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Toxicon

Review

A review of epidemiological, clinical and *in vitro* physiological studies of envenomation by the scorpion *Hemiscorpius lepturus* (*Hemiscorpiidae*) in Iran

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ABSTRACT

Many of the published accounts of envenomation by *Hemiscorpius lepturus* (*H. lepturus*) are in a form that makes it difficult for non Farsi readers to access. The purpose of this review is to summarise the Iranian literature on the toxinological effects of the venom of *H. lepturus* using both *in vivo* and *in vitro* data and where appropriate, details of methods and ethics statements will be reported.

1. Introduction

Despite the great number of scorpion species found in Iran, only a few are considered to be of clinical significance. Epidemiological studies have demonstrated that envenomation by the thin-tailed scorpion *Hemiscorpius lepturus*, which is mostly found in the southern warmer areas of Iran (Farzanpay, 1998), while only accounting for 10–15% of the reported cases of scorpion envenomation in southwest province of Iran Khuzestan (Pipelzadeh et al., 2007), it is responsible for almost 90% of reported deaths.

Most scorpion stings described elsewhere in the world result in cardiovascular, neurologic and pulmonary disorders (Ismail et al., 1992; Amaral et al., 1992). Commonly, scorpion envenomation is thought to activate the autonomic nervous system giving rise to an "autonomic storm" (Ismail, 1994). Although an earlier clinical account of scorpion envneomation reported haemolysis, renal failure and local necrosis twenty-four hours after the sting (Chadha and Leviav, 1979). However, the severity and frequency of occurrence of these symptoms is considerably greater following *H. lepturus* envenomation (Pipelzadeh et al., 2007; Radmanesh, 1998). This would suggest the pathophysiological effects following envenomation by *H. lepturus* are due to a toxic action on blood cells, kidney and liver function. As a consequence, the thin-tailed scorpion has venom that is highly toxic, especially to children and presents a different clinical picture that has not previously been described for in other scorpion species. Therefore, in this review we summarize the findings from clinical, epidemiological, *in vitro* and *in vivo* animal studies on *H. lepturus* envenomation that have been published in the Iranian– (Farsi) based literature.
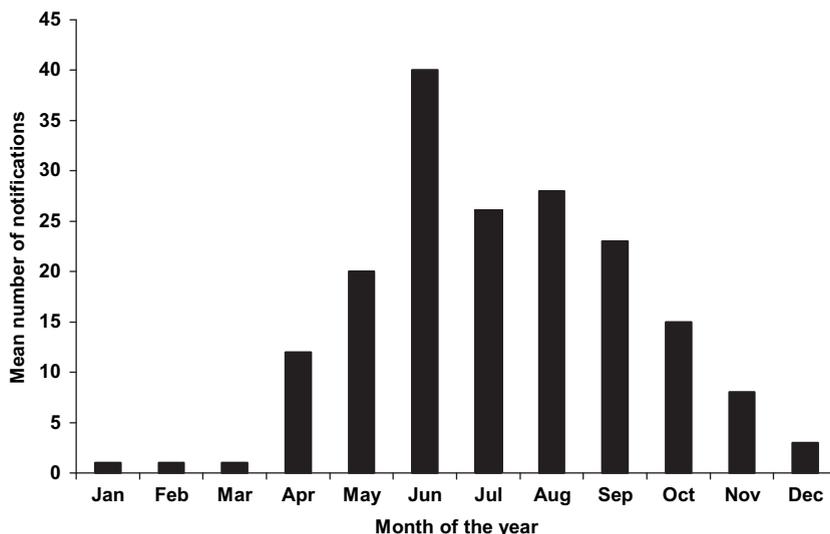
Fig. 1. Mean number of *H. lepturus* notifications by month referred to Ahvaz university hospitals from 1983 to 1987 (Chitnis et al., 1993).

