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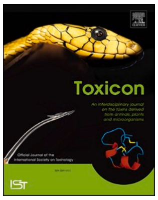

Short communication

Bioactivity profiling of spider venoms reveals predominant hyaluronidase activities

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ABSTRACT

Spider venoms are primarily composed of small neurotoxic peptides. However, recent studies suggested a hitherto overlooked diversity of spider venom enzymes, although their functional space still remains largely unexplored. We tested 10 spider venoms for enzymatic activities covering six enzyme classes and found that all tested enzymatic activities can be detected in at least some of the venoms and that hyaluronidases exhibit particularly high enzymatic activities. With this, our study provides functional evidence for the proposed biological significance of enzymes in spider venoms, but more detailed investigations are required.

Spiders are one of the oldest and most diverse venomous lineages, which evolved over more than 300 million years into highly effective predators of insects and other arthropods (Lüddecke et al., 2022). More than 53,000 species have been described which inhabit most terrestrial ecosystems and are subdivided in three infraorders (Mesothelae, Mygalomorphae, Araneomorphae) (Gloor et al., 2025; Selden and Penney, 2010). The family Theraphosidae, commonly referred to as tarantulas, belongs to the Mygalomorphae and contains some of the most prominent spiders that are popular as pets (Herzig et al., 2023; Lüddecke et al., 2018). Recently, molecular investigation revealed 13 commonly accepted subfamilies (Briggs and Hamilton, 2024; Lüddecke et al., 2018).

All spiders except members of the family Uloboridae are venomous (Peng et al., 2025). Spider venom may contain thousands of different biomolecules, with the majority being small disulfide-rich neurotoxic peptides, linear peptides, and proteins (Pineda et al., 2020). It is estimated, that up to 10 million biomolecules could be isolated from the extant spider species, rendering spider venom a rich source of novel natural products (Lüddecke et al., 2022; Peng et al., 2025; Saez and Herzig, 2019). Particularly, short neurotoxic peptides with an inhibitor cysteine knot (ICK) motif have been the focus of various biomedical studies because of their interaction with ion channels and receptors (Langenegger et al., 2019; Saez et al., 2010). This tremendous emphasis on pharmacologically interesting small neurotoxins caused a prevalent neglect of other venom components and the exploration of the latter, especially of high molecular weight proteins and enzymes, has been declared a grand challenge of future spider toxinology research (Herzig, 2023). In light of that, a recent comprehensive analysis of spider venom proteomes indeed revealed a so far underestimated diversity and abundance of enzymes across various spider venoms (Diniz et al., 2018; Dresler et al., 2024a, 2024b; Kuhn-Nentwig et al., 2019; Langenegger et al., 2018; Lüddecke et al., 2020, 2025). Considering the wide space of potentially catalyzed reactions from the identified enzyme classes, it is reasonable to hypothesize that these enzymes display various pivotal biological functions (Dresler et al., 2024a, 2024b; Herzig, 2023; Kuhn-Nentwig et al., 2019; Lüddecke et al., 2025). For instance, many identified enzymes are hydrolases, which might be involved in the hydrolysis of biomolecules as part of pre-digestive processes, or facilitate the metabolism of extracellular matrix components (Dresler et al., 2024b). However, their functional space remains poorly understood and, apart from some pioneering works focusing on selected enzyme activities of venoms or individual venom components, a comprehensive

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assessment of enzymatic activities from spider venoms is missing (Biner et al., 2015; Do Nascimento et al., 2022; Dresler et al., 2025; García-Arredondo et al., 2015). This is especially unfortunate as a broader comparative analysis would serve as a proof of principle for the enzyme diversity inferred from proteomic studies across spider venoms indeed being of functional relevance.

