Venomics of *Leiurus abdullahbayrami*, the most lethal scorpion in the Levant region of the Middle East

Introduction

The scorpion genus *Leiurus* Ehrenberg, along with genera *Androctonus* Ehrenberg, *Mesobuthus* Vachon, and *Buthus* Leach (family Buthidae) contains the most medically important species in North Africa and the Middle East (MENA region), encompassing the area with the highest incidence and mortality rate due to scorpion envenomation worldwide, representing 42% of the global scorpion sting burden (Jenkins et al., 2021). The genus *Leiurus* currently comprises twenty-two species (as of September 2023), spread across Africa (Algeria, Chad, Egypt, Ethiopia, Libya, Mali, Mauritania, Niger, Somalia, Sudan, and Tunisia) and the Middle East (ME) (Sinai, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates and Yemen) (Al-Qahtni et al., 2023; Alqahtani and Badry, 2020; Lourenço, 2020; Lowe et al., 2014). In the ME area, it was assumed until recently that only *Leiurus quinquestriatus* (range Egypt and Sudan) and *Leiurus hebraeus* (range Sinai, Palestine, Israel, and neighboring areas) were the two species of most medical significance (Abdel-Haleem et al., 2006; Sofer et al., 1991), whose venoms and toxins have been among the most thoroughly characterized biochemically and physiologically due to their toxicity to mammals (Borneman and Hahin, 1993; Gordon et al., 1998). Recent taxonomical updates have uncovered the existence of a distinct species in the Levant region of ME (southern Turkey, northern Lebanon, and Syria), *Leiurus abdullahbayrami* (Yagmur et al., 2009), wich diverges 12–14% at the nucleotide level (16S rRNA) with respect to other *Leiurus* spp. (Alqahtani and Badry, 2020). *L. abdullahbayrami* is reported to possess the highest venom lethality (mouse median lethal dose (LD_{50}) by subcutaneous route = 0.19 mg/kg) among congeners (Ozkan et al., 2011). In accordance with this, the species is responsible for a very acute clinical syndrome in envenomed children, including pulmonary edema and severe myocardial dysfunction refractory to treatment with inotropics (Aslan et al., 2018; Dokur et al., 2017; Yöntem et al., 2020). Fatalities due to *L. abdullahbayrami* have been reported from southeastern Turkey (Caliskan, 2015; Ozkan et al., 2011) and Lebanon (Borges and Yagmur, 2022). This species is possibly also involved in envenoming cases from Syria, where scorpion stings are frequent (Kouli et al., 2023), and *L. abdullahbayrami* is widespread in the northern area (Khalili and Yagmur, 2010).

Scorpion venoms from species in the family Buthidae are heterogeneous mixtures composed of salts, free amino acids, and varying concentrations of peptides and proteins. The latter include voltage-gated sodium-, calcium- and potassium-channel specific neurotoxins, as well as neurotoxin-related molecules such as lipolysis-activating components, ancillary enzymes (hyaluronidases, metalloproteinases, phospholipases and chitinases), and antimicrobial and bradykinin-potentiating peptides, among other components (Smith and Alewood, 2015). Physiopathological effects in humans are chiefly the consequence of the depolarizing action of ion-channel neurotoxins, which bioavailability is potentiated by hyaluronidases (Laraba-Djebari et al., 2015). Considering that specific antivenoms, in conjunction with appropriate pharmacological support

treatments, are the only proven therapy against scorpionism worldwide (Amaral and Rezende, 2000), efforts have been made to increase specificity and availability of anti-scorpion immunoglobulins due to the extensive antigenic diversity exhibited by scorpion neurotoxins, the most lethal venom components (Bouhaouala-Zahar et al., 2011). To the best of our knowledge, few studies have been performed to explore toxin structural and antigenic diversity among *Leiurus* species in the Middle East nor do tailored, specific antivenoms exist in the region against *L. abdullahbayrami*, despite its epidemiological and clinical relevance. Venomics, the in-depth analysis of venom proteins and peptides based on the application of proteomic techniques, has led to a better understanding of scorpion venom composition (Cid-Uribe et al., 2020). This contribution explores the lethality and proteomic venom profile of *L. abdullahbayrami* to allow comparisons with venoms from congeners and other buthid scorpions, paving the way for future immunological studies that could lead to the development of a specific antivenom.