2. Epidemiological studies

In a retrospective study which included 1538 scorpion envenomed children (less than 10 years old) who were admitted to the Abozar Children's University Hospital of Ahvaz between 1994 and 1999, it was noted that two hundred and seventy (17.5%) of these children were stung by *H. lepturus* and the remaining 1368 were due to other scorpion species (Mir Dehghan et al., 2001). Data collected during 1983–1987 from the two University Hospitals of Ahvaz (Ahvaz Jundishapur University) suggests that *H. lepturus* was responsible for 10–15% of all hospital referred scorpion poisoning. Forty three percent of individuals were from rural regions and the remaining 57% were from urban districts. Fifty six percent of scorpion stings occurred during the hot seasons (June–September) (Fig. 1) and stings occurred mainly at night between 7 p.m. and 5 a.m. (26.1% of cases) and early morning 5 and 12 a.m. (18.6% of cases). The incidence of scorpion stings records in both sexes was almost identical. There are two age groups that are statistically more likely to be stung by *H. lepturus*; those individuals aged between 10 and 20 years and those aged between 1 month and 5 years old with incidence of 26.7% and 24.1%, respectively (Fig. 2). Forty one percent of stings were located to the lower limbs, particularly on the foot. Stings were also reported to be located to the trunk, upper extremities and the head and neck, with an incidence of 26%, 23.4% and 9.6%, respectively. There were sixteen reported fatalities over the period of study due to scorpion envenomation (8.5% of the cases) (Chitnis et al., 1993).

3. Clinical findings

Over a one year period, 141 children were admitted to intensive care unit in Abuzar Children's University Hospital of Ahvaz following a sting from *H. lepturus*. Within the *H. lepturus* scorpion envenomed children, different clinical symptoms were observed, which included,

haemoglobinuria, with and without renal failure in 52% and 20% cases, respectively. Only 20% of victims showed neither haemoglobinuria nor renal failure. The percentages of renal involvement found among paediatric patients envenomed by *H. lepturus* were compared with children envenomed by other species such as *Androctonus crassicauda* and *Mesobuthous eupeus* (Afzali and Pezeshki, 1998) (Table 1). All these children had variable degrees of renal failure, however the renal failure was more severe in those patients envenomed by *H. lepturus*, as clinically assessed by the attending paediatrician. It was also noted that renal failure was more severe in those children that had been envenomed in the trunk and those referred late for treatment (Afzali and Pezeshki, 1998). In a study by Chitnis et al., the authors reported that abnormal sodium and potassium serum levels and blood gases were the most prominent biochemical features in those patients that had either clinical manifestations of severe pulmonary oedema (predominantly bilateral type) or had died of respiratory failure (Chitnis et al., 1993). Blood urea nitrogen (BUN),
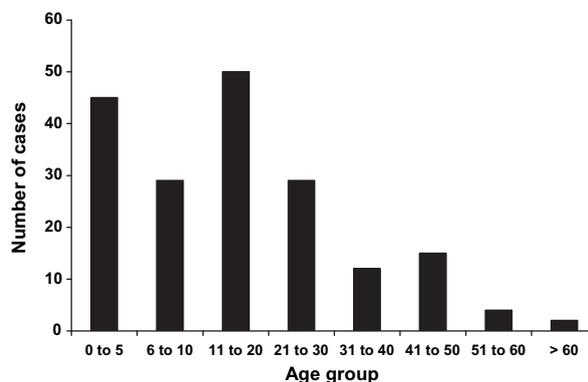

Fig. 2. Number of cases according to age groups of individuals stung by *H. lepturus* referred to Ahvaz university hospitals from 1983–1987 (Chitnis et al., 1993).

Table 1

Percentage of clinical outcome due to stings by *H. lepturus* and other scorpion species among envenomed children under 10 years old admitted to Abuzar Ahvaz Jundishapur university hospital during 1994 (Afzali and Pezeshki, 1998).

Clinical outcome	Percentage due to *H. lepturus* stings	Percentage due to other scorpion stings
Haemoglobinuria without renal failure[a]	52	9.6
Haemoglobinuria with renal failure[a]	20	3.7
No haemoglobinuria or renal failure	20	3.7
Death with DIC[b]	5.8	1.1
Death due to renal failure	2.2	0
Total deaths	8	1.1

[a] Increase in serum creatinine or decrease in its clearance by more than 50% of standard values was considered as renal failure.
[b] Disseminated intravascular coagulation.

haemoglobin and white blood cells (leucocytosis –ranging from 20 to 70×10^9/L) were elevated in the majority of the patients that died (Chitnis et al., 1993).