To close this important gap in our understanding of spider venom biology, we set out to apply activity profiling targeting several enzymatic activities likely to be present in spider venoms. In that context, theraphosid venoms were excellent model systems to facilitate these screenings because, in contrast to most other spider lineages, these large-bodied specimen deliver milligram quantities of venom (Herzig et al., 2019). We therefore focused on theraphosid venoms to explore the functional space of enzyme activities. Specifically, we analyzed venom from nine representative species of eight theraphosid subfamilies as well as one from the family Sparassidae (*Holconia hirsuta)* (see Fig. 1A and Supplementary Table S1).

As a first step, we employed one dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) to explore the general protein composition of the analyzed venoms (see supplementary methods for detailed description). Overall, the venom profiles of the theraphosid spiders were comparatively similar, whereas the venom of *H. hirsuta* appeared to be more complex (see Fig. 1B). With the exception of *Acanthoscurria geniculata* and *Megaphobema velvetosoma* all theraphosid venoms were dominated by small components <15 kDa, which is likely due to the abundance of short neurotoxic peptides (Langenegger et al., 2019; Lüddecke et al., 2022). If enzymatic components were present in the analyzed venoms, protein bands would be expected at a molecular weight exceeding 10 kDa. In line with this expectation, all examined venom samples exhibited multiple intense bands in this region, indicating the presence of high molecular weight proteins or enzymes. Notably, several of these bands correspond to the predicted molecular mass range of known enzyme classes detected in spider venoms. For instance, all theraphosid venoms presented one intense band between 37 and 46 kDa, potentially representing hyaluronidase-like proteins (Nishiduka et al., 2022; Rodríguez-Rios et al., 2017). The venom of *Avicularia* spec.*, Poecilotheria regalis, Cyriopagopus vonwirthi, Pterinochilus* cf. *murinus, Selenocosmia crassipes* and *Monocentropus balfouri* contained several bands between 50 and 80 kDa, corresponding to the expected size of metalloproteases (Lüddecke et al., 2022; Nishiduka et al., 2022). Remaining bands may be associated with phospholipases A_2 at 14–18 kDa, phospholipases D at 30–35 kDa or additional enzymes and proteins, respectively (Dresler et al., 2024a). Therefore, our protein profiling supports the presence of putative enzymes across tested venoms and justifies further experiments to validate these findings.

All venoms have been functionally assessed for their protease, hyaluronidase, phospholipase A_2, chitinase, phospholipase D and acetylcholinesterase activity (see Fig. 2), following protocols described previously (Schulte et al., 2023). Protease activity revealed to be modest in all venoms with the highest activities detected in *A.* spec and *P.* cf *murinus* venom being 32 % and 16 % compared to the 1 μg/mL trypsin control, respectively. Proteases contained in the venom may exhibit functionalities such as the activation of precursors within the venom or

