergent evolution in their venoms. The majority of known neurotoxins act through channel inhibition (Catterall et al., 2007; Kalia et al., 2015), therefore the activation mechanism presents a unique mode of defense. The peptides described above mostly target TRPV1, making them potential candidates for the development of new drugs for pain treatment. However, further research is required because centipede venoms may contain other undiscovered components that induce pain.

3.2. Cardiovascular disorders

The voltage-gated potassium channel subunit Kv7.4 (KCNQ4) channel has been implicated as the potential target for centipede venom to cardiovascular disorders. KCNQ4 channel, involved in neuronal excitability, is critical in the regulation of the pulmonary vascular tone and its inhibition increases the isometric tension of interlobular arteries (Stott et al., 2014).

Recently, Luo et al. (2018) identified and characterized a novel small peptide toxin named Ssm Spooky Toxin (SsTx), from the venom of the golden head centipedes (*Scolopendra subspinipes mutilans*). SsTx is a potent inhibitor of KCNQ4. *In vivo* analysis of SsTx's effect on the cardiovascular system induced vasoconstriction thereby causing acute hypertension in mice. Further experiments of SsTx on macaques also

caused vasospasm and acute hypertension. Additionally, an inverted T wave, a typical syndrome for myocardial ischemia was observed in the monkeys following SsTx injection which is considered to be caused by the coronary spasm. SsTx was confirmed to be the key component of the venom responsible for vessel disorder because an evaluation of the vessel activity induced by SsTx-free crude venom yielded little effect on arterial tension compared to the crude venom.

Structural and functional assays of the interaction between SsTx and KCNQ4 revealed that two key amino acid residues on SsTx; R12 and K13, constitute the bioactive binding sites responsible for the peptide's activity on KCNQ4 channel. Further assays identified D266 in the turret and D288 in the P-loop region as the key toxin binding sites on KCNQ4. The peptide-toxin interaction study revealed that two interacting residue pairs, K13-D266 and R12-D288 are critical for the centipede toxin's functional activity on KCNQ4. Thus, the molecular basis of vasospasm, hypertension and myocardial dysfunction due to centipede bites was elucidated.

In another study, Sun et al. (2015) identified a distinct three-helix peptide toxin, SSD609, from the venom of *Scolopendra dehaani* that acts on KCNE1, which is a single-span transmembrane auxiliary protein that regulates KCNQ1 by slowing its activation and enhancing the channel conductance to generate slow activated potassium (*I_{ks}*) currents (Barhanin et al., 1996). The peptide, SSD609, exhibited *I_{ks}* currents inhibition in cardiomyocytes and current attenuation of KCNQ1/KCNE1 in Chinese hamster ovary (CHO) cells. The functional analysis suggested Glu19 in KCNE1's extracellular helix as the key residue for the interaction with SSD609. This study presents a different molecular basis for the action of centipede venom on the cardiovascular system as reported by Luo et al. (2018) which demonstrates that centipede venom targets alpha subunits of KCNQ family. The proposed KCNE1 binding mechanism is unlikely because it has been suggested that KCNE1 is not a key component in the channel voltage activation rather, it only modulates voltage-dependent current to α subunit (Barhanin et al., 1996; Pusch et al., 1998; Sanguinetti et al., 1996; Tristani-Firouzi and Sanguinetti, 1998).

In comparison with the underlying mechanism in other venomous animals, specifically scorpions induce cardiovascular disorders by targeting large conductance Ca^{2+} - and voltage-dependent K^+ (BK_{Ca}) channels. The toxins induce vasospasm in their sting victims through inhibition of BK_{Ca} channels. BmP09 toxin from *Buthus martensi* Karsch is a specific and reversible blocker of BK_{Ca} channel. The toxin-channel interaction is majorly contributed by the residue Lys-41 in BmP09 which lies at the center of the interface plugging into the channel pore entrance. Aromatic π - π interactions around the center favors the stable binding between BmP09 and BK_{Ca} channel (Yao et al., 2005). Other scorpion toxins; kaliotoxin, BmBKTx1, BmTX1 and BmTX2 identified from scorpion venom also specifically blocks BK_{Ca} (Crest et al., 1992; Goudet et al., 2002; Romi-Lebrun et al., 1997; Xu et al., 2004).

3.3. Respiratory disorders

Clinical symptoms associated with the respiratory system following centipede envenomation are rare. KCNQ channels have been reported to have a significant function in the respiratory system (Brueggemann et al., 2014). Peptide toxin, SsTx, from *Scolopendra subspinipes mutilans* venom can be considered as a critical factor in the manifestation of symptoms associated with the respiratory system. SsTx significantly reduces the respiratory rate while the respiratory amplitude is increased. *In vitro* assays demonstrated that SsTx, as well as the crude venom, can induce bronchial ring contraction (Luo et al., 2018). Considering the contraction effect caused by SsTx, the occurrence of a respiratory disorder following centipede envenomation is a potential symptom. It is noteworthy that despite the presented evidence on the effect of centipede venom or SsTx on the respiratory system, no such symptom has been reported following envenomation.