4. Experimental findings

4.1. Histopathological findings

The following is an account of a number of animal studies investigating the histopathological manifestations of *H. lepturus* venom on rats. These experiments have met with the approval of local ethics committees at the time of the experiments. The main findings included focal necrosis, haemorrhages, with and without oedema in lipid-containing organs such as liver, kidney and spleen of the rats. Clinical and laboratory evidence of focal necrosis or haemorrhage with and without oedema were observed followed administration of 1 LD_{50} dose of the venom. It is of interest to note that *H. lepturus* envenomation has a delayed toxic action and a LD_{50} of 5.6 mg/kg (Latifi and Tabatabai, 1979). The abnormalities were recorded after a 72 h period following subcutaneous injection. They documented histopathological alterations in 71%, 66.8% and 26% of liver, kidney and spleen of envenomed rats, respectively. Table 2). On histophatological examination, morphological changes to the proximal tubular cell and glomerular network of the kidney were seen. Histological observation at the site of injection, induced by one LD_{50}, showed a deep

Table 2

Mean (±SD) percentage of histopathological analysis of the liver, kidney and spleen injected with one LD50 *H. lepturus* dose of venom in rats ($n = 3$) (Dehghani et al., 2004).

Histophathological changes	Kidney	Liver	Spleen
Oedema	45 ± 2.08	49.2 ± 3.05	14 ± 1
Oedema + local necrosis	9.2 ± 0.57	5.2 ± 0.57	–
Local necrosis	9.2 ± 3.04	4 ± 1	–
Haemorrhage + oedema	4.6 ± 0.57	4.6 ± 0.57	6 ± 1.73
Severe haemorrhage + oedema	6 ± 1	4 ± 1	–
Mild haemorrhage	2.6 ± 0.57	4 ± 0.57	6 ± 1
Without histopathological changes	23.2 ± 1.52	29 ± 3.05	74 ± 3

wound or focal necrosis in the majority of cases (55%) 3–4 days post injection (Dehghani et al., 2004).

These typical histopathological effects of *H. lepturus* venom were obtained from a study in which three groups of rats received three doses (0.1, 0.5 and 1 LD50) of venom and the histopathology was subsequently determined at 72 h post injection. The results showed that only the kidney and the skin (at the site of injection) were clearly damaged whereas cardiac and lung tissues were not changed from that of the control group. Subcutaneous injection of the three doses of venom showed change of all skin structures with clear cell aggregation in epidermal and collagen precipitation in dermal layers. There was a marked dermal layer discontinuity, atrophy in subcutaneous layers with severe haemorrhage commonly observed in envenomed rats. There was distinct interstitial oedema induced collapse of proximal and distal tube in a dose dependent manner. Furthermore, histopathological examination of the kidney showed oedema with lymphocyte accumulation near to medulla and cortex area and glomerular destruction present in the majority of the cases (Ajj, 2003).

4.2. Laboratory findings

Clinical analysis of more than 200 child victims of *H. lepturus* envenomation on admission and on follow up upon being referred to the paediatric emergency department of Abozar Children's Hospital in 2000 was performed. On admission, after informed consent was obtained from the child's parents, they were clinically assessed by the physician. Based on the hypothesis that cardiac and skeletal muscles and liver abnormalities will be induced by the venom, the levels of the following enzymes were determined; LDH (Hering et al., 1993), CK, SGPT and SGOT respectively (Mamor et al., 1978; Correa et al., 1997). Most of the children showed significantly higher mean values of these enzymes. The mean serum levels of CK, LDH, SGPT and SGOT enzymes were increased to 650 U/L, 520 U/L, 125 U/L and 140 U/L, respectively 24 h following admission. Hence it was suggested *H. lepturus* scorpion envenomation produces cardiac, muscle and liver abnormalities that manifest as significant increase of the specific enzymes. These results may suggest that change in the level of these enzymes following *H. lepturus* sting may be used as a prognostic tool in human victims (Mir Dehghan and Motlagh, 2001; Pipelzadeh et al., 2006). The recent investigations on alteration of blood parameters after experimentally induced envenomation by *H. lepturus* venom (0.1 LD_{50} and 0.01 LD_{50}) have increased our understanding of the haemopoetic effects in the rat animal model. The test and controls were subjected to full blood count. The red and white blood cell counts, with exception of neutrophils (0.1 LD_{50} dose) were significantly reduced. With low doses of the venom (0.01 LD50), no changes in lymphocyte or neutrophil was observed which contrasts with high doses of venom (0.1 LD50) (Table 3) (Ajj, 2003). In experiments carried out to determine the effect of *H. lepturus* venom on the blood cells from different animals the data showed that if *H. lepturus* venom is mixed with cow, chicken and goat red blood cells, significant and different degrees of haemolysis and osmotic fragility occurred (Salimian et al., 2002).

Table 3
Changes in C.B.C. parameters (Mean ± S.E.M.) 24 h after subcutaneous injection of two doses of *H. lepturus* venom, 0.1 LD50 and 0.01 LD50 ($n = 5$) (Ajj, 2003).