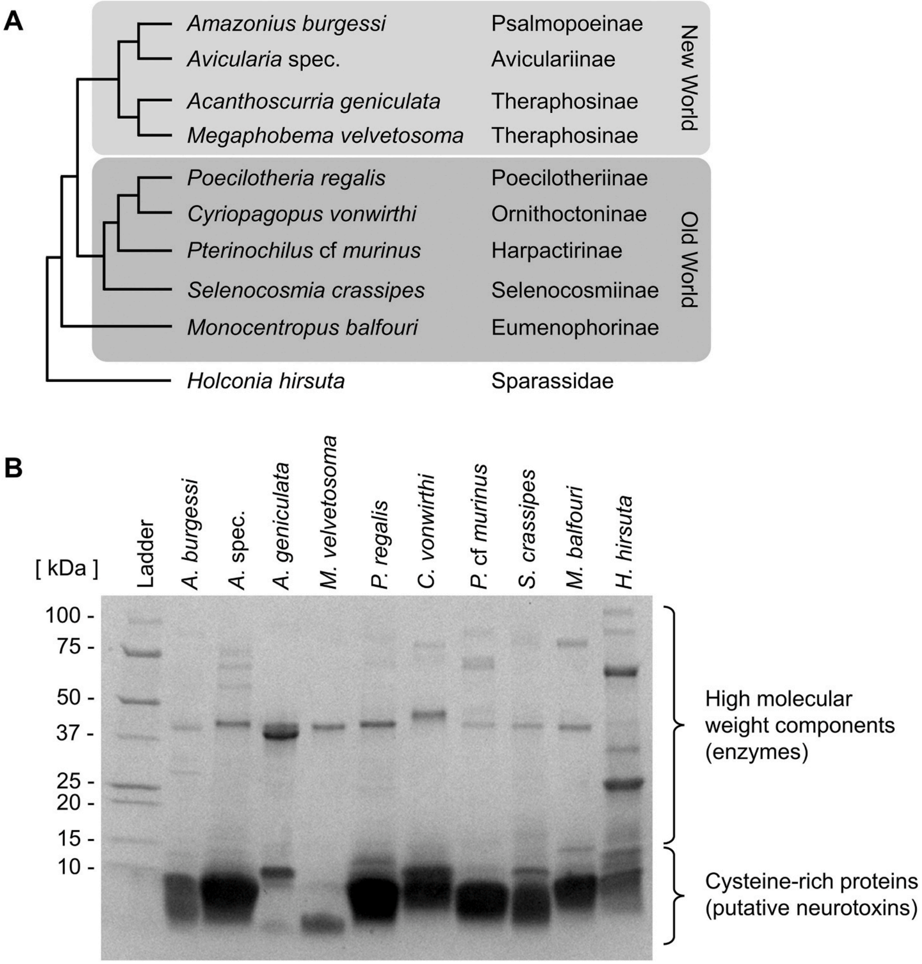

Fig. 1. Relationship and protein profiling of spider venoms. A: Cladogram showing the taxonomic relationships between spiders from which venoms were tested in this study (Foley et al., 2019), **B:** SDS-PAGE analysis under reducing conditions illustrating the protein profiles of the tested venoms (15 μg) and a protein ladder.