3.4. Tissue necrosis

Localized tissue necrosis is one of the most common symptoms caused by centipede attack. Research on centipede crude venom has attributed phospholipase A2 (PLA_2) activities to these localized symptoms. PLA_2 s have been characterized in centipede venom, however, assays on their toxic activities have not been performed except for their phospholipolytic activity. Gonzalez-Morales et al. (2009) identified PLA_2 containing five disulfide bonds from the venom of *Scolopendra viridis* which exhibits high enzymatic activity. Liu et al. (2012) characterized two PLA_2 s; SSD 387 and SSD 1043 from *Scolopendra dehaani* venom. PLA_2 homologs have also been found in the *S. morsitans* and *E. rubripes* venom and transcriptomes of *S. alternans* and *S. morsitans* (Undheim et al., 2014). PLA_2 has also been found in the venom of *S. subspinipes* (Smith and Undheim, 2018).

The SsTx peptide also causes vesicular abnormalities and has been implicated to be an important factor for localized symptoms after envenomation. Injection of SsTx in the dorsal skin of mice induced significant tissue necrosis which was proposed to be caused by capillary vessels' spasm (Luo et al., 2018). Different centipede venom components probably act synergistically to induce the observed local symptoms. Although it may seem that myotoxicity evoked by centipede venom is mainly restricted to tissue necrosis, other severe systemic reactions such as rhabdomyolysis and consequent myoglobinuria, proteinuria and renal failure have also been reported to be induced by the venom, however, the in-depth mechanism still remains unclear.

Other studies have also attempted to elucidate the mechanism involved in local tissue damage induced by other venomous animals. Particularly, metalloproteases and PLA_2 have been implicated to be the cause of local tissue necrosis and myotoxicity following snake envenomation (Gutiérrez and Lomonte, 1995; Hamza et al., 2010; Zychar et al., 2010). These findings from snake venom metalloproteases suggest that the highly myotoxic, edematogenic and hyperalgesic activities elicited by the centipedes, specifically the scolopendromorph venom (Malta et al., 2008), may be partially contributed by the metalloproteases' activity.

3.5. Blood disorders

Centipede venom components exhibit hemorrhagic, anticoagulant and coagulant activities (Bush et al., 2001; Liu et al., 2012; Malta et al., 2008; Said, 1958). Said (1958) determined fibrinolytic activity in the maxilliped extract of *Scolopendra morsitans* and Malta et al. (2008) reported weak fibrinolytic activity from *O. pradoi* and *S. viridicornis* venom. Anticoagulant activity in *S. subspinipes* venom has also been reported (Bush et al., 2001). Comparatively recent, Liu et al. (2012) reported SSD14-coding mature protein from *Scolopendra dehaani* that has hemolytic activity against rabbit and mouse cells. However, the molecule failed to exhibit the hemolytic activity against human erythrocytes. Phylogenetic assays of SSD14 showed that it has high similarity with human gamma-glutamyl transferase (GGT) (Courtay et al., 1992) which implies that certain GGT members are involved in both the catalysis of transfer reaction and platelet aggregation. In the same study, a protein fraction encoded by SSD431 also showed anticoagulant activity.

However, in viperid snake venoms, the metalloproteases are the key components which act as hemorrhagic factors. The biochemical mechanism for their activity is the proteolytic degradation of the basement membrane and the extracellular matrix surrounding small vessels and capillaries (Bjarnason and Fox, 1994). These protease toxins also disrupt coagulation, hence complementing blood loss from the vascular system (Bjarnason and Fox, 1994; Gutiérrez and Rucavado, 2000). Metalloproteases have also been described in araneomorph spiders venom where they principally act as haemorrhagins (Nagaraju et al., 2007; Trevisan-Silva et al., 2010).

In summary, the basic mechanism by which the hemorrhagic toxins

induce hemorrhage is through proteolytic disruption of basement membrane structures, thereby permitting the release of the capillary constituents into the stroma. The differences in the hemorrhagic activity among the centipede toxins are probably because of various factors such as proteolytic activity, substrate specificity, rate of inhibition and/or elimination by endogenous inhibitors, and the capacity to modify the platelet aggregation inhibition. However, as more information on the structure and biochemistry of hemorrhagic toxins as well as other non-hemorrhagic venom metalloproteinases is available, we anticipate that the unresolved questions associated with centipede venom-induced hemorrhage will be resolved.

4. Conclusion

In conclusion, the underlying molecular mechanisms of the different clinical symptoms detailed above may not solely elucidate the basis of the envenomation consequences. Different venom components may act synergistically to induce the observed clinical symptoms. Additionally, the venomous animals may have evolved strategies of venom optimization by minimizing expenditure (Morgenstern and King, 2013), thus, centipede venom may as well have evolved to target multiple essential physiological systems. For instance, the centipede toxin SsTx simultaneously disrupts the cardiovascular, nervous, muscular and respiratory systems by targeting the broadly distributed KCNQ channels (Luo et al., 2018), thereby may potentially induce neurotoxic symptoms such as seizure, cardiovascular disorders such as myocardial ischemia, vasospasm and hypertension and respiratory alterations which are rare. The molecular mechanism of SsTx suggests a simple therapeutic intervention with retigabine, a KCNQ opener, can reverse the toxic effects of either crude centipede venom or purified SsTx. Therefore, more research should be carried out to determine the targets of the different venom components to reveal their molecular basis of action. However, considering the remarkable recent discoveries of the centipede venom components and their potential targets in the body system, the molecular basis of action of some of the constituents have been revealed.

Ethical statement

The authors declare that this manuscript complies with the Elsevier Ethical Guidelines for Journal Publication and acknowledge the Duties of Authors described therein.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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