Parameter	Control	0.1 LD$_{50}$	0.01 LD$_{50}$
RBC (10^6 mm^3)	9.68 ± 0.13	●6.93 ± 0.2∗∗ ↓	●8.34 ± 0.18∗↓
HGB (g/dl)	16.1 ± 0.21	●11 ± 0.12∗∗ ↓	●13.2 ± 0.23∗↓
WBC (10^3 mm^3)	8.1 ± 0.12	●4.1 ± 0.08∗∗∗ ↓	●7.2 ± 0.21∗↓
Lympocyte (%)	67 ± 3.1	●56 ± 5.5∗ ↓	●68 ± 1.5–
Neutrophil (%)	30 ± 1.3	●41 ± 4.68∗ ↑	●30 ± 1.1–
Monocyte (%)	3 ± 0.16	2 ± 0.27∗ ↓	2 ± 0.13∗ ↓

∗$P < 0.05$ between test and control groups.
∗∗$P < 0.01$ between test and control groups.
∗∗∗$P < 0.001$ between test and control groups.
●$P < 0.05$ between two test groups.
↓ Decreased; ↑ Elevated; – without change.

The results from urinalysis of rat receiving 0.1 LD$_{50}$ of venom indicate proteinuria and haematuria was accompanied with a significant rise in urine haemoglobin (Ajj, 2003). Furthermore, they concluded that excision of the site 15 min after subcutaneous injection of the venom is not an effective method for the treatment of envenomed animals as was commonly believed (Ajj, 2003).

5. Discussion

In this review we have demonstrated that the toxicity arising from *H. lepturus* sting from *Hemiscorpiidae* family (Prendini, 2000) differs significantly in type, duration and severity from other Iranian scorpion envenomations. The spectrum of severe clinical effects resulting from *H. lepturus* stings and its potential to exert significant and some times fatal effects were discussed in respect to skin manifestations and other clinical symptoms of envenomation (Radmanesh, 1998; Radmanesh, 1990a). Despite these common dermal effects, the sting of this scorpion does not induce and acute painful response immediately upon envenomation, (which is quite different to the stings of many other scorpions), but generally gives rise to a delayed swelling that may be accompanied by necrosis which if extensive the necrotic tissue may require surgical excision.

Renal injury has been reported following envenomation by venomous animals. Several venoms and venom-derived toxins from snakes, spiders have been described that target the kidney e.g. in man and rodents (Mizuno et al., 2007, Ratcliffe et al., 1989; Amaral et al., 1985). Renal involvement and nephrotoxicity has been demonstrated in patients following *H. lepturus* envenomation that are clinically important as demonstrated by the development of proteinuria and presence of intact RBCs in the urine. These findings correlate with the histopathological findings in rats following experimental envenoming with *H. lepturus* (Pipelzadeh et al., 2006; Correa et al., 1997). Proteinuria and haemolysis were seen simultaneously within 24 h after injection of the venom in rats. Therefore, it seems that proteinuria may be used as an indicator for early occurrence of renal failure (Pipelzadeh et al., 2006), because renal failure secondary to haemolysis needs more time to appear. Whether these alterations were due to a direct effect on kidney function, secondary to haemolysis, acute-phase inflammatory (De Matos et al., 1999) hemodynamic

alterations (Rowan et al., 1992; Murthy et al., 1991) or as a consequence of neurotransmitter release (Freire-Maia and Campos, 1989), remains to be investigated.

The speed of development of clinical signs and symptoms following *H. lepturus* stings contrasts those reported for other hazardous scorpion species. While rapid development of abnormalities in cardio-vascular, neurologic and pulmonary systems are commonly reported for *Buthidae* family (Correa et al., 1997; Mazzei de Davila et al., 1997; Ismail et al., 1995), these toxic manifestations do not appear rapidly and are not common features, except in severe cases of envenomation by *H. leprtus*.

The significant alteration induced in the plasma concentrations of LDH, SGOT, SGPT and CK enzymes levels following *H. lepturus* stings have not been observed in studies of other scorpions (Hering et al., 1993, Amaral et al., 1992; Sofer and Gueron, 1988). These results may support the notion that the different clinical picture observed following envenomation by this scorpion i.e. a dramatic increase in the concentration of intracellular enzymes, may be due to direct tissue damage. However, also it has also been suggested that the observed alterations in prognostic enzymes may be due to stimulation of chemical mediators which trigger their release (Correa et al., 1997). While it is widely believed that the majority of the symptoms resulting from scorpion envenomation is due to the massive amounts of neurotransmitters that are release during the "autonomic storm" (Ismail, 1995; Freire-Maia et al., 1994), there is however, some evidence that the venom from *H. lepturus* has direct haemolytic, nephrotoxic and hepatotoxic actions (Pipelzadeh et al., 2007, 2006).