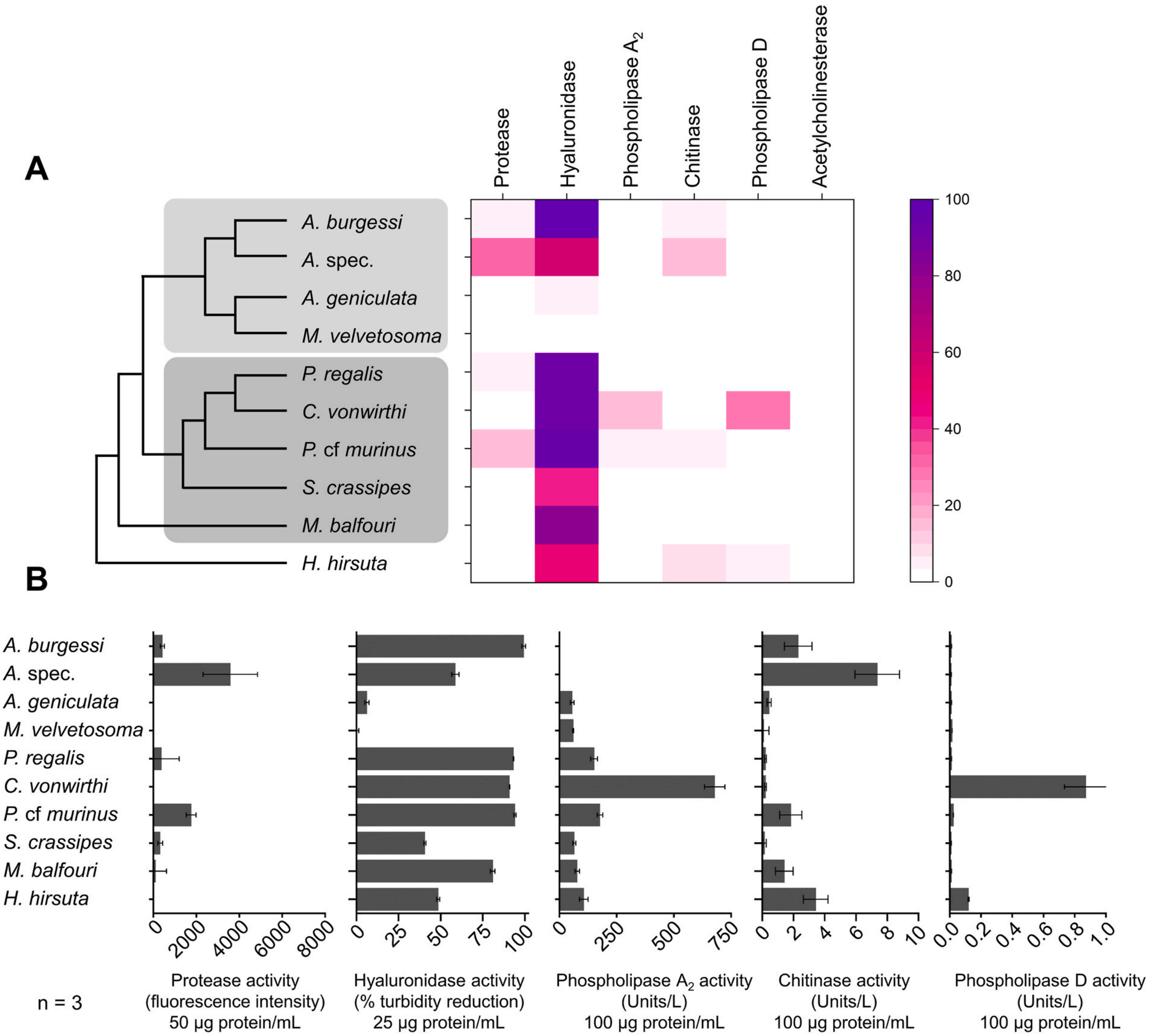

Fig. 2. Enzymatic activity profile of 10 investigated spider venoms. Protease and acetylcholinesterase activity were assessed using 50 µg protein/mL venom, hyaluronidase activity using 25 µg protein/mL and the remaining activities were determined using 100 µg protein/mL venom. All activities were assayed in triplicates. **A:** Heatmap illustrating the percentual enzymatic activities calculated by normalization against corresponding assay standards. For protease activity, the fluorescence intensity of 1 µg/mL trypsin served as assay standard. Hyaluronidase activity was calculated as the reduction of turbidity in relation to the turbidity of the substrate (negative control). Phospholipase A_2 activity was normalized against a 5000 Units/L bee venom phospholipase A_2. For chitinase activity, 50 µmol/L *p*-nitrophenol standard served as internal standard, while a choline standard served as internal standard for the phospholipase D activity. The Acetylcholinesterase activity of all venom samples was below the detection limit of the kit (see supplementary methods for details). **B:** Enzymatic activities displayed in their corresponding units with standard deviation, except for acetylcholinesterase activity, which was absent in all venoms.

pre-digestion and aiding toxin distribution in the prey's body after envenomation. The observed protease activities were modest, which might have been caused by protease inhibitors contained in the crude venom or by absence of required activation conditions such as pH values or additional cofactors (DaSilveira et al., 2002). Contrary to the modest protease activity, a high activity against hyaluronic acid has been observed in all venoms except of those from the subfamily Theraphosinae (*A. geniculata, M. velvetosoma*). Hyaluronidases have been subject to a number of studies due to their wide distribution in animal venoms (Bordon et al., 2015). These revealed their important role in local and systemic effects of envenomation in which they facilitate the spread of other toxins present in the venom through disintegration of extracellular matrix components (Bordon et al., 2015; García-Arredondo et al., 2015; Rodríguez-Rios et al., 2017). However, the biological role of spider venom hyaluronidases has been discussed intensively due to their broad specificity to hyaluronic acid and chondroitin derivates (Biner et al., 2015). However, the determination of substrate specificity revealed to be highly depending on the assay methodology applied, often leading to misinterpretations of the obtained data (Biner et al., 2015; Honda et al., 2012). Given that the extracellular matrix of insects lacks hyaluronic acid and contains chondroitin and its sulfated form, the role of spider venom hyaluronidases has been discussed in regard to vertebrate predation and a potential defensive mechanism against vertebrate predators (Bordon et al., 2015; Dresler et al., 2024a; Girish and Kemparaju, 2007). Theraphosid and sparassid spiders, amongst others, have been reported to occasionally predate on small vertebrates (Biner et al., 2015; Nyffeler and Gibbons, 2022). Our results revealed a low hyaluronidase activity in Theraphosinae venoms, which are infamous for using urticating setae as their primary defensive strategy (Foley et al., 2019). This may suggest a defensive role of venom hyaluronidases in other spiders, which is replaced by urticating setae as an alternative defense strategy in the sub-family Theraphosinae. However, further studies are required to verify this hypothesis. Phospholipase A_2, chitinase and phospholipase D activity revealed to be generally below 3

% in most venoms and none of the venoms displayed acetylcholinesterase activity within the detection limits of the kit. However, highest phospholipase A_2 activity, in comparison to the used control, could be determined for *C. vonwirthi* (14 %) and *P.* cf. *murinus* (4 %). Phospholipase A_2 is a common venom component found in the venom of many snakes and in defensive arthropods such as honeybees (*Apis mellifera*) where it causes multiple physiological effects, including cytotoxic effects, local inflammation and pain (Lüddecke et al., 2025; Zambelli et al., 2017). Furthermore, we analyzed the venoms for potential exochitinase activity. Exochitinase activity was observed for venoms of *A. burgessi* (5 %) and *A.* spec. (16 %), *P.* cf. *murinus* (4 %) and *H. hirsuta* (7 %). Chitinases are a diverse enzyme family, known for their ability to cleave internal bonds (endochitinases) or progressive cleavage of external residues (exochitinases) (Yuli et al., 2004). In the venom they may therefore facilitate prey capture and pre-digestion prior to the extra-oral digestion of the prey. Phospholipase D activity was absent in all venoms except *C. vonwirthi* (29 %) and *H. hirsuta* (4 %). Contrary to most spider venom enzymes, phospholipase D has been investigated in detail due to its clinical relevance. It has been primarily described in the venoms of sicarriid spiders of the genera *Loxosceles*, where is it responsible for severe dermo-necrosis after envenomation (Dresler et al., 2024a; Senff-Ribeiro et al., 2008).

Overall, our analysis provides functional evidence for the widespread occurrence of various enzymatic activities across theraphosid spider venoms. This might even be valid to spider venoms more broadly, considering that venom of the sparassid *H. hirsuta*, which was used as an outgroup, also exerted various enzymatic activities. However, our exploration is based on only a few enzyme classes and is carried out on a small fraction of spider taxa. Therefore, our data needs to be interpreted with caution. Future studies investigating a broader set of activities and a higher diversity of spiders are needed to fully grasp the biological role of spider venom enzymes and to unveil their presence across the spider kingdom. Nevertheless, we report the first comparative enzymatic bioactivity profiling of spider venoms, including nine representatives of Theraphosidae alongside one araneomorph outgroup. Our analysis revealed detectable enzymatic activities across the six enzyme classes that were tested except for acetylcholinesterase activity, which was absent. Although the overall enzymatic activities were generally low, certain venoms displayed comparatively higher activities, particularly in the case of hyaluronidase activity. These findings provide functional evidence for the recently suggested significance of enzymes for spider venoms, both within Theraphosidae and across spiders more broadly. However, this study only examined the venoms from 2 out of 139 known spider families. More work is therefore required to obtain a general overview of the activities of venom enzymes across the order Araneae.

CRediT authorship contribution statement

Josephine Dresler: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Volker Herzig:** Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis. **Lennart Schulte:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Tim Lüddecke:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Ethical Statement

Ethical Statement not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.toxicon.2025.108667.

Data availability

All data available as a supplement.

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