The morbidity and mortality ratio, in humans, following being stung by *H. lepturus* has in recent years been measured at greater than 5%; paediatric patients appear to have the greatest risk (Fig. 2) (this ratio is lower in other animal species) (Krifi et al., 1998; Freier-Maia et al., 1994; Ismail, 1994). The fact that the morbidity and mortality ratio reported in the group aged 10–20 was not significantly higher than those from group aged less than 10 suggested that high risk of mortality following *H. lepturus* envenomation in children may be attributed to the differences in the dose of the venom in relation to victim's body weight (Padilla et al., 2003).

The available data show that mean time between the scorpion sting and the administration of the anti-venom for *H. lepturus* is more than 4 h. The time elapsed between the scorpion sting and antivenom therapy appears critical because scorpion venom is distributed throughout the victim very rapidly fast, as reported in a number of clinical and experimental reports (Krifi et al., 1998; De Rezende et al., 1995; Ismail and Abd-El Salam, 1988). This delay in referring patients may explain why the total mortality rate has remained constant over the past 10 years. The data would suggest that scorpion envenomation in Iran is a greater public health problem in comparison to other known countries endemic with scorpions e.g. Mexico (Simard and Watt, 1990) and Brazil (Freire-Maia et al., 1994; Freire-Maia and Campos, 1987). However, new data from the Iranian Ministry of Health show that the mortality rate due to scorpion stings has rapidly decreased in the past 2 years, possibly because of early referral and availability of

more effective antivenom as well as increase in public awareness of the dangers associate with this scorpion.

It is interesting to note that while there was no difference in clinical severity following *H. lepturus* stings in relation to the gender of the victim amongst the different age groups, the data does suggest that males were more frequently stung than females (Al-Asmari and Al-Saif, 2004; De Roodt et al., 2003, Pardal et al., 2003). However, a more recent report suggests that females accounted for the majority of victims (Forrester and Stantley, 2004). This recent finding is not in agreement with the results of a study carried out on the distribution of scorpion stings that occurred in Tunisia where both males and females were equally affected (Goyfflon et al., 1982).

The extremities accounted for almost 67% of the recorded sites for stings, a frequency that is not very different from other studies (De Roodt et al., 2003; Al-Sadoon and Jarrar, 2003). These findings may be explained on the basis that exposed limbs are common in most manual activities and stings occur when moving or entering the scorpion retreats. Stings on other parts of the body, such as neck and head most likely occur when resting or sleeping. The data also shows that the frequency of stings increase in the months of June–September with the maximum frequency recorded in June. This increase in the frequency of stings is likely to be linked to the fact that the activity of this scorpion increases during the hotter months of the year.

According to the health authority data, more than 95% of scorpion sting victims in Iran received the polyvalent antivenom prepared in Razi Institute of Vaccine and Serum Production in Karaj from the purified plasma of healthy horse, which have been immunized against the most dangerous scorpions in Iran (Latifi and Tabatabai, 1979). The appropriate treatment of *H. lepturus* envenoming remains controversial as the use of this anti-venom has not generally been accepted as the standard treatment protocol among the attending physicians (Pipelzadeh et al., 2006). However, the therapeutic efficacy of the anti-venom has been reported for this species and the benefit of anti-venom serotherapy is both a reduction in the severity of symptoms and a reduced death rate (Pipelzadeh et al 2007). Polyvalent anti-venoms have a number of short comings i.e. the potency of the anti-venom is measured in mice; there is no clear rational for a particular dose of anti-venom; the most clinically effective route of injection is still open for debate; there is a danger of anaphylaxis or serum sickness. For these reasons, we suggested that it may be worth developing a monovalent antivenom specifically against the venom of *H. lepturus* in an attempt to improve on its relative potency and its clinical effectiveness (Ozkan and Carhan 2008).

H. lepturus venom elicits a complex pattern of clinical signs and symptoms that are dissimilar to other scorpion envenonations (Pipelzadeh et al., 2007) in Iran such as *Odonthubuthus doriae* (Jalali et al., 2007; Zare et al., 2006), owing to the ability of the venom from *H. lepturus* to disrupt the neuromuscular, cardiovascular and respiratory systems. Laboratory data (Table 3) is in accordance with other unpublished results that show a reduction in the number of blood cells following *H. lepturus* envenomation (probably caused by the action of haemolytic toxins). However, other studies on different scorpion venoms have shown an increase in number of red blood cells (possibly in part due to the action of the released catecholamines by the scorpion venom) (Abdel-Haleem et al., 2006). Furthermore, a recent biochemical study (Zare et al., 2007) indicate that *H. lepturus* venom is similar to most scorpion venoms, in that the venom can affect ionic currents either as a consequence of release of peripheral neurotransmitters or through a direct action of peptide toxins blocking ion channels (Pipelzadeh et al., 2007) As a consequence, envenomation induces abnormal sympathetic stimulation in most victims (about 50% of cases) and these victims show clinical signs of autonomic disturbances i.e restlessness, fever and sweating (Radmanesh 1998). Furthermore, it has been suggested that the pulmonary oedema which is seen in a number of clinical and experimental studies appears to be partly neurogenic in its origin and it is likely to have been precipitated by the elevated activity of the autonomic nervous system i.e. through releasing large amounts of catecholamine (Mazzei de Davila et al., 2002). In addition, the venom ($<20 \mu g/g$ sc in mice) increased osmotic fragility and lyses of erythrocytes (Zare et al., 2007) which probably accounts for the intravascular haemolysis (Kankonkar et al., 1992) and is responsible for the haematuria and the development of anaemia (Radmanesh, 1990a,b) in envenomed animals.

The data described here does show, unequivocally, that *H. lepturus* venom does not act in a manner that would be expected of typical scorpion venom. The presence of clearly discernible renal, skin and blood abnormalities suggest that the *H. lepturus* venom is a heterogeneous mixture of toxins, quite dissimilar to other scorpion species found in Iran (Bergman, 1997). While some experts consider using the specific anti-venom for correct clinical management on scorpion stings (Abrough et al., 1999; Sofer et al., 1994), others recommended the use of the polyvalent scorpion antivenom (Possani, 2000; Ghalim et al., 2000; Ismail, 1994; Freire-Maia and Campos, 1987). Antivenin is found to be effective in prevention or abolition of the various manifestations in human scorpionism if the antivenom is administered less that 6 h after the mean time from envenomation (Pipelzadeh et al., 2007). Due to the severity of *H. lepturus* envenoming we would advise that appropriate treatment, mainly antivenom, be started as soon as possible after the sting (Ghalim et al., 2000). As there is strong evidence that patient who received antivenin very early in the course of the envenomation present with mild cardiovascular disturbances (Mazzei de Davila et al., 2002) and delayed renal impairment.

To date there is insufficient data on the action of *H. lepturus* venom to speculate on any mechanisms that may underly the clinical manifestation of *H. lepturus* envenomation. Before an understanding of the pharmacology and toxicology of the whole venom can be considered the venom must be separated into its component parts using chromatographic techniques. The purified toxins can then be analysed in detail both chemically and biologically such as those that where carried out for *O. doriae* (Abdel-Motalleb et al., 2006, Abdel-Haleem et al., 2006; Jalali et al., 2007, 2005). Recently, two peptides (Hemicalcin and Hemitoxin) have been isolated and pharmacologically characterised. Hemicalcin has been shown to interact with

the ryanodine– sensitive calcium channels (Shahbazzadeh et al., 2007) and hemitoxin been shown to block a number of Kv1.x channels expressed in *Xenopus oocytes* (Srairi-Abid et al., 2008). As Kv1.x channels are important in controlling neurotransmitter release hemitoxin may be an important player in the generation of the "autonomic storm" following envenomation (Meir et al., 1999).

In conclusion, a significant number of fatal scorpion stings that occur in the Khuzestan province of Iran are due to *H. lepturus*. There are other hazardous scorpions commonly found in Iran i.e. *A. crassicuda* (Sadeghian, 2003; Radmanesh, 1990b), *M. eupeus*, *A. petrigus*, *Scorpio maurus*, *O. doriae* and *Hotentota (Buthotus) saulcyi* but these scorpions produce venoms that are less toxic relative to *H. lepturus*. The reviewers would conclude that the results of these investigations indicate that *H. >lepturus* is the most dangerous scorpion of Iran.

Acknowledgment

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